Eighth Edition

GHAI Essential Pediatrics

Editors

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Introduction to Pediatrics

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The branch of medicine that deals with the care of children and adolescents is *pediatrics*. This term has roots in the Greek word *pedo pais* (a child) and *iatros* (healer). Pediatrics covers the age group less than 18 yr of age. A physician who specializes in health care of children and adolescents is a *pediatrician*. The goal of the specialty is to enable a child to survive, remain healthy, and attain the highest possible potential of growth, development and intellectual achievement. Child health encompasses approaches, interventions and strategies that preserve, protect, promote and restore health of children at individual and population level.

Children under 15 yr of age comprise about 30% of India's population. Childhood is the state when the human being is growing and developing. It is time to acquire habits, values and lifestyles that would make children responsible adults and citizens. The family, society and nation are duty-bound to make children feel secure, cared for, and protected from exploitation, violence and societal ills. Female children face gender bias in access to healthcare and nutrition. A civilized society nurtures all its children, girls and boys alike, with love, generosity and benevolence.

Child is not a miniature adult. The principles of adult medicine cannot be directly adapted to children. Pediatric biology is unique and risk factors of pediatric disease are distinct. Clinical manifestations of childhood diseases may be different from adults. Indeed, many disorders are unique to children. Drug dosages in children are specific and not a mathematical derivation of the adult doses. Nutrition is a critical necessity for children not only to sustain life, but to ensure their growth and development.

Pediatrics as a Specialty

Pediatrics is a fascinating specialty. It encompasses care of premature neonates on the one hand, and adolescents, on the other. The discipline of pediatrics has branched into well-developed superspecialties (such as neonatology, nephrology, pulmonology, infectious disease, critical care, neurology, hematooncology, endocrinology and cardiology). Pediatrics covers intensive care of neonates and children using the most sophisticated technology, on the one hand, and providing home care to newborns and children, on the other. Child health is thus a state-of-art clinical science as well as a rich public health discipline.

Medical students should possess competencies for the care of healthy and sick children. The agenda of high child mortality due to pneumonia, neonatal infections, preterm birth complications, diarrhea, birth asphyxia and vaccine preventable diseases is still unfinished. The benefits of advancing pediatric specialties must reach all children. Besides, an increasing body of knowledge on pediatric origins of noncommunicable diseases of the adult is set to change the paradigm of child health. Primary prevention, identification of early markers and timely treatment of adult disorders are the emerging imperatives in pediatrics.

Historical Perspective

Medical care of children finds place in the ancient Indian, Greek and Chinese systems of health. But as a formal discipline, pediatrics took root in Europe and the US in the 19th century when some of the famous children hospitals were established. BJ Hospital for Children, Mumbai was the first child hospital to be established in India in 1928. Postgraduate diploma in pediatrics was started there in 1944; postgraduate degree programs began in the fifties. Pediatrics became an independent subject in MBBS course in mid-nineties. The first DM program in neonatology started in 1989 at PGIMER, Chandigarh and in pediatric neurology at AIIMS in 2004.

Challenge of High Child Mortality

India has the highest number of child births as well as child deaths for any single nation in the world. Each year, as many as 27 million babies are born in the country. This comprises 20% of the global birth cohort. Of the 7.8 million

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under 5 child deaths in the world in 2010, 1.7 million (23%) occur in our country. The mortality risk is highest in the neonatal period. National programs focus generally on child deaths under the age of 5 yr (under-5 mortality). Table 1.1 provides the most recent figures on the key child mortality indices.

Table 1.1: Child mortality indices in India

Indices	Level in 2012
Under 5 mortality rate (U5MR)	52 per 1000 live births
Infant mortality rate (IMR)	42 per 1000 live births
Neonatal mortality rate (NMR)	29 per 1000 live births
Early neonatal mortality rate (ENMR)	23 per 1000 live births

U5MR Number of deaths under the age of 5 years per 1000 live births
IMR Number of deaths under the age of 1 year per 1000 live births
NMR Number of deaths under the age of 28 days per 1000 live births
ENMR Number of deaths under the age of 7 days per 1000 live births

In terms of under 5 mortality (U5MR), India ranks 46th among 193 countries. The U5MR in India (52 per 1000 live births) is unacceptably high given our stature as an economic, scientific and strategic power. U5MR in Japan (3), UK (5), USA (8), Sri Lanka (17), China (18) and Brazil (19) is worth comparing with that of India. Great nations not only have negligible child mortality, but also ensure good health, nutrition, education and opportunities to their children. Majority (56%) of under 5 deaths occur in the neonatal period (<28 days of life), and the neonatal mortality accounts for 70% infant deaths.

There has been a steady decline in child deaths. U5MR has declined by almost 50% between 1990 and 2010 from 117 to 59 per 1000 live births. However, decline in neonatal mortality rate (NMR) has been slower. In the decade of 2001–10, infant mortality rate (IMR) declined by 34%, while NMR decreased by 17.5% (Fig. 1.1). More worrying is the fact that the level of early neonatal mortality (deaths under 7 days of life) has remained unchanged.

Reduction in infant mortality is the foremost development goal of the country. India is a signatory of the millennium declaration and thereby committed to the Millennium Development Goals (MDG). The MDG 4 encompasses reduction of U5MR by two-thirds by 2015 from the 1990 baseline. Since the U5MR in 1990 was 117 per 1000 live births, the MDG 4 goal is to attain U5MR of 39 per 1000 live births by 2015. This corresponds to an IMR of 29 per 1000 live births. Given the prevailing levels (Fig. 1.1), India would have to further accelerate her child survival action to attain MDG 4. This is difficult, but achievable. The XII Plan aims to bring IMR to 25 per 1000 live births by 2017.

Why do children die?

The eight important causes of under 5 mortality in children in India are: (i) pneumonia (24%), (ii) complications of prematurity (18%), (iii) diarrhea (11%), (iv) birth asphyxia (10%), (v) neonatal sepsis (8%), (vi) congenital anomalies (4%), (vii) measles (3%), and (viii) injuries (3%) (Fig. 1.2). The above causes are the proximate conditions that lead to death. Poverty, illiteracy, low caste, rural habitat, harmful cultural practices, and poor access to safe water and sanitation are important determinants of child health. Undernutrition is a critical underlying intermediate risk factor of child mortality, associated with 35% of under 5 child deaths. Undernutrition causes stunting and wasting, predisposes to infections and is associated with adult disorders (hypertension, diabetes, heart disease) and low economic productivity.

Health System in India

The rural health system in India is depicted in Fig. 1.3. At the bottom of the pyramid is the village with an average population of 1,000. There are two workers at this level, an Accredited Social Health Activist (ASHA) who is a woman volunteer from the same village placed as the frontline worker of the health sector, and an Anganwadi

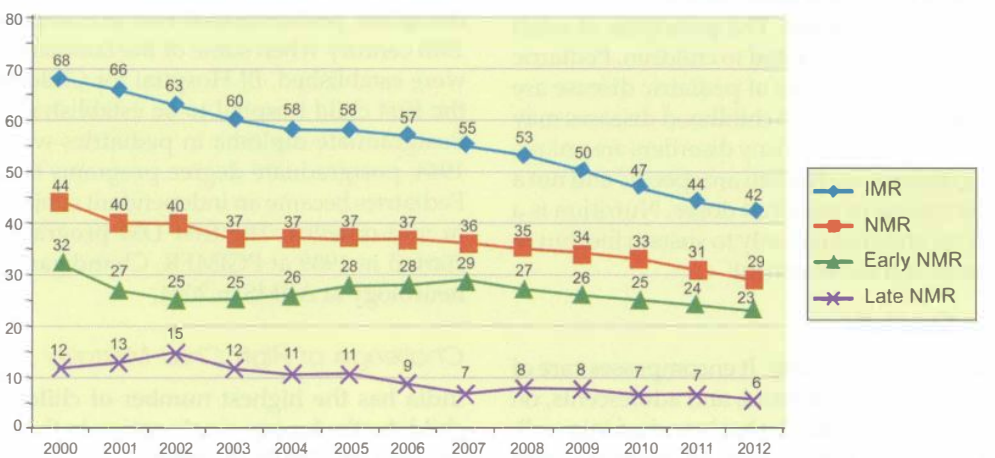

Fig. 1.1: Trends in neonatal and infant mortality rates (Data from Sample Registration System)

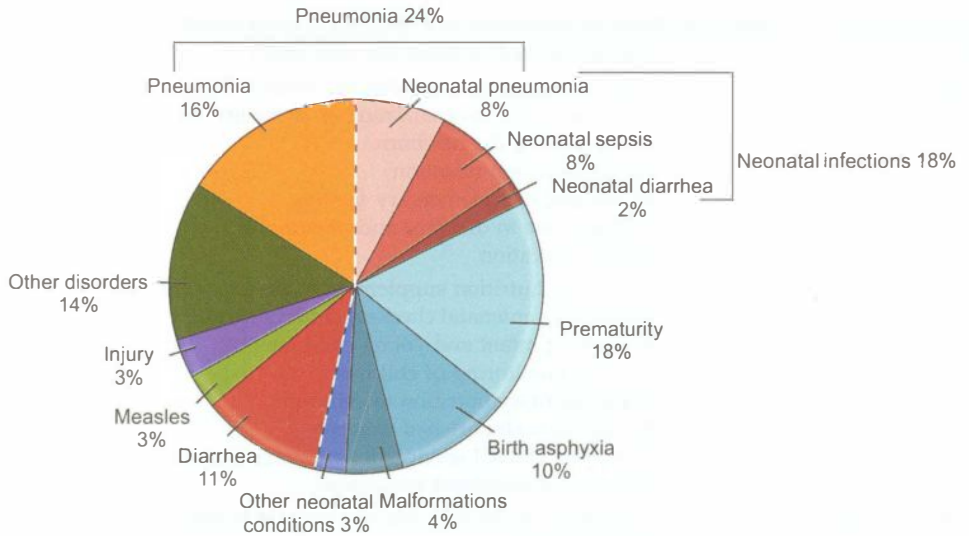

Fig. 1.2: Causes of under 5 child deaths. The area to the right of the dotted line indicates neonatal conditions

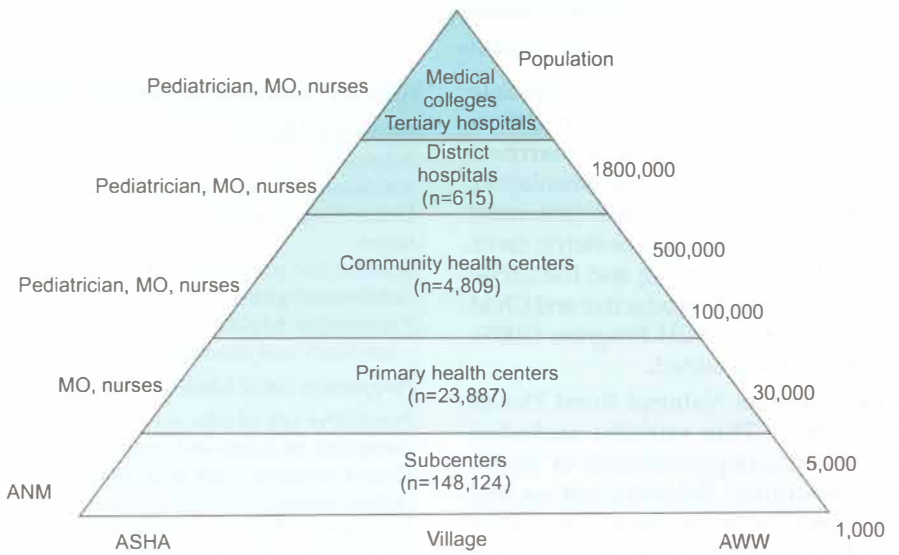

Fig. 1.3: Rural health system in India. ANM auxiliary nurse midwife; ASHA accredited social health activist; AWW anganwadi worker, MO medical officer

worker of the health sector, and an Anganwadi Worker (AWW), belonging to the Integrated Child Development Services (ICDS), and responsible for nutrition and child development services. For every 5,000 population, there is a subcenter where 1–2 Auxiliary Nurse Midwives (ANM) are posted. The roles of ASHA, AWW and ANM in maternal, newborn and child health are shown in Table 1.2.

A primary health center (PHC) caters to a population of 30,000 and is manned by one or two medical officers and nurses. A community health center (CHC) covers a population of 100,000 and has provision for general medical officers as also specialists, including a pediatrician. District hospitals and medical college hospitals provide more advanced specialty services. The private practitioners and facilities are primarily located in urban areas. Rural population also accesses services of unqualified practitioners which are not a part of the formal health sector. Unlike the rural system, the urban health system is unstructured with multiple providers and dominance of private sector for health care services.

National Programs on Child Health

Child health has been at the core of our health policy. The Universal Immunization Program launched in 1985 focused on immunization against six diseases (tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus and measles). The Diarrheal Disease Control Program was initiated in 1981 and Acute Respiratory Infections Control Program in

Table 1.2: Roles of grassroots functionaries in child health

Provider	*Role in maternal, newborn and child health*
Accredited Social Health Activist (ASHA)	Mobilizing pregnant mother for antenatal check and care Accompanying pregnant mother to facility for delivery Home care of the newborn Facilitating immunization Promoting complementary feeding Primary care in diarrhea and pneumonia Health education
Anganwadi Worker (AWW)	Providing nutrition supplement to pregnant mother Facilitating antenatal checks and immunization Promoting infant and young child feeding Growth monitoring of children Supplementary nutrition to children Managing malnourished children Providing IMNCI services for neonates and children Nonformal preschool education
Auxiliary Nurse Midwife (ANM)	Antenatal checks and care of pregnant mothers Immunization Supervising ASHA and AWW in newborn and child care Providing IMNCI services for neonates and children Health education

IMNCI Integrated Management of Neonatal and Childhood Illness

1990. In 1992, India launched the Child Survival and Safe Motherhood Program (CSSM) by combining interventions for child survival (immunization, control of diarrheal disease, respiratory infections, vitamin A supplementation, essential newborn care) and maternal health (antenatal care, deliveries in institutions, emergency obstetric care). In 1997, the Program for Family Planning and the CSSM Program were merged to create the Reproductive and Child Health Program. In phase 2 of the RCH Program (2005), adolescent health component was added.

The government launched the National Rural Health Mission (NRHM) in 2005. This mission included investment in public health, improvements in health systems, focus on communities, decentralization and demand-side interventions to improve effectiveness of the programs. The RCH Program was integrated into the NRHM, with prime focus on child and maternal health. Strategies include deployment of more than 900,000 ASHAs; an increase in ANMs, nurses and doctors; setting up of village health and sanitation; strengthened primary health care infrastructure; strengthened program management capacity, establishment of patient welfare committees at facilities and creation of emergency transport networks.

The RMNCH+A Strategy (2013): Ongoing Programs for Neonates, Children and Adolescents

In 2013, the government reviewed maternal and child health program under NRHM and launched a Strategic Approach to Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH+A) under the XII Plan. The intervention packages under the RMNCH+A strategy are summarized in Table 1.3; details are shown in Table 1.4.

Table 1.3: Intervention packages under the RMNCH+A Strategy

Adolescent health
Adolescent nutrition and folic acid supplementation
Adolescent Friendly Health Services (Adolescent Health Clinics)
Counseling on adolescent reproductive health and other health issues
Scheme for promotion of menstrual hygiene among rural adolescent girls
Preventive health checkups and screening for diseases, deficiency and disability
Pregnancy, child birth and immediate newborn care
Preventive use of folic acid in periconceptional period
Antenatal package and tracking of high-risk pregnancies
Skilled obstetric care and essential newborn care including resuscitation
Emergency obstetric and newborn care (EmONC)
Postpartum care for mother and baby
Postpartum IUCD insertion and sterilization
Implementation of preconception and prenatal diagnostic techniques Act
Newborn and child care
Home based newborn care
Facility based newborn care
Integrated Management of Common Childhood Illnesses
Immunization
Child health screening and early intervention (*Rashtriya Bal Swasthya Karyakram*)
Reproductive health
Community based doorstep distribution of contraceptives
Promotion of spacing methods
Sterilization services
Comprehensive abortion care
Prevention and management of sexually transmitted diseases or reproductive infections

IUCD intrauterine contraceptive device

Future of Child Health

The nation is addressing child health challenges with greater dynamism than ever before. Investments are being made for health programs and health system strengthening. Conditional cash transfers and entitlements are enshrined to stimulate demand for maternal, newborn and child health care. ICDS is being strengthened, particularly in high burden districts to address childhood undernutrition. The country is surging ahead with stronger economy and accelerated development. India is poised to attain low child mortality rate, and improve remarkably the health and nutrition status of her children in near future.

Table 1.4: Summary of maternal, newborn and child health services in the RMNCH+A Strategy under NRHM

Pregnancy, childbirth and immediate newborn care	**Interventions**
Skilled obstetric care and essential newborn care including resuscitation	*Package* Facility deliveries by skilled birth attendants Neonatal resuscitation Essential newborn care (warmth, hygienic care, breastfeeding, extra care of small babies, problem detection) Linkages to facility-based newborn care for sick neonates
Emergency obstetric and newborn care (EmONC) Postpartum care for mother and baby	*Program drivers:* The schemes that drive uptake of the intervention packages *Janani Suraksha Yojana (JSY)* that provides cash incentive to the woman (and to the ASHA) for delivery in the facility *Janani Shishu Suraksha Karyakram (JSSK)* that entitles the mother and less than one month neonate to free delivery, medicines/blood, diet, pickup and drop in government facilities *Navjat Shishu Suraksha Karyakram* that aims to train nurses and doctors in neonatal resuscitation
Newborn and child care	**Interventions**
Home-based newborn care	Home visits by ASHAs (six for facility born babies, on days 3, 7, 14, 21, 28 and 42; an extra visit on day 1 for home births) **Interventions for infants** Examination; counsel for warmth; breastfeeding; hygiene; extra care of low birthweight babies; detection of sickness, referral **Interventions for mother** Postpartum care and counseling for family planning ASHA given cash incentive for home care, birthweight record, birth registration and immunization (BCG, first dose OPV and DPT)
Facility-based newborn care	**Special newborn care units (SNCU)** These specialized newborn units at district hospitals with specialized equipments including radiant warmers. These units have a minimum of 12–16 beds with a staff of 3 physicians, 10 nurses and 4 support staff to provide round the clock services for new born requiring special care, such as those with very low birthweight, neonatal sepsis/pneumonia and common complications **Newborn stabilization units (NBSU)** These are step down units providing facilities for neonates from the periphery where babies can be stabilized through effective care. These are set up in CHCs and provide services, including resuscitation, provision of warmth, initiation of breastfeeding, prevention of infection and cord care, supportive care: oxygen, IV fluids, provision for monitoring of vital signs and referral **Newborn care corners (NBCC)** These are special corners within the labor room at all facilities (PHC, CHC, DH) where deliveries occur. Services include resuscitation, provision of warmth, prevention of infections and early initiation of breastfeeding **Program drivers:** The schemes that drive uptake of the intervention packages *Janani Shishu Suraksha Karyakram (JSSK)* that entitles the mother and neonate to free delivery, medicines/blood, diet, pickup and drop in government facilities

Contd...

Table 1.4: Summary of maternal, newborn and child health services in the RMNCH+A Strategy under NRHM *(Contd.)*

Newborn and child care	Interventions
Integrated management of common childhood illness	Integrated Management of Neonatal and Childhood Illness (IMNCI) by Anganwadi Workers and first level facility (PHC) **Facility – IMNCI** at first referral level (e.g. CHC). Focuses on providing inpatient management of major causes of childhood mortality such as asphyxia, sepsis, low birth-weight and pneumonia, diarrhea, malaria, meningitis and severe malnutrition
Immunization	Universal Immunization Program now includes 7 vaccine preventable diseases (TB, polio, diphtheria, pertussis, tetanus, measles and hepatitis B) for all children Pentavalent (DPT, hepatitis B and Haemophilus) vaccine introduced in several states MMR vaccine introduced by some states such as Delhi Japanese encephalitis vaccine in endemic districts; combine with routine immunization OPV supplementary doses administered on National Immunization Days to keep India polio free
Child health screening and early intervention services (*Rashtriya Bal Swasthya Karyakram*)	Launched in January 2013, the program envisages child health screening and early intervention services through mobile health teams at block level Screening of all children (0–6 yr old) enrolled at least twice a year for 30 disorders (4Ds) **Defects** (neural tube defect, Down syndrome, cleft lip/palate, club foot, dysplasia hip, congenital cataract or deafness, congenital heart diseases and retinopathy of prematurity) **Deficiencies** (anemia, vitamin A deficiency, vitamin D deficiency, severe acute malnutrition and goiter) **Diseases** (skin conditions, otitis media, rheumatic heart disease, reactive airway disease, dental caries and convulsions) **Development delays and disabilities** (vision or hearing impairment, neuromotor impairment, motor delay, cognitive delay, language delay, behavior disorder, learning disorders, attention deficit hyperactivity disorder) **Optional** (congenital hypothyroidism, sickle cell anemia, beta thalassemia) Free management of these children at District Early Interventions Centers or identified tertiary level institutions

CHC community health center; DH district hospital; PHC primary health center

Suggested Reading

Government of India, Ministry of Health and Family Welfare. A strategic approach to Reproductive, Maternal Newborn, Child and Adolescent Health (RMNCH+A) in India January 2013

Liu L, Johnson HL, Cousens S, et al. Global, regional and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151–61

2 Normal Growth and its Disorders

Ramesh Agarwal, Naveen Sankhyan, Vandana Jain

Growth is an essential feature that distinguishes a child from an adult. The process of growth starts from the time of conception and continues until the child grows into a fully mature adult. The terms 'growth' and 'development' are often used together, but are not interchangeable because they represent two different facets of the dynamics of change, i.e. those of quantity and quality.

The term *growth* denotes a net increase in the size or mass of tissues. It is largely attributed to multiplication of cells and increase in the intracellular substance. Hypertrophy or expansion of cell size contributes to a lesser extent to the process of growth.

Development specifies maturation of functions. It is related to the maturation and myelination of the nervous system and indicates acquisition of a variety of skills for optimal functioning of the individual.

Growth and development usually proceed concurrently. While they are discussed separately, both growth and development are closely related; hence, factors affecting one also tend to have an impact on the other. During early embryonic period of life, an exponential increase in the number of cells occurs. At the early embryonic stage, fetal cells divide and differentiate to form tissues and organs. In the later half of pregnancy and early childhood, there is also an increase in cell size. This manifests as increase in the protein to DNA ratio. The cell size continues to enlarge until about ten years of age. The body cells remain in a state of dynamic equilibrium; hence aging cells are continuously replaced by new cells. The rate of turnover of cells in different tissues is variable.

FACTORS AFFECTING GROWTH

Fetal Growth

Fetal growth is influenced primarily by fetal, placental and maternal factors. In humans, 40% of variation in the birth-weight is due to genetic factors while the rest is due to environmental factors. The fetus has an inherent growth potential, and under normal circumstances, grows into a healthy appropriate sized newborn. The maternal-placental-fetal unit acts in harmony to provide the needs of the fetus.

Genetic potential. Parental traits are usually transmitted to the offspring. Thus, tall parents have tall children; the size of the head is more closely related to that of parents than are the size and shape of hands and feet. Similarly, the structure of the chest and fatty tissue has better genetic association than other somatic characteristics.

Sex. Boys are generally taller and heavier than girls at the time of birth.

Fetal hormones. Human fetus secretes thyroxine from the 12th week of gestation. Thyroxine and insulin have an important role in regulating tissue accretion and differentiation in the fetus. Both hormones are required for normal growth and development, particularly during late gestation. Glucocorticoids also play an important role, primarily towards the end of gestation and influence the prepartum maturation of organs such as liver, lungs and gastrointestinal tract. Growth hormone, though present in high levels in fetus, is not known to influence fetal growth.

Fetal growth factors. A large number of growth factors are synthesized locally in fetal tissues, and act principally by autocrine and paracrine mechanisms. Their prime effect is on cell division, though they also influence other aspects of tissue growth. These factors can be both growth promoting or inhibitory. The insulin like growth factor (IGF)-I and IGF-II are among the most extensively studied fetal growth factors. Other growth promoting factors include epidermal growth factor (EGF), transforming growth factor (TGF-α), platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and nerve growth factor. Inhibitory factors include TGF-β, Müllerian inhibitory substance and inhibin/activin family of proteins.

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Placental factors. As in most species, fetal weight directly correlates with placental weight at term. Fetal growth is highly dependent on the structural and functional integrity of the placenta. With advancing gestation, the weight of the placenta increases to cater to the increased needs of the baby. There are important functional and structural changes in the placenta that make this adaptation more efficient. The total villous surface area increases, the diffusion distance decreases, the fetal capillaries dilate and the resistance in fetoplacental vasculature falls. This positive remodeling facilitates nutrient transport across the placenta.

Maternal factors. The mother's own fetal and childhood growth and her nutrient intake and body composition at the time of conception and during pregnancy, play an important role in determining fetal size. Teenage or advanced age, recent pregnancy, high parity and anemia negatively influence fetal size and health. Maternal intake of tobacco (smoked or chewed) and drug or alcohol abuse also retard fetal growth. Obstetric complications such as pregnancy induced hypertension, pre-eclampsia and multiple pregnancies produce fetal growth restriction. Pre-existing chronic systemic disease (chronic renal failure, congestive heart failure) and acquired infections (rubella, syphilis, hepatitis B, HIV, CMV, toxoplasmosis) may influence fetal growth.

Postnatal Period

The growth of the child during postnatal life is determined by genetic potential as well as internal and external influences.

Genetic factors. Both chromosomal disorders and mutations in specific genes can affect growth. Chromosomal defects like Turner syndrome and Down syndrome manifest as growth retardation. Mutation of single genes may result in inherited retardation of growth, e.g. Prader-Willi syndrome and Noonan syndrome. While most disorders lead to short stature, some genetic defects can also result in tall stature, e.g. Klinefelter syndrome and Sotos syndrome.

Intrauterine growth restriction (IUGR). IUGR resulting in low birthweight (LBW) constitutes an important risk factor for postnatal malnutrition and poor growth. LBW increases the odds of underweight, stunting and wasting in the first 5 yr of life by 3 to 5 times. At 6 months of age, approximately one-third each of underweight (28%), stunting (28%) and wasting (22%) are attributable to LBW. At ages between 1 and 5 yr, LBW accounts for 16–21% of wasting, 8–16% of stunting and 16–19% of underweight. It was recently reported that a third and a fifth of infants have wasting and stunting, respectively, even at birth (Fig. 2.1).

During early infancy, exclusive breastfeeding provides adequate nutrition, prevents infections and protects the infants from further undernourishment. However, at 3–5 months, the common practice of supplementing the infants with animal milk increases morbidity due to infections leading to underweight and stunting. Subsequently, faulty complementary feeding practices (starting too late, using too little and very less calorie dense foods) along with poor hygiene lead to a further rise in rates of underweight and stunting.

Hormonal influence. Normal development cannot proceed without the right milieu of hormones in the body throughout childhood and adolescence. Absence of growth hormone or thyroxine results in dwarfism, underscoring the importance of these factors in promoting growth. These hormones influence both somatic and skeletal growth. During adolescence, androgens and estrogens have an important influence on the growth spurt and final adult height.

Sex. The pubertal growth spurt occurs earlier in girls. However, their mean height and weight in girls are usually less than those in boys of corresponding ages at the time of full maturity.

Nutrition. Growth of children suffering from protein-energy malnutrition, anemia and vitamin deficiency states is retarded. Calcium, iron, zinc, iodine and vitamins A and D are closely related to disorders of growth and development

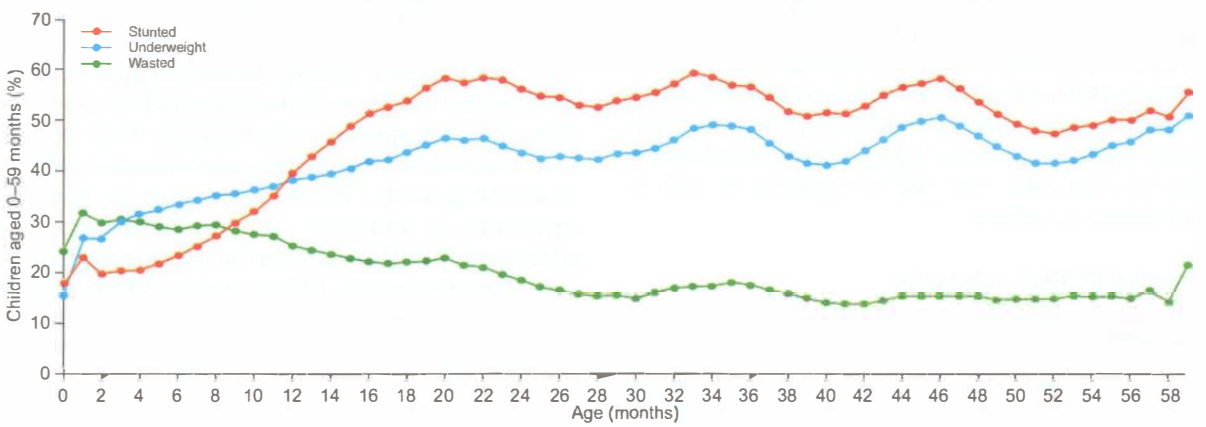

Fig. 2.1: Proportion of children with stunting, underweight and wasting among children from birth to 5 yr. Reproduced with permission from Paul, et al. Lancet 2011;377:332–49

and their deficiency is associated with adverse health events in childhood (*see* Chapter 7). On the other hand, overeating and obesity accelerate somatic growth.

Infections. In low resource settings, one of the commonest contributors to poor childhood growth are infections. Persistent or recurrent diarrhea and respiratory tract infections are common causes of growth impairment. Systemic infections and parasitic infestations may also retard the velocity of growth. The risk of stunting at 2 yr of age is shown to increase with each episode of diarrhea and with each day of diarrhea before 2 yr of age. It was also shown that the attributable risk for stunting for 5 or more episodes of diarrhea before 24 months of age was 25%.

Chemical agents. Administration of androgenic hormones initially accelerates the skeletal growth. However, androgens cause the epiphyses of bones to close prematurely, leading to early cessation of bone growth.

Trauma. A fracture at the end of a bone may damage the growing epiphysis, and thus hamper skeletal growth.

Social Factors

Socioeconomic level. Children from families with high socioeconomic level usually have better nutritional state. They suffer from fewer infections because of better nutrition and hygienic living conditions.

Poverty. Hunger, undernutrition and infections, often associated with poverty, cause poor growth.

Natural resources. Plentiful natural resources encourage industrial and agricultural enterprise in the country. Improved nutrition of children in the community is facilitated when there is a climb in gross national product and per capita income is high.

Climate. The velocity of growth may alter in different seasons and is usually higher in spring and low in summer months. Infections and infestations are common in hot and humid climate. Weather also has a pivotal effect on agricultural productivity, ready availability of food and capacity for strenuous labor by the population.

Emotional factors. Children from broken homes and orphanages do not grow and develop at an optimal rate. Anxiety, insecurity and lack of emotional support and love from the family prejudice the neurochemical regulation of growth hormone release. Parents who had happy childhood and carry a cheerful personality are more likely to have children with similar countenance.

Cultural factors. Methods of child rearing and infant feeding in the community are determined by cultural habits and conventions. There may be religious taboos against consumption of particular types of food. These affect the nutritional state and growth performance of children.

Parental education. Mothers with more education are more likely to adopt appropriate health promoting behaviors, which have direct and indirect influences on growth and development.

Consequences of Impaired Growth

Maternal and child undernutrition are the underlying cause of 3–5 million deaths annually and account for 35% of the disease burden in children younger than 5 yr. It is estimated that India has more than 61 million stunted children, that amounts to 34% of the global total.

Several major disorders of later life, including coronary heart disease, hypertension and type 2 diabetes, originate from impaired intrauterine growth and development. These diseases may be consequences of 'programming', whereby a stimulus or insult at a critical, sensitive period of early life has permanent effects on structure, physiology and metabolism. The 'fetal origins' hypothesis (Barker hypothesis) proposes that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing individuals to cardiovascular, metabolic and endocrine disease in adult life. As a result, infants born with low birthweight have increased risk of diabetes, hypertension, coronary artery disease and hyperlipidemia in adult life.

Laws of Growth

Growth and development of children is a continuous and orderly process There are specific periods in a child's life when the rate of growth is steady, accelerates or decelerates (Table 2.1). The fetus grows fast in the first half of gestation. Thereafter, the rate of growth is slowed down until the baby is born. In the early postnatal period the velocity of growth is high, especially in the first few months. Thereafter, there is slower but steady rate of growth during mid-childhood. A second phase of accelerated growth occurs at puberty. Growth decelerates thereafter for some time and then ceases altogether. The general body growth

Table 2.1: Periods of growth

Prenatal period	
Ovum	0 to 14 days of gestation
Embryo	14 days to 9 wks
Fetus	9 wks to birth
Perinatal period	22 wks to 7 days after birth
Postnatal period	
Newborn	First 4 wks after birth
Infancy	First year
Toddler	1–3 yr
Preschool child	3–6 yr
School age child	6–12 yr
Adolescence	
Early	10–13 yr
Middle	14–16 yr
Late	17–20 yr

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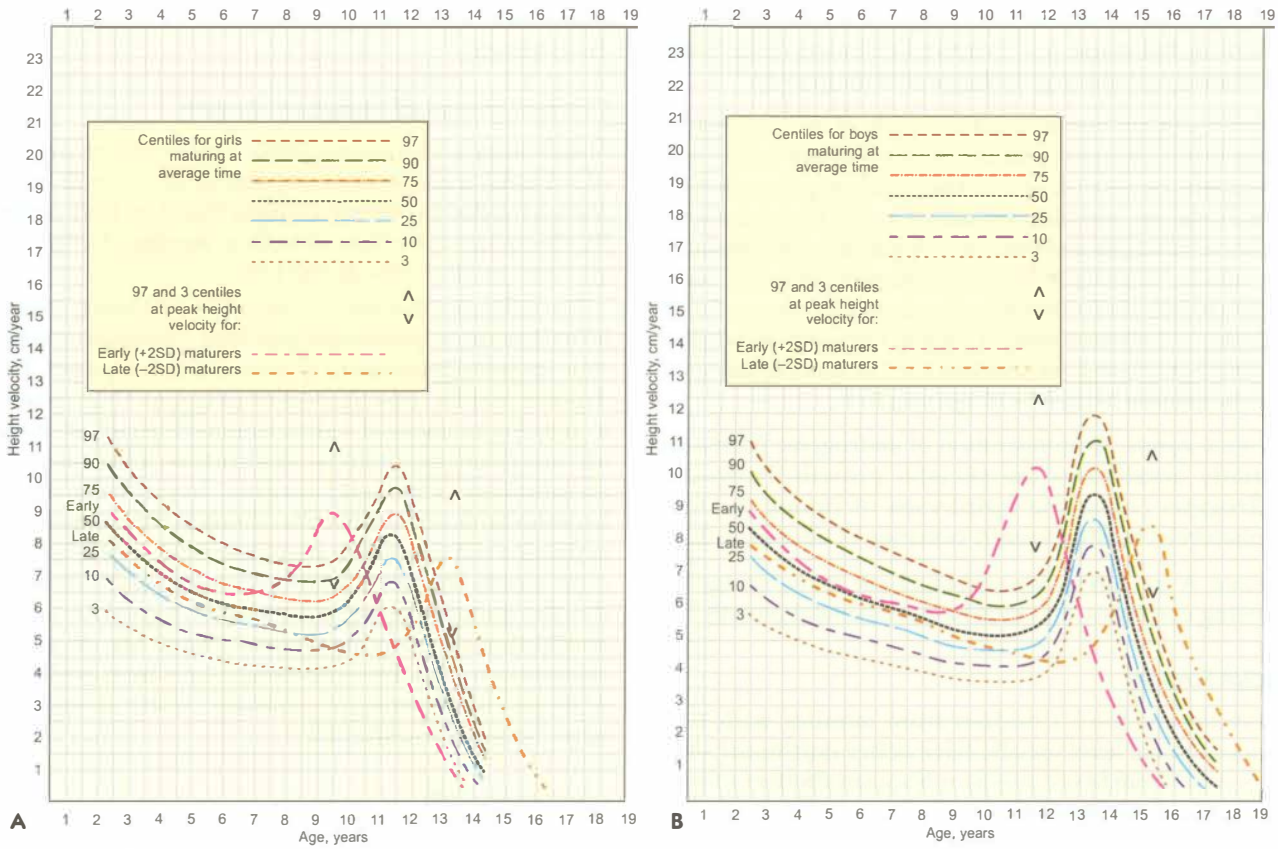


Fig. 2.2: Normal height velocity (A) girls and (B) boys according to age. Curves for height velocity at 50th centile for early and late maturers are also depicted. The open arrow heads indicate the third and 97th centile for peak height velocity for these individuals. Reprinted from J Pediatr 1985;107:317–29; with permission from Elsevier

is rapid during the fetal life, first one or two years of postnatal life and also during puberty (Fig. 2.2). In the intervening years of mid childhood, the somatic growth velocity is relatively slowed down.

Growth pattern of every individual is unique Order of growth is cephalocaudal and distal to proximal. During fetal life, growth of head occurs before that of neck, and arms grow before legs. Distal parts of the body such as hands increase in size before upper arms. In the postnatal life, growth of head slows down but limbs continue to grow rapidly.

Different tissues grow at different rates (Fig. 2.3)

Brain growth. The brain enlarges rapidly during the latter months of fetal life and early months of postnatal life. At birth, the head size is about 65–70% of the expected head size in adults. It reaches 90% of the adult head size by the age of 2 yr. Thus, the fetal phase and the first two years are crucial periods for brain development. Later periods are also important for acquiring neuromotor functions and cognitive ability.

Growth of gonads. Gonadal growth is dormant during childhood and becomes conspicuous during pubescence.

Lymphoid growth. The growth of lymphoid tissue is most notable during mid-childhood. During this period, the lymphoid tissue is overgrown and its mass may appear to be larger than that of the fully mature adult. A sign of

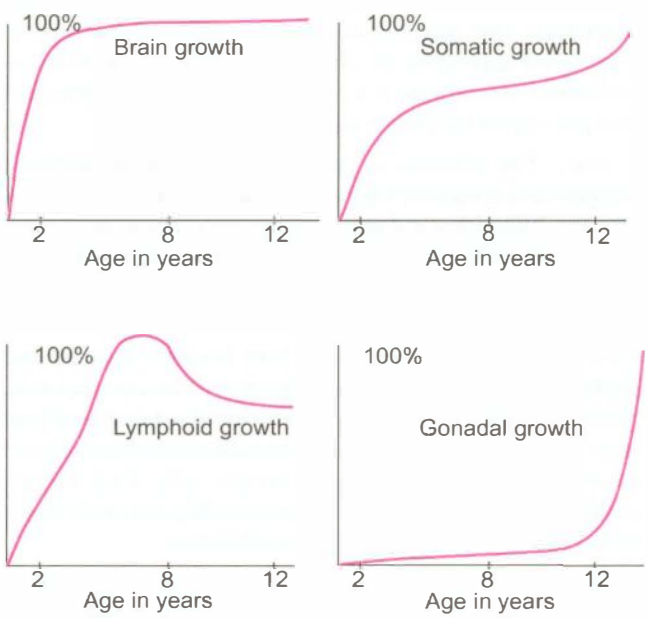


Fig. 2.3: Rates of growth of different tissues and organs

accelerated lymphoid growth is the frequent finding of large tonsils and palpable lymph nodes in normal children between 4 and 8 yr.

Growth of body fat and muscle mass. Body tissues can be divided into fat and fat-free components. The lean body mass includes muscle tissue, internal organs and skeleton and contains only a small amount of fat. The growth in lean body mass is primarily due to increase in muscle mass. Lean body mass correlates closely with stature. Taller children have greater lean body mass than shorter children of the same age. After the pubertal growth spurt, boys have greater lean body mass compared to girls. Body fat is the storehouse of energy. It is primarily deposited in the subcutaneous adipose tissue. Girls have more subcutaneous adipose tissue than boys. Moreover, the sites and quantity of adipose tissue differs in girls and boys. Girls tend to add adipose tissue to breasts, buttocks, thighs and back of arms during adolescence.

SOMATIC GROWTH

Skeletal Growth

Skeletal growth is a continuous process occurring during the whole of childhood and adolescence. It is steady until the pubertal growth spurt when it accelerates and subsequently slows considerably. The skeleton is mature once the epiphysis or growth plates at the end of long bones fuse to the shaft or diaphysis. This occurs by about 18 yr in girls and 20–22 yr in boys. The degree of skeletal maturation closely correlates with the degree of sexual maturation. A child who has advanced sexual maturity will also have earlier skeletal maturation.

Skeletal maturation is assessed by noting the appearance and fusion of epiphysis at the ends of long bones. Apart from this, bone mineral density can be ascertained by dual energy X-ray absorptiometry [DXA]. This method allows assessment of bone mineral content and density at different ages.

Bone Age Estimation

Assessment of bone age postnatally is based on (i) number, shape and size of epiphyseal centers and (ii) size, shape and density of the ends of bones. Tanner and Whitehouse described 8 to 9 stages of development of ossification centers and gave them 'maturity scoring'. Fifty percent of the score was given for carpal bones, 20% for radius, ulna and 30% for phalanges. Twenty ossification centers are generally used for determining the bone age. These include: (i) carpal bones, (ii) metacarpals, (iii) patella, (iv) distal and proximal toes in both sexes; and (v) distal and middle phalanges in boys and distal and proximal phalanges in girls. To determine the skeletal age in infants between 3 and 9 months, a radiograph of shoulder is most helpful. A single film of hands and wrists is adequate in children between the ages of 1 and 13 yr. For children between 12 and 14 yr, radiographs of elbow and hip give helpful clues.

Eruption of Teeth

Primary teeth. The teeth in the upper jaw erupt earlier than those in the lower jaw, except for lower central incisors and second molar (Table 2.2).

Permanent teeth. The order of eruption is shown in Table 2.2. The first molars are the first to erupt.

ASSESSMENT OF PHYSICAL GROWTH

Weight. The weight of the child in the nude or minimal light clothing is recorded accurately on a lever or electronic type of weighing scale (Fig. 2.4). Spring balances are less accurate. The weighing scale should have a minimum unit of 100 g. It is important that child be placed in the middle of weighing pan. The weighing scale should be corrected for any zero error before measurement. Serial measurement should be done on the same weighing scale.

Length. Length is recorded for children under 2 yr of age. Hairpins are removed and braids undone. Bulky diapers should be removed. The child is placed supine on a rigid

Table 2.2: Timing of dentition

Primary dentition	Time of eruption, months		Time of fall, years	
	Upper	*Lower*	*Upper*	*Lower*
Central incisors	8–12	6–10	6–7	6–7
Lateral incisors	9–13	10–16	7–8	7–8
First molar	13–19	14–18	9–11	9–11
Canine	16–22	17–23	10–12	9–12
Second molar	25–33	23–31	10–12	10–12

Permanent teeth	Time of eruption, years				
	Upper	*Lower*		*Upper*	*Lower*
First molar	6–7	6–7	First premolar	10–11	10–12
Central incisors	7–8	6–7	Second premolar	10–12	10–12
Lateral incisors	8–9	7–8	Second molar	12–13	11–13
Canine	11–12	10–12	Third molar	17–21	17–21

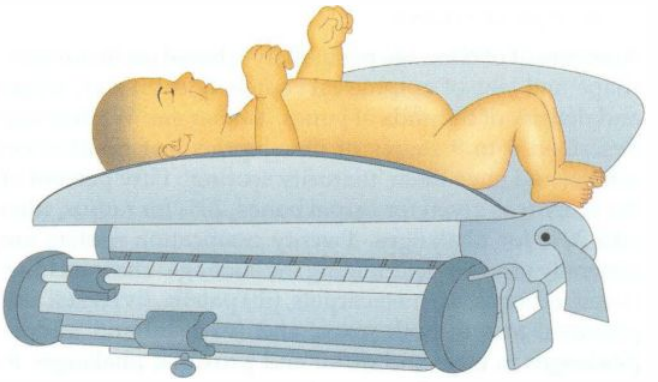


Fig. 2.4: Beam scale for accurate measurement of weight. The child should be nude or in minimal light clothing

measuring table or an infantometer. The head is held firmly in position against a fixed upright head board by one person. Legs are straightened, keeping feet at right angles to legs, with toes pointing upward. The free foot board is brought into firm contact with the child's heels (Fig. 2.5). Length of the baby is measured from a scale, which is set in the measuring table. Measurement of length of a child lying on a mattress and/or using cloth tapes, is inaccurate and not recommended.

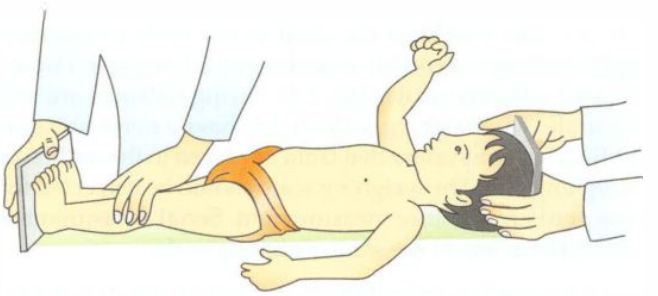


Fig. 2.5: Measurement of length on an infantometer. Note how the knees are gently straightened while the head and feet are aligned

Standing height. For the standing height, the child stands upright. Heels are slightly separated and the weight is borne evenly on both feet. Heels, buttocks, shoulder blades and back of head are brought in contact with a vertical surface such as wall, height measuring rod or a stadiometer. The head is so positioned that the child looks directly forwards with Frankfort plane (the line joining floor of external auditory meatus to the lower margin of orbit) and the biauricular plane being horizontal. The head piece is kept firmly over the head to compress the hair (Fig. 2.6).

Head circumference. Hair ornaments are removed and braids undone. Using a nonstretchable tape, the maximum circumference of the head from the occipital protuberance to the supraorbital ridges on the forehead is recorded. The crossed tape method, using firm pressure to compress the hair, is the preferred way to measure head circumference (Fig. 2.7).

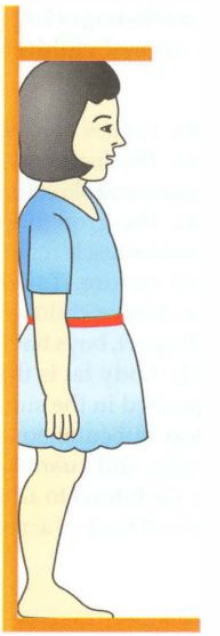


Fig. 2.6: Method of recording height. Note the erect posture and the bare feet placed flat on the ground. The back of heels, buttocks, shoulders and occiput are touching the wall

Chest circumference. The chest circumference is measured at the level of the nipples, midway between inspiration and expiration. The crossed tape method, as recommended for head circumference measurement, is used for measuring chest circumference (Fig. 2.8).

Mid upper arm circumference. To measure the mid upper arm circumference, first mark a point midway between the tip of acromian process of scapula and the olecranon of ulna, while the child holds the left arm by his side (Fig. 2.9). Thereafter, the crossed tape method is used for measuring the circumference. It should be ensured that the tape is just tight enough to avoid any gap as well as avoid compression of soft tissues.

Normal Growth

It is difficult to precisely define the normal pattern of growth. Generally, it implies an average of readings obtained in a

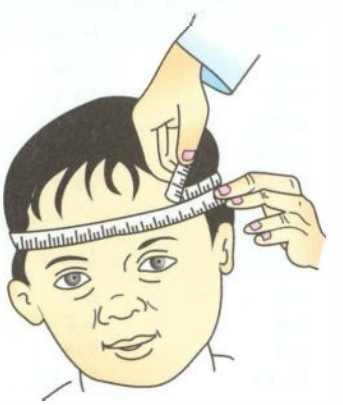


Fig. 2.7: Method of recording head circumference. Note the crossed tape method

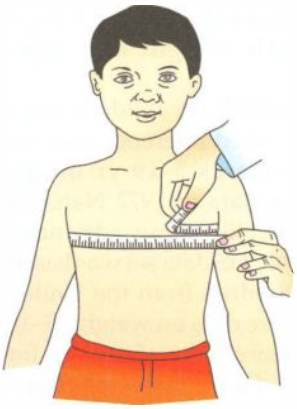


Fig. 2.8: Method of measurement of chest circumference at the level of nipples

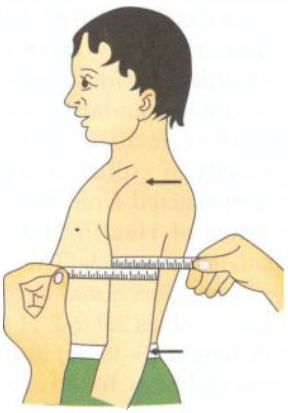


Fig. 2.9: Measurement of mid upper arm circumference. Note how the anatomical landmarks are first located (arrows) to accurately measure the circumference

group of healthy individuals, along with a permissible range of variation, i.e. between the third and ninety-seventh percentiles. Most healthy children maintain their growth percentile on the growth charts as the years pass by. Significant deviation in a child's plotted position on the growth chart can be due to a recent illness or over- or undernutrition. It is also important to take into account the gestation age of infants born prematurely. The duration of prematurity is subtracted from the infant's chronological age. This correction, however, is not required after 2 yr of age.

Weight. The average birthweight of neonates is about 3 kg. During the first few days after birth, the newborn loses extracellular fluid equivalent to about 10% of the body weight. Most infants regain their birthweight by the age of 10 days. Subsequently, they gain weight at a rate of approximately 25–30 g per day for the first 3 months of life. Thereafter, they gain about 400 g weight every month for the remaining part of the first year. An infant usually doubles his birthweight by the age of 5 months. The birthweight triples at 1 yr and is four times at 2 yr of age. Thus, the weight at 5 months, 1 yr and 2 yr is approximately 6, 9 and 12 kg, respectively. The weight of a child at the age of 3 yr is approximately five times that of the birthweight. At 5 yr, the expected weight can be calculated by multiplying the birthweight by 6, at 7 yr by 7 and at 10 yr by 10. It follows that the expected weight at 3, 5, 7 and 10 yr is approximately 15, 18, 21 and 30 kg, respectively. On an average, a child gains about 2 kg every year between the ages of 3 and 7 yr, and 3 kg per year after that till the pubertal growth spurt begins (Table 2.3).

Length or height. The infant measures approximately 50 cm at birth, 60 cm at 3 months, 65 cm at 6 months 70 cm at 9 months, 75 cm at 1 yr and 90 cm at 2 yr. A normal Indian child is 100 cm tall at the age of 4 yr. Thereafter, the child

Table 2.3: Approximate anthropometric values by age

Age	*Weight (kg)*	*Length or height (cm)*	*Head circumference (cm)*
Birth	3	50	34
6 months	6 (doubles)	65	43
1 yr	9 (triples)	75	46
2 yr	12 (quadruples)	90	48
3 yr	15	95	49
4 yr	16	100	50

gains about 6 cm in height every year, until the age of 12 yr. After this, increments in height vary according to the age at the onset of puberty. There is a marked acceleration of the growth during puberty.

Head circumference (HC). Head growth is rapid, especially in the first half of infancy. It reflects the brain growth during this period. The head growth slows considerably thereafter. Beginning at 34 cm at birth, the head circumference increases approximately 2 cm per month for first 3 month, 1 cm per month between 3–6 month and 0.5 cm per month for the rest of the first year of life. The head circumference is approximately 40 cm at 3 month, 43 cm at 6 month 46–47 cm at 1 yr, 48 cm at 2 yr. By 12 yr it is 52 cm.

Chest circumference. The circumference of chest is about 3 cm less than the head circumference at birth. The circumference of head and chest are almost equal by the age of 1 yr. Thereafter, the chest circumference exceeds the head circumference.

Body mass index (BMI). The formula to calculate BMI is weight (kg)/height (meter)^2. BMI is primarily used to assess obesity. BMI at or above the 95th centile for age or more than 30 kg/m^2 is obesity.

Growth Charts

If the growth measurements are recorded in a child over a period of time and are plotted on a graph, the deviation in the growth profile of the child from the normal pattern of growth for that age can be easily interpreted. This is a satisfactory tool to diagnose deviation of growth from normal. Allowed normal range of variation in observations is conventionally taken as values between 3rd and 97th percentile curves. Percentile curves represent frequency distribution curves. For example, 25th percentile for height in a population would mean that height of 75% of individuals is above and 24% are below this value. One standard deviation (SD) above the mean coincides with 84th percentile curve. Likewise 16th percentile curve represents one SD below the mean. Values between third and 97th percentile curve correspond to mean ± 2 SD.

Z scores: In a population with observations in a typical Gaussian (normal) distribution, any individual value can be expressed as how many SDs it lies above or below the

mean. This is the Z score for that observation. Thus, if a child's weight is at 2 SD below the mean, it is equivalent to –2 Z. If the value lies above the mean, Z score is positive, otherwise it is negative. The formula for calculating the Z score is:

$$Z\text{ score} = \frac{\text{Observed value} - \text{mean value}}{\text{Standard deviation}}$$

Z score allows comparison of different observations between individuals. For example, one can compare the height and weight of two individuals by obtaining the respective Z scores.

Growth Standards

Growth standards represent norms of growth and can be presented in tabular or graphical manner. These are obtained by either cross-sectional or longitudinal studies in large populations. Based on data obtained from US children, the National Center for Health Statistics (NCHS) developed growth charts in 1977. In the year 2000, revised growth charts provided by CDC offered an improved tool to assess child health. However, these charts were based on data obtained from US children who were formula fed.

Sensing the need for more internationally applicable growth standards, the WHO conducted the 'Multicentre Growth Reference Study' (MGRS) and published new growth charts for infants and children up to 5 yr of age in 2006. The MGRS was a community-based, multi-country project conducted in Brazil, Ghana, India, Norway, Oman and the United States. The children included in the study were raised in environments that minimized constraints to growth such as poor nutrition and infection. In addition, their mothers followed healthy practices such as breast-feeding their children and did not smoke during and after pregnancy. These WHO child growth standards are unique on several counts. They provide data on 'how children should grow', and go beyond the traditional descriptive references. The new standards make breastfeeding the biological norm and establishes the breastfed infant as the normative growth model. The pooled sample from the six participating countries makes it a truly international standard (in contrast to the previous international reference based on children from a single country) and reiterates the fact that child populations grow similarly across the world's major regions when their needs for health and care are met. These standards also include new growth indicators beyond height and weight that are particularly useful for monitoring the increasing epidemic of childhood obesity, such as skinfold thickness. The study's longitudinal nature further allows the development of growth velocity standards, enabling the early identification of under or overnourishment. Figures 2.10 to 2.19 provide percentile curves for weight, length or height, weight for height and head circumference for girls and boys up to 5 yr of age based on WHO MGRS standards. Tables 2.4 to 2.8 summarize the data on length, weight and head circumference for these children.

Growth standards are not available for children older than 5 yr. In 2007, the WHO provided reference data for growth in children and adolescents 5–19 yr of age reconstructed from the reference data of 1977 National Centre of Health Statistics (NCHS) using advanced statistical methods. The original NCHS data set was based on a cross-sectional survey of children from the United States. Tables 2.9 to 2.11 summarize data on weight (5–10 yr), height (5–19 yr) and body mass index (5–19 yr), for girls and boys, based on this data. Detailed growth charts are available at www.who.int/growthref/en. As an alternative, growth charts generated for Indian children by Agarwal *et al* may be used. These curves, generated for weight and height using information taken from affluent Indian children in 1989–1991 are available at http://indianpediatrics.net/mar2007/mar-187-197.htm.

Velocity of Growth

Plotting a child's height and weight on a growth chart helps to determine if he or she is within the expected normal range for his or her age. One time measurement, however, does not indicate if the rate of growth of the child has been normal in the recent past the position on the growth chart becomes evidently abnormal only when the factors retarding growth are profound or have persisted for a long time. On the other hand, serial measurements provide rate of growth per unit time. Plotting growth velocity is useful tool for early identification of factors affecting growth and also for assessing utility of social and remedial measures. Velocity of growth more accurately helps in predicting the ultimate adult height.

Growth Monitoring

The Indian Academy of Pediatrics has given guidelines to monitor growth during childhood (Table 2.12). During infancy the monitoring is conveniently done during visits for vaccination. Later it can be integrated into visits for vaccination, minor illnesses or into school health program. During adolescence sexual maturity rating (SMR) staging is an additional measure to be monitored.

Suggested Reading

Agarwal DK, Agarwal KN, et al. Physical and sexual growth pattern of affluent Indian children from 5–18 yr of age. Indian Pediatrics 1992;29:1203–82

Agarwal DK, Agarwal KN, et al. Physical growth assessment in adolescence. Indian Pediatrics 2001;38:1217–35

Graham CB. Assessment of bone maturation—methods and pitfalls. Radiol Clin North Am 1972,10:185–202

World Health Organisation. http://www.who.int/nut-growthdb/en. Guidelines on growth monitoring from birth to 18 yr

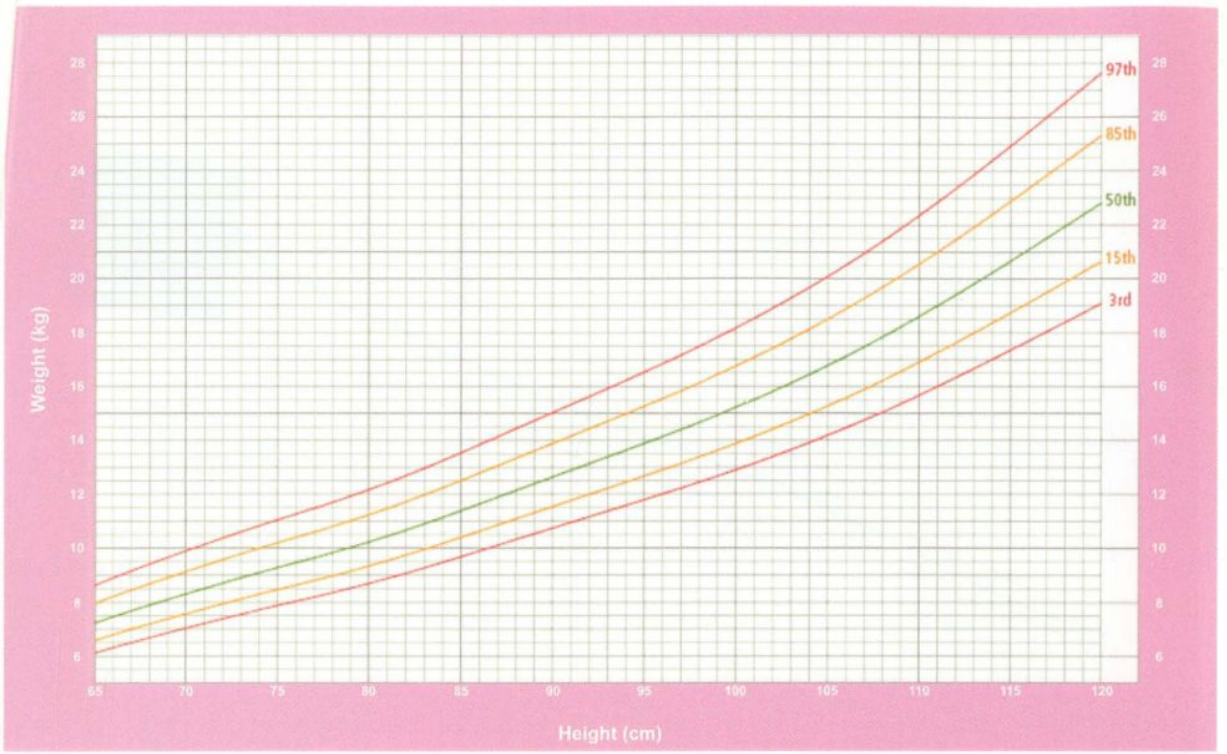


Fig. 2.16: Weight for height (girls) from 2 to 5 yr (percentiles)

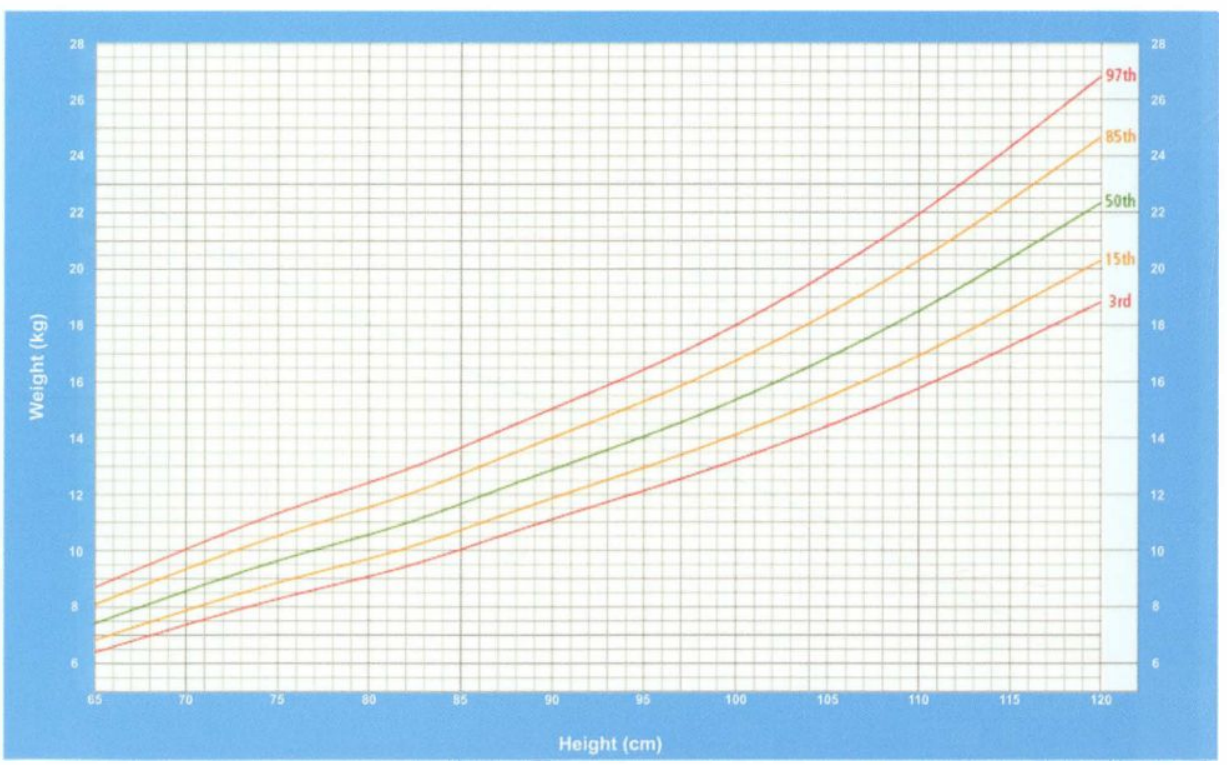


Fig. 2.17: Weight for height (boys) from 2 to 5 yr (percentiles)

Table 2.12: Suggested growth monitoring in children of different ages

Age	*Height/length*	*Weight*	*Head circumference*	*Other*
Birth	✓	✓	✓	
1½, 3 ½, 6, 9, 15 mo	✓	✓	✓	
18 mo–3 yr	✓ (6 monthly)	✓ (6 monthly)	✓(6 monthly)	
3.5–5.5 yr	✓ (6 monthly)	✓ (6 monthly)		
6–8 yr	✓ (6 monthly)	✓ (6 monthly)		BMI (yearly)
9–18 yr	✓ (yearly)	✓ (yearly)		BMI and SMR (yearly)

Adapted from guidelines given by Indian Academy of Pediatrics (2006)
BMI body mass index, SMR sexual maturity rating

DISORDERS OF GROWTH

Short Stature

Definition and Epidemiology

Short stature is defined as height below third centile or more than 2 standard deviations (SDs) below the median height for age and gender (<–2 SD) according to the population standard. As is evident from the definition, approximately 3% of children in any given populations will be short. Children whose stature is more than 3 SD below the population mean for age and gender (<–3 SD) are more likely to be suffering from pathological short stature, as compared to those with stature between –2 and –3 SD, who are more likely to be affected by physiological, i.e. familial or constitutional short stature.

Etiology

Short stature can be attributable to many causes (Table 2.13). Undernutrition and chronic systemic illness are the common etiological factors, followed by growth hormone deficiency (GHD) and hypothyroidism.

Table 2.13: Causes of short stature

Physiological short stature or normal variant

Familial
Constitutional

Pathological

Undernutrition
Chronic systemic illness
Cerebral palsy
Congenital heart disease, cystic fibrosis, asthma
Malabsorption, e.g. celiac disease, chronic liver disease
Acquired immunodeficiency syndrome, other chronic infections
Endocrine causes
Growth hormone deficiency, insensitivity
Hypothyroidism
Cushing syndrome
Pseudohypoparathyroidism
Precocious or delayed puberty
Psychosocial dwarfism
Children born small for gestational age
Skeletal dysplasias, e.g. achondroplasia, rickets
Genetic syndromes, e.g. Turner, Down syndrome

Steps in Assessment

Accurate height measurement. For children below 2 yr, supine length should be measured using an infantometer with a rigid headboard on one side and a moveable footboard on the other side, while holding the infant straight on the horizontal board (*see* Fig. 2.5). For older children, height should be measured with a stadiometer, as explained in previous section (*see* Fig. 2.6).

Assessment of height velocity. Height velocity is the rate of increase in height over a period of time expressed as cm/year. The average height velocity is 25 cm/yr in the first year, declines to 4–6 cm/yr in prepubertal children between 4 and 9 yr of age and increases during puberty to a peak height velocity of 10–12 cm/yr. If height velocity is lower than expected for age, the child is likely to be suffering from a pathological cause of short stature.

Comparison with population norms. The height should be plotted on appropriate growth charts and expressed in centile or as standard deviation score.

Comparison with child's own genetic potential. Parents' height significantly affects the child's height. Mid parental height (MPH) gives an approximate estimate of the child's genetically determined potential.

$$\text{MPH for boys} = \frac{\text{Mother's} + \text{Father's height (cm)}}{2} + 6.5 \text{ cm}$$

$$\text{MPH for girls} = \frac{\text{Mother's} + \text{Father's height (cm)}}{2} - 6.5 \text{ cm}$$

This value is then plotted on the growth chart at 18–20 yr (adult equivalent) of age. This gives an estimate of the target height for the child and the percentile that he/she is likely to follow.

Assessment of body proportion. Short stature can be proportionate or disproportionate. The proportionality is assessed by upper segment (US): lower segment (LS) ratio and comparison of arm span with height. US can be measured by taking the sitting height of the child. Child is made to sit on a square stool placed against the vertical rod of the

stadiometer. The headboard is brought down to the vertex similarly as for taking height. The height of the stool is subtracted from the reading obtained to get sitting height. LS can be obtained by subtracting US from height. Alternatively, LS can be measured by taking the length from pubic symphysis to the ground while the child is standing erect. For measuring arm span, child is asked to stand straight with both arms extended outwards parallel to the ground. Length between the tips of the middle finger of the outstretched hands is the arm span.

Normally, US : LS ratio is 1.7 at birth, 1.3 at 3 yr, 1.1 by 6 yr, 1 by 10 yr and 0.9 in adults. Increase in US : LS ratio is seen in rickets, achondroplasia and untreated congenital hypothyroidism. Decrease in US : LS ratio is seen in spondyloepiphyseal dysplasia and vertebral anomalies. Arm span is shorter than length by 2.5 cm at birth, equals height at 11 yr and thereafter is slightly (usually, <1 cm) greater than height.

Sexual maturity rating (SMR). SMR stage should be assessed in older children (*see* Chapter 4). Height spurt is seen in early puberty in girls and mid-puberty in boys. Precious puberty can lead to early height spurt followed by premature epiphyseal fusion and ultimate short stature. On the other hand, delayed puberty can also present with short stature in adolescents as the height spurt is also delayed.

Differential Diagnosis

Diagnosis is based on a detailed history, examination and laboratory evaluation. Careful history and examination can unravel many clues to the etiology of short stature (Tables 2.14 and 2.15). The investigative work up to be done is guided by clues from history and physical examination.

Bone age assessment should be done in all children with short stature. The appearance of various epiphyseal centers and fusion of epiphyses with metaphyses tells about the skeletal maturity of the child. Bone age is conventionally read from radiograph of the left hand and wrist using either Gruelich-Pyle atlas or Tanner-Whitehouse method. It gives an idea as to what proportion of the adult height has been achieved by the child and what is the remaining potential for height gain. Bone age is delayed compared to chronological age in almost all causes of short stature. Exceptions to this are familial short stature, in which bone age equals chronological age, and precocious puberty, in which bone age exceeds chronological age. In case of constitutional delay, undernutrition and systemic illness, bone age is less than chronological age and corresponds to height age. In cases of growth hormone deficiency and hypothyroidism, bone age may be lower than height age if the endocrine condition is diagnosed late.

Table 2.14: Clues to etiology of short stature from history

History	*Etiology*
Low birthweight	Small for gestational age
Polyuria	Chronic renal failure, renal tubular acidosis
Chronic diarrhea, greasy stools	Malabsorption
Neonatal hypoglycemia, jaundice, micropenis	Hypopituitarism
Headache, vomiting, visual problem	Pituitary or hypothalamic space occupying lesion, e.g. craniopharyngioma
Lethargy, constipation, weight gain	Hypothyroidism
Inadequate dietary intake	Undernutrition
Social history	Psychosocial dwarfism
Delayed puberty in parent(s)	Constitutional delay of growth and puberty

Table 2.15: Clues to etiology of short stature from examination

Examination finding	*Etiology*
Disproportion	Skeletal dysplasia, rickets, hypothyroidism
Dysmorphism	Congenital syndromes
Pallor	Chronic anemia, chronic renal failure
Hypertension	Chronic renal failure
Frontal bossing, depressed nasal bridge, crowded teeth, small penis	Hypopituitarism
Goiter, coarse skin	Hypothyroidism
Central obesity, striae	Cushing syndrome

In addition, all children with disproportionate short stature require *skeletal survey* to rule out skeletal dysplasia and rickets. Essential screening investigations that should be done in all children with short stature are listed in Table 2.16. If these investigations are normal and bone age is delayed, level 2 investigations should be done. If these investigations are also normal, then the major diagnostic possibilities are growth hormone deficiency and malabsorption. If the child has borderline short stature, i.e. height between –2 and –3 SD, then it is prudent to wait for 6–12 months and observe for height velocity. On the other hand, if the child is significantly short(<–3 SD) or has documented poor height velocity over 6–12 months, one should proceed to level 3 investigations.

Specific Etiologies

Familial short stature The child is short as per definition (height <3rd centile) but is normal according to his own genetic potential determined by the parents' height. These children show catch-down growth between birth and 2 yr of age, so that the height and weight come to lie on their target (mid-parental) centiles by the age of 2 yr. Subsequently, the growth velocity remains normal throughout childhood and adolescence. The body proportion is appropriate and

Table 2.16: Stepwise investigative work-up for short stature

Level 1 (essential) investigations

Complete hemogram with ESR
Bone age
Urinalysis including microscopy, osmolality and pH
Stool examination for parasites, steatorrhea and occult blood
Blood urea, creatinine, bicarbonate, pH, calcium, phosphate, alkaline phosphatase, fasting glucose, albumin and transaminases

Level 2 investigations

Serum thyroxin, thyroid stimulating hormone
Karyotype in girls (to rule out Turner syndrome)

Level 3 investigations

Celiac serology (antiendomysial, antitissue transglutaminase antibodies)
Provocative growth hormone testing
Serum insulin-like growth factor-1, and insulin-like growth factor binding protein-3 levels
MRI brain (focussed on pituitary and hypothalamus) for those with low peak growth hormone levels

bone age equals the chronological age. Puberty is achieved at appropriate age and final height is within their target range (Fig. 2.20).

Constitutional growth delay These children are born with a normal length and weight and grow normally for the first 6–12 months of life. Their growth then shows a deceleration so that the height and weight fall below the 3rd centile. By 3 yr of age, normal height velocity is resumed and they continue to grow just below and parallel to the 3rd centile with a normal height velocity. The onset of puberty and adolescent growth spurt is also delayed in these children but final height is within normal limits. Bone age is lower than chronological age and corresponds to the height age. History of delayed puberty and delayed height spurt is usually present in one or both parents. (Fig. 2.21).

Table 2.17 lists features that distinguish between these two common causes of short stature.

Undernutrition Stunted growth caused by chronic undernutrition is one of the commonest cause for short stature in our country. A detailed dietary history and presence of other features of malnutrition such as low mid upper arm circumference and low weight for height suggest the diagnosis.

Endocrine causes These are discussed in detail in Chapter 17.

Skeletal dysplasias Inborn errors in the formation of cartilage and bone, cause chondrodysplasias or skeletal dysplasias, inherited or sporadic conditions that are usually associated with abnormal skeletal proportions and severe short stature (except hypochondroplasia, where growth retardation is mild). A careful elicitation of family

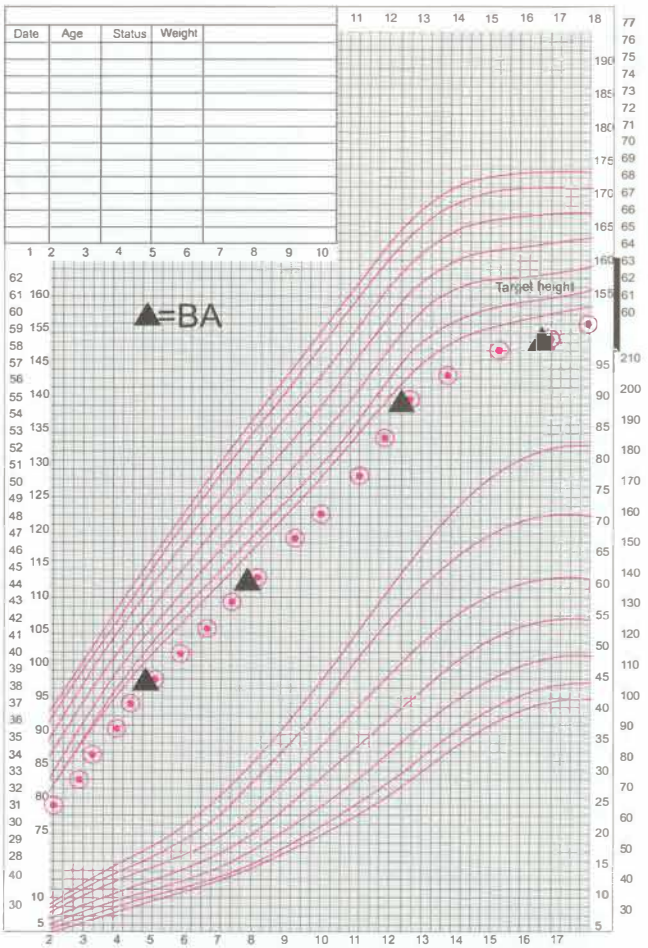


Fig. 2.20: Growth chart of a girl with familial short stature. The child is growing below and parallel to 3rd centile from early childhood till adulthood, height velocity is normal, bone age (BA) corresponds to chronological age and target height (range indicated by vertical bold bar) is low

Table 2.17: Distinction between constitutional delay in growth and familial short stature

Feature	*Constitutional growth delay*	*Familial short stature*
Height	Short	Short
Height velocity	Normal	Normal
Family history	Delayed puberty	Short stature
Bone age	Less than chronological age	Normal
Puberty	Delayed	Normal
Final height	Normal	Low but normal for target height

history, measurement of body proportions, examination of the limbs and skull and skeletal survey are required for diagnosis.

Genetic syndromes Turner syndrome, with an incidence of 1:2000 live births, is a common cause of short stature in girls and should be ruled out even if the typical phenotypic

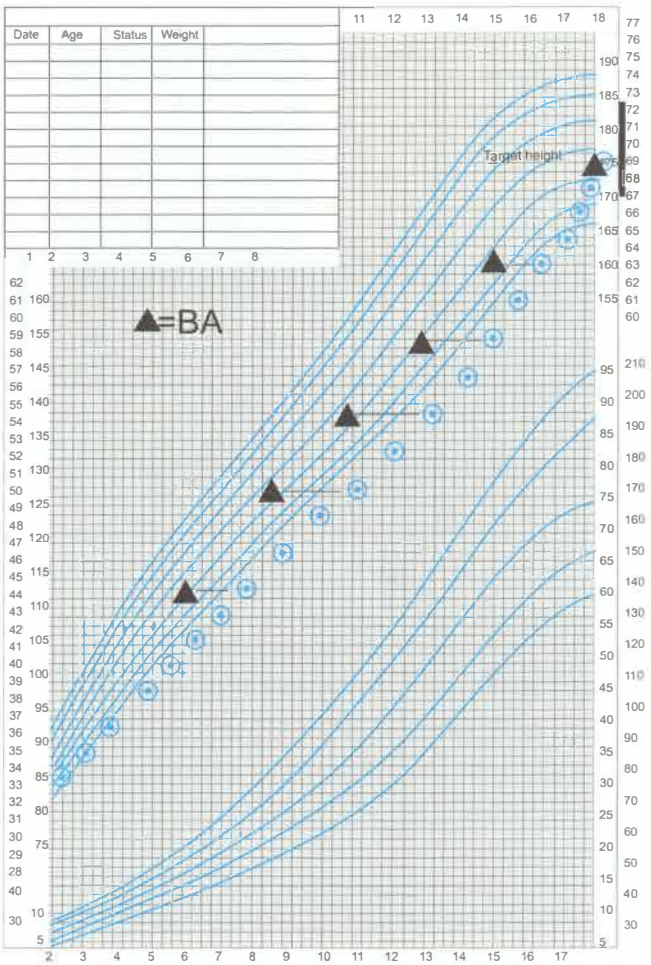


Fig. 2.21: Growth chart of a boy with constitutional delay of growth and puberty. The child falls to a lower centile in early childhood, grows below and parallel to 3rd centile in childhood, with an apparent downward deviation of growth curve during the normal time of pubertal growth, with later acceleration of growth and reaching target height (range indicated by vertical bold bar). Bone age (BA) is lower than chronological age by 2–3 yr

features are absent. Other syndromes associated with short stature are Down, Prader-Willi, Russell-Silver and Seckel syndromes.

Psychosocial dwarfism This condition, also known as emotional deprivation dwarfism, maternal deprivation dwarfism or hyperphagic short stature, is seen in children in unhappy homes where the emotional needs of the child are totally neglected. It is characterized by functional hypopituitarism indicated by low IGF-1 levels and inadequate response of GH to stimulation. Therapy with GH is however, not beneficial. Good catchup growth is usually seen when the child is placed in a less stressful environment and nurtured with love and affection.

Children born small for gestational age (SGA) Birthweight below the 10th centile for gestational age can be caused by maternal, placental or fetal factors. Most of these infants show catchup growth by 2 yr of age. However, an estimated 20–30% of babies born SGA fail to show catchup growth and remain short. Subtle defects in the growth hormone and insulin like growth factor (GH-IGF) axis are considered responsible for the short stature.

Management

The general principles of management for any child who presents with short stature include counseling of parents and dietary advice. Parents should be counseled to highlight the positive aspects in child's personality and not put undue emphasis on stature. Intake of a balanced diet containing the recommended amounts of macro- and micronutrients should also be recommended. The specific management depends on the underlying cause. For physiological causes, reassurance and annual monitoring of height and weight is sufficient. Dietary rehabilitation for undernutrition and treatment of underlying condition such as renal tubular acidosis or celiac disease are generally associated with good catchup growth. With any form of therapy, monitoring with regular and accurate recording of height is mandatory for satisfactory outcome.

For skeletal dysplasias, limb lengthening procedures are offered at few orthopedic centers. For hypothyroidism, levothyroxine replacement is advised. For growth hormone deficiency, treatment with daily subcutaneous injections of GH is recommended. GH therapy is also approved for several other conditions though the doses required are generally higher and improvement in final height smaller and more variable as compared to GH deficiency. Some of these conditions are Turner syndrome, SGA with inadequate catchup growth and chronic renal failure prior to transplant.

Failure to Thrive

Definition and Epidemiology

Failure to thrive (FTT) is a descriptive term rather than diagnosis and is used for infants and children up to 5 yr of age whose physical growth is significantly less than their peers of same age and sex. FTT usually refers to weight below 3rd or 5th centile, failure to gain weight over a period of time or a change in rate of growth that has crossed two major centiles, e.g. 75th to 50th, over a period of time. The prevalence of FTT varies according to the population sampled.

Etiology

Traditionally FTT is classified as organic, where the child has some known underlying medical condition, and non-organic or psychosocial, where poor growth is the result of inadequate caloric provision and or emotional deprivation. Organic and nonorganic etiological factors may coexist, e.g. in children with cerebral palsy or multiple congenital anomalies. FTT is nonorganic in up to 80% of cases. The common etiological factors are listed in Table 2.18.

Table 2.18: Causes of failure to thrive

Organic causes

Gastrointestinal: Gastroesophageal reflux, malabsorption, inflammatory bowel disease, pyloric stenosis
Neurological: Mental retardation, cerebral palsy
Renal: Renal tubular acidosis, chronic renal failure
Cardiopulmonary: Congenital heart disease, cystic fibrosis, asthma
Endocrine: Hypothyroidism, diabetes mellitus
Infections: Chronic parasitic infections of gastrointestinal tract, tuberculosis, human immunodeficiency virus
Genetic: Inborn errors of metabolism, chromosomal anomalies
Miscellaneous: Lead poisoning, malignancy

Nonorganic causes

Poverty
Misperceptions or lack of knowledge about diet and feeding
Lack of breastfeeding, feeding diluted formulae
Dysfunctional parent child relationship

Clinical Features

These children present with poor growth, often associated with poor development and cognitive functioning. The degree of FTT is usually measured by calculating weight, height and weight-for-height as percentage of the median value for age based on appropriate growth charts (Table 2.19).

Diagnosis

History, physical examination and observation of parent–child interaction are important. Detailed laboratory investigations are needed only if history and physical examination suggest that an organic cause is responsible for FTT and to localize the systems involved. For initial evaluation the following investigations are adequate: (i) complete blood count with ESR; (ii) urine and stool microscopy and culture and (iii) renal and liver function test and serum electrolytes. Weight gain in response to adequate calorie feeding establishes the diagnosis of psychosocial FTT.

Management

The goals of management are nutritional rehabilitation, treatment of organic causes if present, and remedial measures for psychosocial factors. Important indications for hospitalization include: (i) severe malnutrition; (ii) diagnostic and laboratory evaluation needed for organic cause; (iii) lack of catch up growth during outpatient treatment; and (iv) suspected child abuse or neglect. The management of these patients depends on the underlying cause. Nutritional rehabilitation is necessary.

Prognosis

If managed early and adequately, the prognosis for physical growth recovery is good. However, the outlook for cognitive, emotional and behavioral development is variable and less certain. The growth and development of these children should be monitored regularly.

ABNORMALITIES OF HEAD SIZE AND SHAPE

Head growth may be affected by abnormal growth of the skull bones or alterations in brain parenchyma, cerebrospinal fluid or bone.

Macrocephaly

Macrocephaly is defined as an occipitofrontal circumference greater than two standard deviations (SD) above the mean for age and sex. Table 2.20 lists important causes of macrocephaly. Megalencephaly or enlargement of the brain parenchyma may be familial or associated with inherited syndromes or neurometabolic disease. Infants with benign familial megalencephaly have increased head size at birth that persists through infancy along the upper growth curve percentiles, and is associated with normal body size, neurologic examination and development. Children with metabolic causes have normal head circumference at birth; macrocephaly is noted as the child gets older. Diagnosis is suggested by accompanying features and biochemical abnormalities. Hydrocephalus, characterized by an excessive amount of CSF, may be caused by increased production, decreased absorption or obstruction to CSF flow. Most patients show postnatal rapid increase in head size and are symptomatic due to underlying disease or raised intracranial pressure (nausea, vomiting and irritability). Benign enlargement of the subarachnoid space is relatively common and is characterized by head growth velocity that slows to normal by 6 months of age; development assessment and neurological examination are normal.

Evaluation for macrocephaly is indicated if the head circumference is above 3 SD of the mean for age and sex, or when serial measurements reveal progressive enlargement, as suggested by an increase by >2 cm per month during first 6 months of life or the crossing of one or more major

Table 2.19: Degree of failure to thrive

Degree of failure to thrive	Weight-for-age (% of median)	Length/height-for-age (% of median)	Weight-for-height (% of median)
Mild	75–90	90–95	81–90
Moderate	60–74	85–89	70–80
Severe	<60	<85	<70

Table 2.20: Causes of macrocephaly

Megalencephaly
Benign familial
Neurocutaneous syndromes: Neurofibromatosis, tuberous sclerosis, Sturge-Weber, Klippel-Trenaunay-Weber, linear sebaceous nevus
Others: Sotos, Fragile X syndrome
Leukodystrophies: Alexander, Canavan, megalencephalic leukoencephalopathy
Lysosomal storage diseases: Tay-Sachs, mucopolysaccharidosis, gangliosidosis
Increased cerebrospinal fluid
Hydrocephalus
Benign enlargement of subarachnoid space
Hydranencephaly, choroid plexus papilloma
Enlarged vascular compartment
Arteriovenous malformation
Subdural, epidural, subarachnoid or intraventricular hemorrhage
Increase in bony compartment
Bone disease: Achondroplasia, osteogenesis imperfecta, osteopetrosis, hyperphosphatasia, cleidocranial dysostosis
Bone marrow expansion: Thalassemia major
Miscellaneous causes
Intracranial mass lesions: Cyst, abscess or tumor
Raised intracranial pressure: Idiopathic pseudotumor cerebri, lead poisoning, hypervitaminosis A, galactosemia

percentile lines between routine visits. Measurement of head size in parents is useful in diagnosing familial cases. Majority of patients require cranial imaging, ultrasonography or computed tomography (CT) scan.

Children with asymptomatic familial megalencephaly or benign enlargement of the subarachnoid space do not require treatment. Infants with hydrocephalus may require neurosurgical intervention (e.g. placement of a ventriculoperitoneal shunt).

Microcephaly

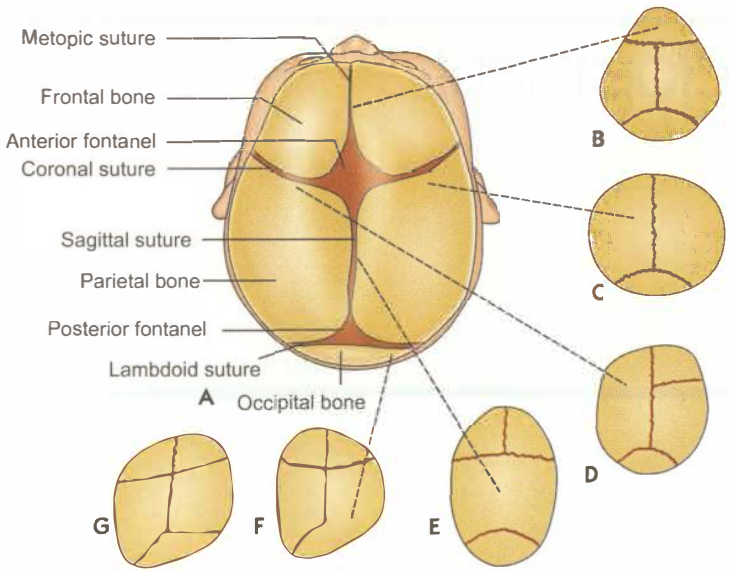
Microcephaly is defined as an occipitofrontal circumference more than 3 standard deviations (SD) below the mean for given age, sex and gestation. Defining microcephaly as >3 SD below the mean is more likely to be associated with genetic and non-genetic disorders affecting brain than if defined as >2 SD below the mean, since the latter may include intellectually normal healthy children with head circumference at the lower end of the population distribution. The term *primary* microcephaly is used to describe conditions associated with reduced generation of neurons during neural development and migration. Secondary microcephaly follows injury or insult to a previously normal brain causing reduction in the number of dendritic processes and synaptic connections. Microencephaly (micrencephaly) is the term used for an abnormally small brain, based on findings on neuroimaging or neuropathology. Since head growth is driven by brain growth, microcephaly usually implies microencephaly (except in craniosynostosis in which skull growth is restricted).

Important causes of microcephaly are listed in Table 2.21. Isolated inherited microcephaly, most commonly as an autosomal recessive phenotype, is associated with reduced OFC since birth, normal cerebral anatomy and absence of neurologic signs with or without learning difficulties. Other associations include structural brain malformations, inherited syndromes, congenital or acquired infections, hypoxicischemicinsults and rarely, metabolic disorders.

Evaluation for microcephaly should be initiated if a single head circumference measurement is more than 2–3 SD below the mean or when serial measurements reveal progressive decrease in head size. Careful history and physical examination are necessary, including development assessment and measurement of head size of parents. Need for neuroimaging is determined by the age at onset, severity of microcephaly, head circumference in parents, history of antenatal insult(s) and associated clinical features. An abnormal head shape and ridges along the suture lines are

Table 2.21: Causes of microcephaly

Isolated microcephaly
Autosomal recessive, autosomal dominant or X-linked
Syndromic
Trisomies 21, 18, 13
Monosomy 1p36 deletion
Syndromes: William, Cri-du-chat, Seckel, Smith Lemli Opitz, Cornelia de Lange, Rubinstein Taybi, Cockayne, Angelman
Structural diseases
Neural tube defects (anencephaly, hydranencephaly, encephalocele, holoprosencephaly)
Lissencephaly, schizencephaly, polymicrogyria, pachygyria (macrogyria)
Metabolic disorders
Phenylketonuria, methylmalonic aciduria, citrullinemia
Neuronal ceroid lipofuscinosis
Maternal: diabetes mellitus, untreated phenylketonuria
Infections
Congenital: Cytomegalovirus, herpes simplex virus, rubella, varicella, toxoplasmosis, HIV, syphilis, enterovirus
Meningitis
Teratogens
Alcohol, tobacco, marijuana, cocaine, heroin, toluene
Antineoplastic agents, antiepileptic agents
Radiation
Perinatal insult
Hypoxic ischemic encephalopathy, hypoglycemia
Endocrine
Hypothyroidism, hypopituitarism, adrenal insufficiency



Figs 2.22A and B: (A) Head of normal neonate showing fontanelles and sutures. The common forms of craniosynostosis (secondary to premature fusion of sutures) include; (B) trigonocephaly (metopic suture); (C) brachycephaly (bilateral coronal sutures); (D) left anterior plagiocephaly (left coronal suture); (E) scaphocephaly (sagittal suture); (F) right posterior plagiocephaly (right lambdoid suture). Children with deformation plagiocephaly; (G) have positional skull flattening without sutural fusion

suggestive of craniosynostosis. The prognosis depends upon the underlying cause, and is worse for secondary than primary microcephaly. The child should be managed in consultation with genetics and pediatric neurology services.

Craniosynostosis

Craniosynostosis is the premature fusion of one or more cranial sutures, either major (e.g. metopic, coronal, sagittal, and lambdoid) or minor (frontonasal, temporosquamosal, and frontosphenoidal) (Fig. 2.22A). Cranial sutures normally fuse during early childhood, starting with the metopic suture (beginning at 2 months), followed by sagittal, coronal and lambdoid sutures (22–26 months), such that the frontonasal and frontozygomatic sutures close last (68–72 months). Premature fusion restricts the growth of the skull perpendicular to the affected suture. Compensatory skull growth occurs parallel to the affected suture in order to accommodate the growing brain. The resulting skull deformity is termed as scaphocephaly, plagiocephaly or trigonocephaly based on the suture involved (Fig. 2.22B to F). Cloverleaf skull deformity is caused by the fusion of multiple sutures and is associated with hydrocephalus. Patients with tower skull or acrocephaly have combined sagittal, coronal and lambdoid synostosis, often as part of Apert or Crouzon syndrome. Oxycephaly or turricephaly refers to a tall cranium resulting from delayed repair of brachycephaly, and is often syndromic.

Apert syndrome is an autosomal dominant or sporadic disorder caused by defects in the fibroblast growth factor (FGF) gene, characterized by bicoronal synostosis and maxillary hypoplasia, associated with recessed forehead, flat midface, protruding eyes, hypertelorism, antimongoloid slant of eyes and low-set ears. Most patients have a high arched palate, malocclusion, cleft palate and complex syndactyly (mitten hand). Other findings are strabismus, conductive hearing loss, airway compromise and severe acne.

Crouzon syndrome is an autosomal dominant disorder caused by mutations in *FGFR2* or *FGFR3*, and characterized by tall, flattened forehead (secondary to bicoronal synostosis), proptosis, beaked nose and midface hypoplasia. Many patients have cervical spine abnormalities. The degree of facial deformity is milder than in Apert syndrome and patients do not show cleft palate, syndactyly and mental retardation. Other conditions associated with craniosynostosis are Carpenter syndrome and Pfeiffer syndrome.

3 Development

Ramesh Agarwal, Vandana Jain, Naveen Sankhyan

NORMAL DEVELOPMENT

Development refers to maturation of functions and acquisition of various skills for optimal functioning of an individual. The maturation and myelination of the nervous system is reflected in the sequential attainment of developmental milestones. Developmental milestones are important, easily identifiable events during the continuous process of development, e.g. turning over, sitting, reaching for objects, and pointing to objects. Increasingly complex skills are learnt, matching the formation of new synapses in the brain.

While development is a global process reflected in new motor abilities and language, social and cognitive skills, intelligence pertains to the part of the development dealing with cognitive or adaptive behavior. Intelligence is the ability to apply knowledge to manipulate one's environment or to think abstractly and refers to the aggregate or global capacity of the individual to act purposefully, think rationally and to deal effectively with the environment. Different researchers define intelligence variably; an objective measurement is done using multiple criteria in tests of intelligence quotient (IQ).

Rules of Development

To understand the complex process of human development, some basic facts should be understood:

i. Development is a *continuous process*, starting *in utero* and progressing in an orderly manner until maturity. The child has to go through many *developmental stages* before a milestone is achieved.
ii. Development *depends on the functional maturation of the nervous system*. Maturity of the central nervous system is essential for a child to learn a particular milestone or skill; no amount of practice can make a child learn new skills in its absence. However, in absence of practice, the child may be unable to learn skills despite neural maturation, since the capability to perform the skills remains dormant.
iii. The *sequence of attainment of milestones is the same in all children*. For example, all infants babble before they speak in words and sit before they stand. Variations may exist in the time and manner of their attainment.
iv. The *process of development progresses in a cephalocaudal direction*. Hence, head control precedes trunk control, which precedes ability to use lower limbs. The control of limbs proceeds in a proximal to distal manner, such that hand use is learnt before control over fingers.
v. Certain *primitive reflexes have to be lost* before relevant milestones are attained. For example, palmar grasp is lost before voluntary grasp is attained and the asymmetric tonic neck reflex has to disappear to allow the child to turnover.
vi. The initial *disorganized mass activity is gradually replaced by specific and wilful actions*. Hence, when shown a bright toy, a 3–4 month old squeals loudly and excitedly moves all limbs, whereas a 3–4 yr old may just smile and ask for it.

Factors Affecting Development

Development depends on a variety of mutually interactive factors such as hereditary potential, biological integrity, physical and psychosocial environment and emotional stimulation. The brain matures through a dynamic interplay of genetic, biological and psychosocial factors. Infancy and early childhood are the most crucial phases during which development takes place.

Appropriate sensory inputs through hearing and vision, a secure environment and responsive parenting provide the bases for healthy patterns of learning, behavior and health. Poverty is among the most important risk factors associated with poor development. Poverty exposes the child to many other risk factors such as lack of stimulation or excessive stress, malnutrition, exposure to environmental toxins, and concurrent diseases that adversely affect development. Such early influences have

negative effect on hypothalamic–pituitary–adrenocortical system and change electrical activity of the brain related to efficiency of cognitive processing. The factors that influence child development are listed below.

Prenatal Factors

Genetic factors Intelligence of parents has direct correlation on the final IQ of the child. Moreover, certain developmental patterns are observed to follow parental patterns like speech. There are numerous genetic causes for developmental delay and subsequent mental retardation (MR). Prominent genetic factors include chromosomal abnormalities (e.g. Down syndrome), X-linked MR (fragile X and other mutations), subtelomeric deletions, single gene disorders causing disorders of brain formation (lissencephaly) and other metabolic disorders (phenylketonuria).

Maternal factors A host of factors which impair growth *in utero* also can potentially affect brain growth, particularly if they are severe and/or sustained:

i. *Maternal nutrition.* There is suggestion that maternal malnutrition (of macronutrient as well as micronutrients) has adverse effect on birth weight and child development. Studies from developing countries suggest that nutrition supplements including multiple micronutrient supplements have positive impact on birth weight as well as child development. It has been shown that the overall quality of maternal care can produce lasting changes in stress reactivity, anxiety and memory in the child.

ii. *Exposure to drugs and toxins.* Various drugs and toxins such as maternal drug or alcohol abuse, antiepileptic drugs and environmental toxins can have adverse effect on child development.

iii. *Maternal diseases and infections.* Pregnancy induced hypertension, hypothyroidism, malnutrition and fetoplacental insufficiency due to any cause. Acquired infections (e.g. syphilis, toxoplasmosis, AIDS, rubella, CMV, herpes) can have a severe impact on fetal physical and brain growth. Exposure to free radicals and oxidants *in utero* (e.g. chorioamnionitis) has been incriminated in the causation of cerebral palsy and developmental impairment.

Neonatal Risk Factors

Intrauterine growth restriction Intrauterine growth restriction (IUGR) indicates constraints in fetal nutrition during a crucial period for brain development. In developing countries, intrauterine growth restriction is mainly due to poor maternal nutrition and infections. Studies have shown that IUGR infants are disadvantaged compared to their normal birth weight counterparts in terms of short-term as well as longterm neurocognitive development.

Prematurity Babies born before 37 weeks of gestation are more likely to have developmental impairment compared to term counterparts with babies born before 32 weeks gestation being at the highest risk. Premature babies are at risk due to complications, including intracranial bleed, white matter injury, hypoxia, hyperbilirubinemia and hypoglycemia.

Perinatal asphyxia Significant asphyxia occurs in approximately 2% of total births. Studies have indicated that over 40% of survivors of significant asphyxia suffer from major neurocognitive disabilities.

Postneonatal Factors

Infant and child nutrition Severe calorie deficiency, as evident by stunting, is associated with apathy, depressed affect, decreased play and activities and insecure attachment. Calorie deficiency is often associated with deficiency of multiple micronutrients and vitamins (including zinc, vitamins A, B12, D, E, riboflavin and iodine) that contribute to developmental impairment.

Linear growth retardation or stunting occurs in nearly one-third of children aged less than 5 yr in low-income and middle-incomecountries. There is positive association between early height-for-age and cognitive or language ability, rates of school enrolment and grades attained by late adolescence and formal employment at age 20–22 yr.

Early growth faltering (<24 months) seems to be more detrimental to childhood development. Increase in weight to cause a change by one standard deviation from birth to 24 months was associated with increased rates of schooling and inversely related to grade failures. Macronutrient supplementation to promote better growth consistently shows concurrent developmental benefits.

Iron deficiency Iron deficiency has been shown to be associated with electrophysiological evidence of delayed brain maturation, poorer cognitive, motor and social–emotional development in infancy and early childhood.

Iodine deficiency Iodine is a constituent of thyroid hormones, which affect central nervous system development and regulate many physiological processes. Iodine deficiency can lead to congenital hypothyroidism and irreversible mental retardation, making it the most common preventable cause of mental retardation. Children growing in iodine deficient areas have an IQ 12.5 points lower than those growing in iodine sufficient areas.

Infectious diseases A variety of infectious morbidities such as diarrhea, malaria, other parasitic infections and HIV are associated with poorer neurodevelopment.

Environmental toxins Children exposed to environmental toxins (lead, arsenic, pesticides, mercury and polycyclic aromatic hydrocarbons) prenatally through maternal exposure and postnatally through breast milk, food, water,

house dust, or soil can have adverse influence on their neurocognitive development.

Acquired insults to brain Traumatic or infectious insults (meningitis, encephalitis, cerebral malaria) and other factors (near drowning, trauma), particularly during early years of life, can have a permanent adverse effect on brain development.

Associated impairments Impairments particularly those involving sensory inputs from the eyes or ears can have a significant impact on attainment of milestones. These impairments have to be actively sought in any child with delay as they offer opportunity for intervention.

3

Psychosocial Factors

During the critical period of development and learning, several social factors have an important bearing on not only cognition but also attitudes, social–emotional competence and sensorimotor development.

Parenting Cognitive stimulation, caregiver's sensitivity and affection (emotional warmth or rejection of child) and responsiveness to the child in the setting of other factors such as poverty, cultural values and practices have an important bearing on child development. Apart from these, parental attitudes, involvement, education and desire for the child also have an impact on the development of the child.

Higher levels of maternal warmth and responsiveness are associated with higher cognitive ability and reduced levels of behavioral problems in young children.

Poverty This is possibly the *most common underlying factor* for impaired child development worldwide. It acts throughout the lifetime of the individual and also affects the next generation.

A variety of risk factors such as biological, environmental, nutritional and psychosocial that are associated with poverty lead to cumulative adverse effect on early child development, which prevent child attaining their full potential and adult productivity and thereby perpetuates the poverty cycle.

Lack of stimulation Social and emotional deprivation and lack of adequate interaction and stimulation is an important cause of developmental impairment, particularly evident in the setting of poverty.

Violence and abuse Domestic and community violence are emerging threats to child development. Child abuse, physical and sexual, can have a profound psychological effect on the child. Problems of attention and cognition are more common in children exposed to violence or abuse. Apart from the direct effect, there are indirect consequences due to change in family dynamics and effect on the caregiver. Early life experiences have been shown to have a bearing on behavioral patterns later in life.

Maternal depression Low to middle income countries have a high incidence of maternal depressive symptoms, which is negatively associated with early child development and quality of parenting by virtue of unresponsive caregiving.

Institutionalization Institutional care (e.g. orphanages) during early life increases the risk of poor growth, ill-health, attachment disorders, attention disorders, poor cognitive function, anxiety, and autistic-like behavior.

The interaction of risk factors and protective factors interact to determine the developmental trajectory of a child (Fig. 3.1). In presence of protective factors, children attain their developmental potential. Presence of a variety of risk factors in early life lowers the developmental trajectory of the child. Timely intervention can help children achieve near normal potential.

Protective Factors

Breastfeeding Breastfeeding has a protective and promotive effect on childhood development.

Maternal education Maternal education is a protective factor reducing child mortality and promoting early child development. Infant and young children of educated mothers have higher levels of cognitive development.

Domains of Development

Normal development is a complex process and has a multitude of facets. However, it is convenient to understand and assess development under the following **domains:**

i. Gross motor development
ii. Fine motor skill development
iii. Personal and social development and general understanding
iv. Language
v. Vision and hearing

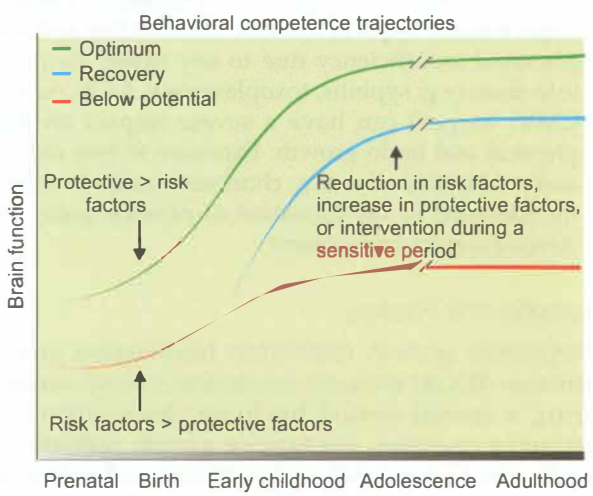


Fig. 3.1: Differing trajectories of brain and behavioral development as a function of exposure to risk and protective factors. Reproduced with permission from Walker, et al. Inequalities in early childhood Lancet 2011;378:1325–38

Gross Motor Development

Motor development progresses in an orderly sequence to ultimate attainment of locomotion and more complex motor tasks thereafter. In an infant it is assessed and observed as follows:

Supine and pull to sit The infant is observed in supine and then gently pulled to sitting position. Control of head and curvature of the spine is observed. In the newborn period, the head completely lags behind and back is rounded (Fig. 3.2). Starting at 6 weeks, the head control develops and by 12 weeks there is only a slight head lag. The spine curvature also decreases accordingly (Fig. 3.3). The child has complete neck control by 20 weeks (Fig. 3.4). This can be ascertained by swaying him gently 'side-to-side' when sitting. At this age, the baby loves to play with his feet, and may take his foot to mouth as well. Infant lifts head from the supine position when about to be pulled at 5 months (Fig. 3.5).

Ventral suspension The child is held in prone position and then lifted from the couch, with the examiner supporting the chest and abdomen of the child with the palm of his hand. Up to 4 weeks of age, the head flops down (Fig. 3.6). At 6 weeks, the child momentarily holds

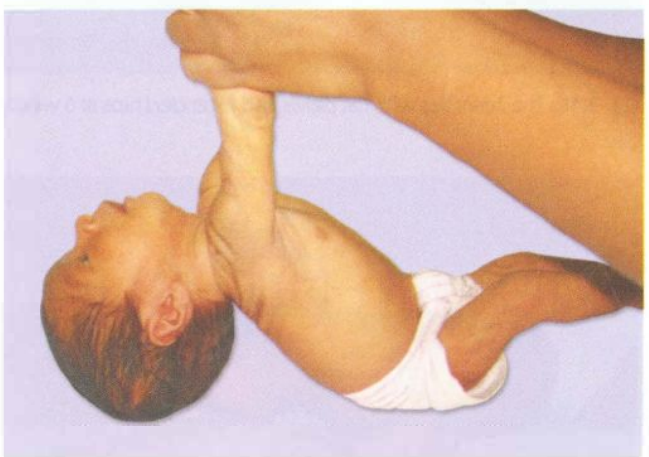


Fig. 3.2: Pull to sit; complete head lag in a newborn

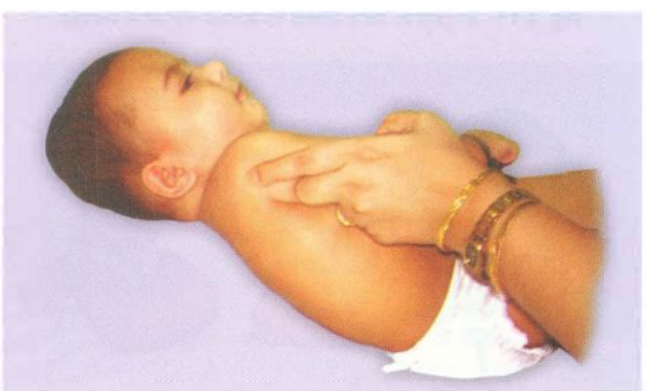


Fig. 3.3: Pull to sit; no head lag at 4 months

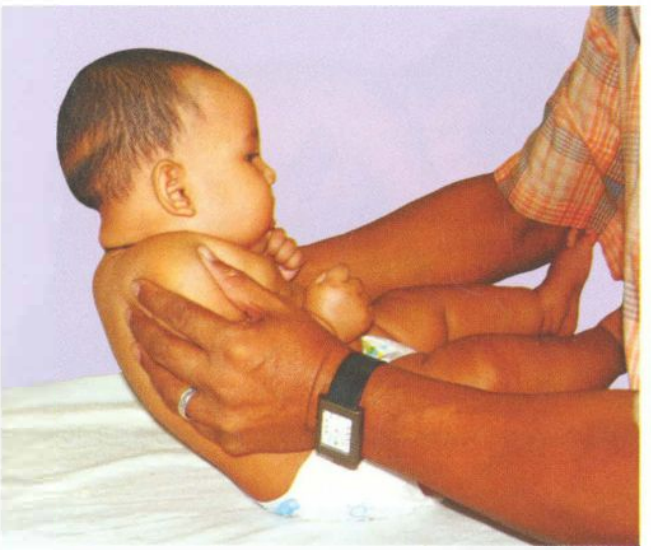


Fig. 3.4: Pull to sit; flexes the head on to chest at 5 months

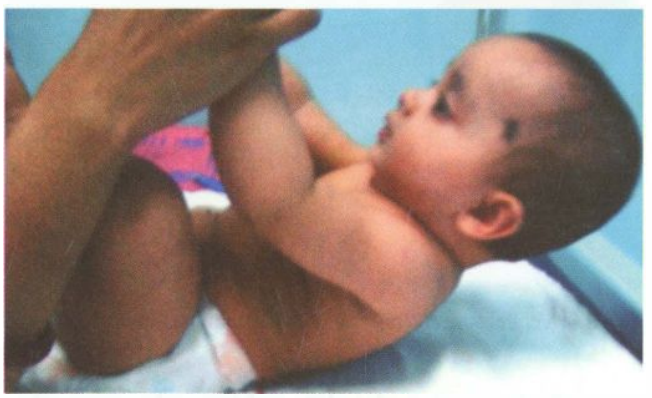


Fig. 3.5: Infant lifts head from the supine position when about to be pulled at 5 months

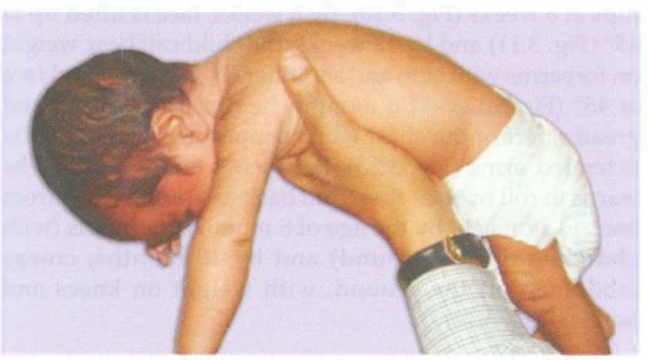


Fig. 3.6: Ventral suspension; unable to hold neck in the line with trunk at 4 weeks

head in the horizontal plane and by 8 weeks, he can maintain this position well (Fig. 3.7). By 12 weeks, he can lift his head above the horizontal plane (Fig. 3.8).

Prone position At birth or within a few days, the newborn turns the head to one side. At 2 weeks, the baby

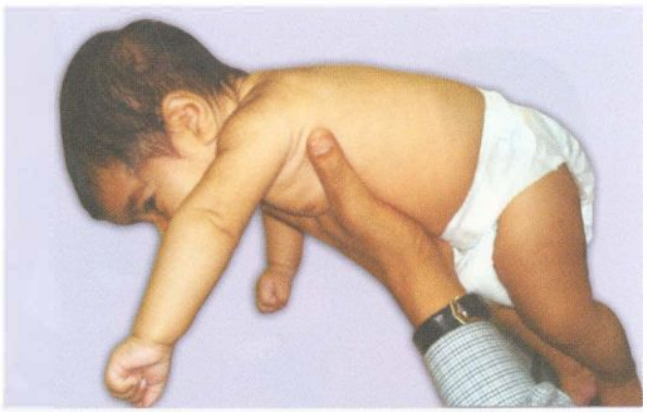


Fig. 3.7: Ventral suspension; head in line with the trunk at 8–10 weeks

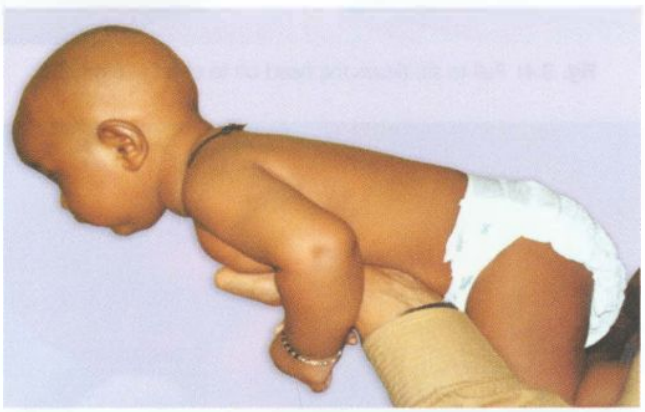


Fig. 3.8: Ventral suspension; head in line with the trunk at 12 weeks

lies on the bed with high pelvis and knees drawn up (Fig. 3.9). At 4 weeks, the infant lifts the chin up momentarily in the midline. The infant lies with flat pelvis and extended hips at 6 weeks (Fig. 3.10). By 8 weeks, face is lifted up at 45° (Fig. 3.11) and by 12 weeks, the child can bear weight on forearms with chin and shoulder off the couch and face at 45° (Fig. 3.12). At 6 months, he can lift his head and greater part of the chest while supporting weight on the extended arms (Fig. 3.13). Between 4 and 6 months, he learns to roll over, at first from back to side and then from back to stomach. By the age of 8 months, he crawls (with abdomen on the ground) and by 10 months, creeps (abdomen off the ground, with weight on knees and hands) (Fig. 3.14).

Sitting By the age of 5 months, the child can sit steadily with support of pillows or the examiner's hands (Figs 3.15 and 3.16). At first the back is rounded but gradually it straightens (Figs 3.15 and 3.16). He independently sits with his arms forward for support (tripod or truly 'sitting with support') by the age of 6–7 months (Fig. 3.17). Steady sitting without any support generally develops at around 8 months (Fig. 3.18). By 10–11 months, he can pivot in sitting position to play around with toys (Fig. 3.19).

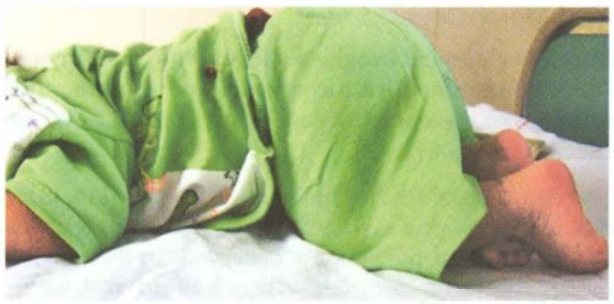


Fig. 3.9: The infant lies on the bed with high pelvis and knees drawn up at 2 weeks

Fig. 3.10: The infant lies with flat pelvis and extended hips at 6 weeks

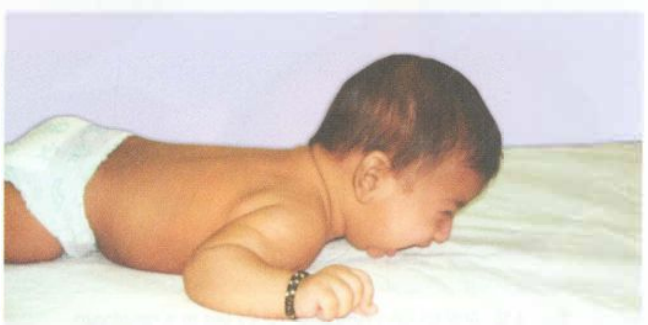


Fig. 3.11: In prone: face lifted to about 45° at 8 weeks

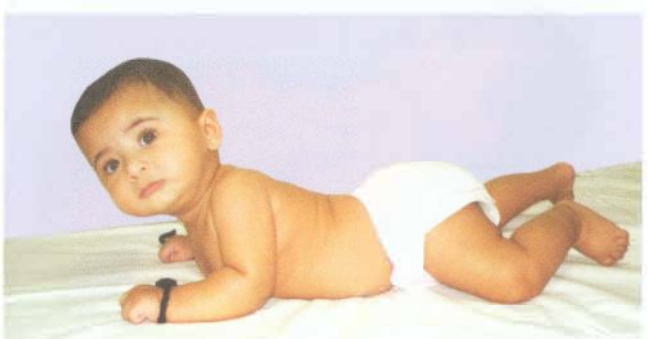


Fig. 3.12: In prone: face, head and chest off the couch at 3 months

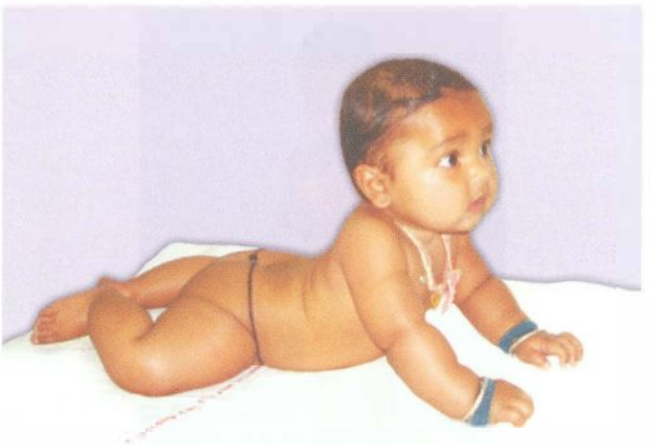


Fig. 3.13: In prone: weight on hands with extended arms at 6 months

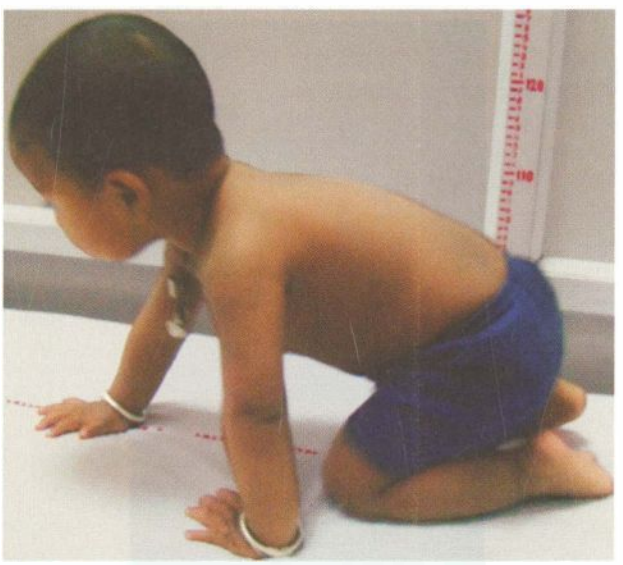


Fig. 3.14: Creep position at 10 months of age (abdomen off ground and weight on hands and knees

Standing and walking By 6 months, the child can bear almost all his weight when made to stand (Fig. 3.20). At 9 months, the child begins to stand holding onto furniture and pulls himself to standing position. By 10 and 11 months, the child starts cruising around furniture. At about 12–13 months the child can stand independently (Fig. 3.21) and can walk with one hand held (Fig. 3.22). Between the ages of 13 and 15 months the child starts walking independently. He runs by 18 months and at this age he can crawl up or down stairs and pulls a doll or wheeled toy along the floor. By 2 yr, the child can also walk backwards. He climbs upstairs with both feet on one step at 2 yr. By 3 yr he can climb upstairs with one foot per step and by 4 yr he can move down the stairs in the same fashion (Fig. 3.23). He can ride a tricycle at 3 yr. He can hop at 4 yr and skip at 5 yr (Table 3.1).

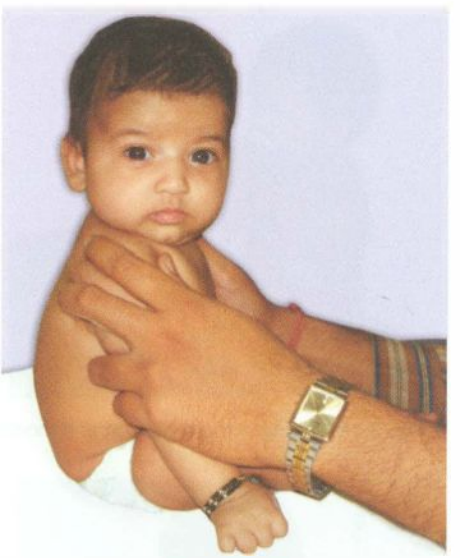


Fig. 3.15: Sitting; back rounded but able to hold head at 8 weeks

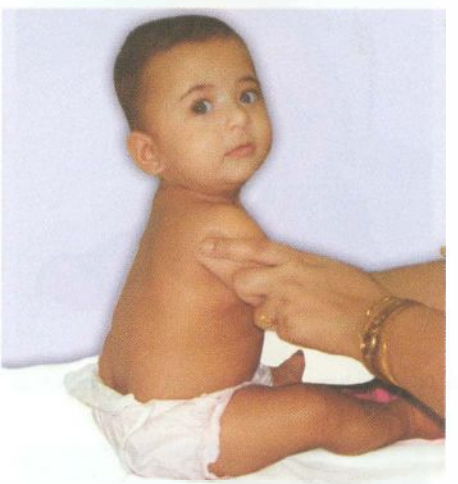


Fig. 3.16: Sitting; back much straighter at 4 months

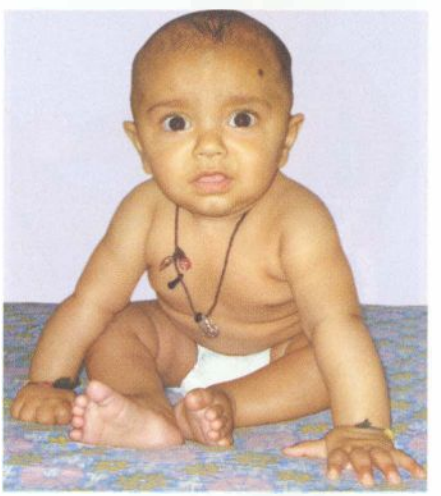


Fig. 3.17: Sitting with support of hands at 6 months

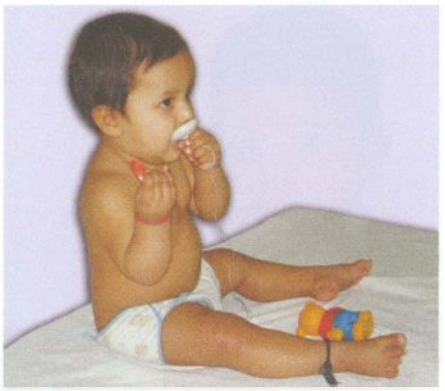


Fig. 3.18: Sitting without support at 8 months

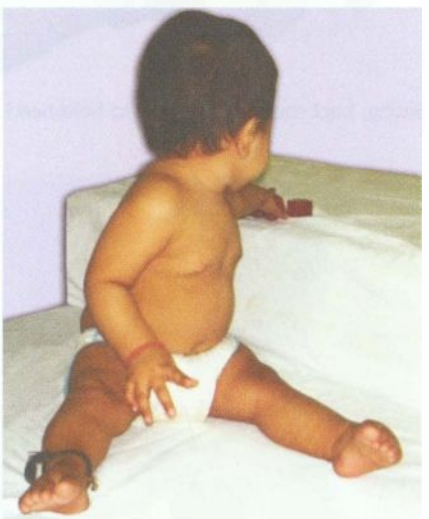


Fig. 3.19: Pivoting; turns around to pick up an object at 11 months

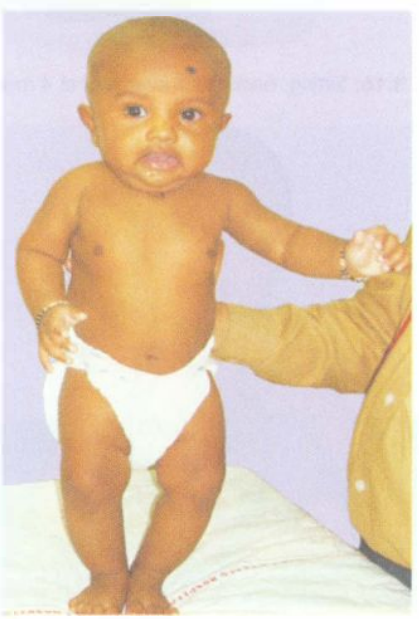


Fig. 3.20: Bears almost entire weight at 6 months

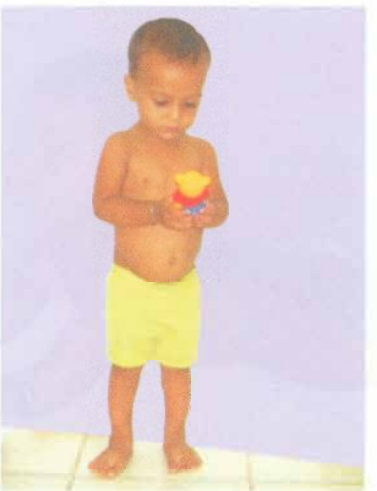


Fig. 3.21: Stands well at 12 months

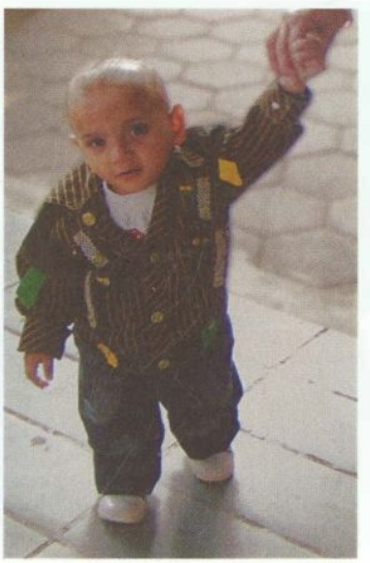


Fig. 3.22: Child walking with one hand-held at 12–13 months

Fig. 3.23: The child is able to walk upstairs and downstairs one foot per step at 4 yr

Table 3.1: Key gross motor developmental milestones

Age	*Milestone*
3 mo	Neck holding
5 mo	Rolls over
6 mo	Sits in tripod fashion (sitting with own support)
8 mo	Sitting without support
9 mo	Stands holding on (with support)
12 mo	Creeps well; walks but falls; stands without support
15 mo	Walks alone; creeps upstairs
18 mo	Runs; explores drawers
2 yr	Walks up and downstairs (2 feet/step); jumps
3 yr	Rides tricycle; alternate feet going upstairs
4 yr	Hops on one foot; alternate feet going downstairs

Fine Motor Development

This primarily involves the development of fine manipulation skills and coordination with age.

Hand eye coordination Between 12 and 20 weeks, the child observes his own hands very intently, this is called hand regard (Fig. 3.24). Its persistence after 20 weeks is considered abnormal. At 3 to 4 months, hands of the child come together in midline as he plays (Fig. 3.25). If a red ring is dangled in front of him, he fixes his attention on it, and then tries to reach for it (Fig. 3.26). Initially he may overshoot but eventually he gets it and brings it to his mouth.

Grasp is best assessed by offering a red cube to the child. A 6-month-old infant reaches and holds the cube (larger object) in a crude manner using the ulnar aspect of his hand (Fig. 3.27). He can transfer objects from one hand to other by 6–7 months. The child is able to grasp from the radial side of hand at 8–9 months (Fig. 3.28). By the age of 1 yr mature grasp (index finger and thumb) is evident (Fig. 3.29).

Fig. 3.24: Hand regard (between 12 and 20 weeks)

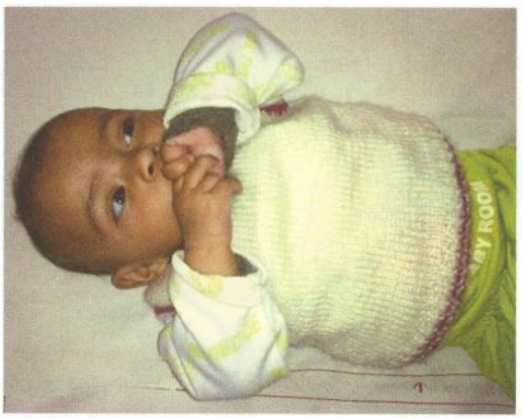


Fig. 3.25: The child brings hands in midline as he plays at 3 to 4 months of age

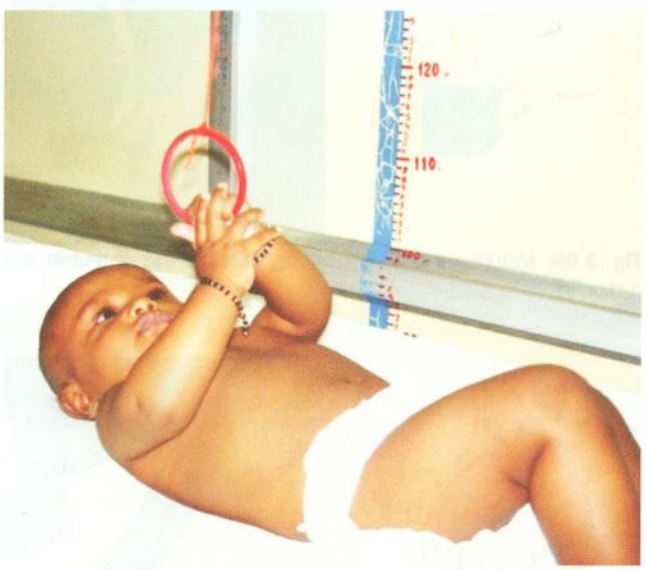


Fig. 3.26: Bidextrous grasp approach to a dangling ring at 4 months

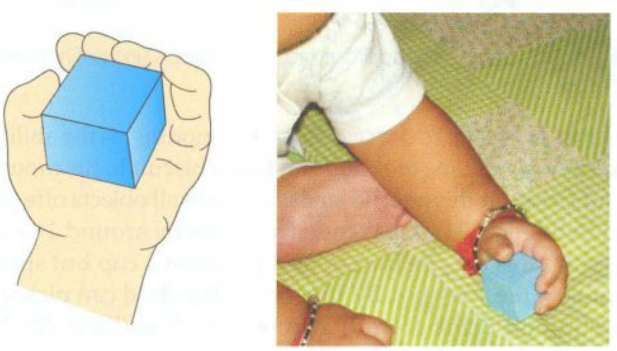


Fig. 3.27: Immature grasp at 6 months (palmar grasp)

By offering pellets (smaller object), finer hand skills are assessed. By 9–10 months, the child approaches the pellet by an index finger and lifts it using finger thumb apposition, termed 'pincer' grasp (Fig. 3.30).

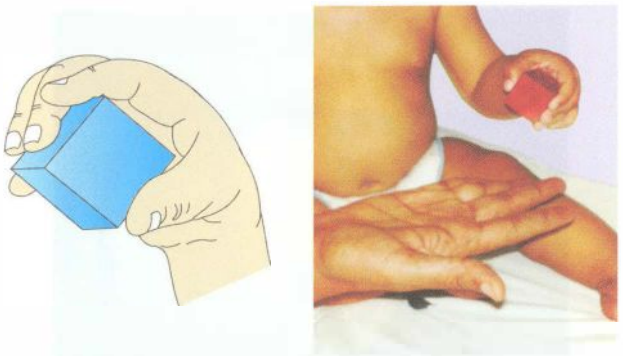


Fig. 3.28: Intermediate grasp at 8 months, beginning to use radial aspect of the hand

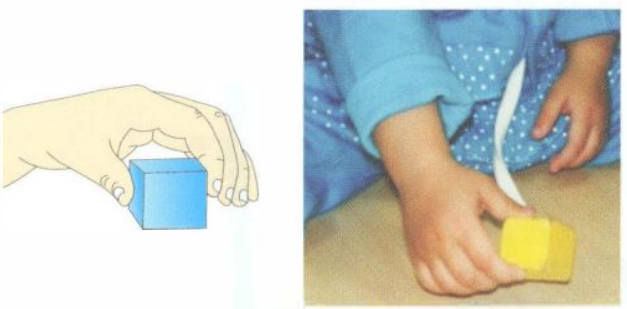


Fig. 3.29: Mature grasp at 1 yr of age, note the use of thumb and index finger

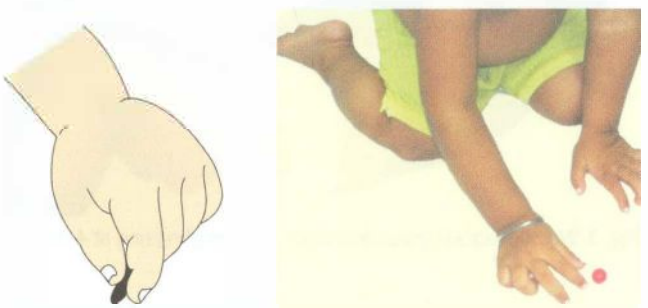


Fig. 3.30: Pincer grasp approach to small objects (index finger and thumb)

Hand-to-mouth coordination At 6 months, as the ability to chew develops, the child can take a biscuit to his mouth and chew. At this age, he tends to mouth all objects offered to him (Fig. 3.31). This tendency abates by around 1 yr of age. By this age, he tries to feed self from a cup but spills some of the contents. By 15 months, the child can pick up a cup and drink from it without much spilling. By 18 months, he can feed himself well using a spoon.

Advanced hand skills With advancing age, the child can use hands to perform finer activities. Much of the advanced skills depend partly on the opportunity given by the caretakers to the child. At around 15 months, he turns 2–3 pages of a book at a time and scribbles on a paper if given a pencil (Fig. 3.32). By 18 months, he can build a tower of 2–3 cubes and draw a stroke with pencil. By 2 yr, he can unscrew lids and turn door knobs and his block skills also advance (Table 3.2, Fig. 3.33). He now draws a circular stroke. He now can turn pages of a book, one at a time.

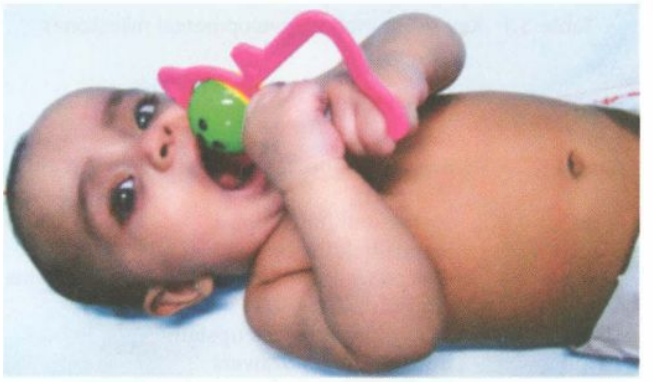


Fig. 3.31: A child mouthing an object at 6 months of age

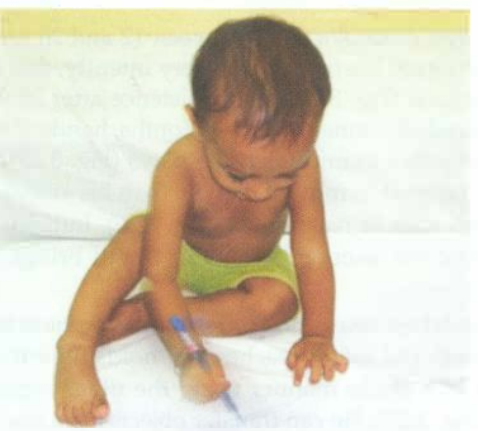


Fig. 3.32: Scribbles spontaneously at 15 months

Table 3.2: Key fine motor developmental milestones

Age	*Milestone*
4 mo	Bidextrous reach (reaching out for objects with both hands)
6 mo	Unidextrous reach (reaching out for objects with one hand); transfers objects
9 mo	Immature pincer grasp; probes with forefinger
12 mo	Pincer grasp mature
15 mo	Imitates scribbling; tower of 2 blocks
18 mo	Scribbles; tower of 3 blocks
2 yr	Tower of 6 blocks; vertical and circular stroke
3 yr	Tower of 9 blocks; copies circle
4 yr	Copies cross; bridge with blocks
5 yr	Copies triangle; gate with blocks

Fig. 3.33: A child makes tower of 5–6 cubes at 2 yr of age

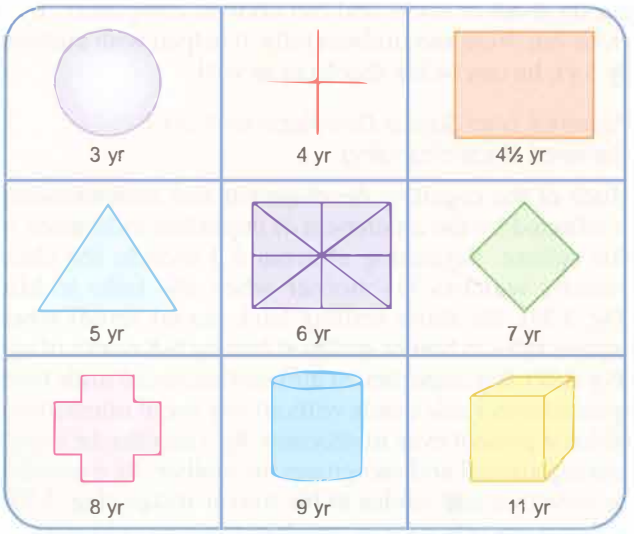


Fig. 3.34: Drawing skills at various ages

Drawing and block skills at various ages are shown in Figs 3.34 and 3.35, respectively. In general copying of the skill comes 6 months after imitating the skills (doing it while seeing).

Dressing Between 18 and 30 months of age, children are very eager to learn dressing skills. Undressing being easier, is learned before dressing. At 1 yr the child starts to pull off mittens, caps and socks. At around 18 months, he can unzip, but fumbles with buttons. By 2 yr, he can

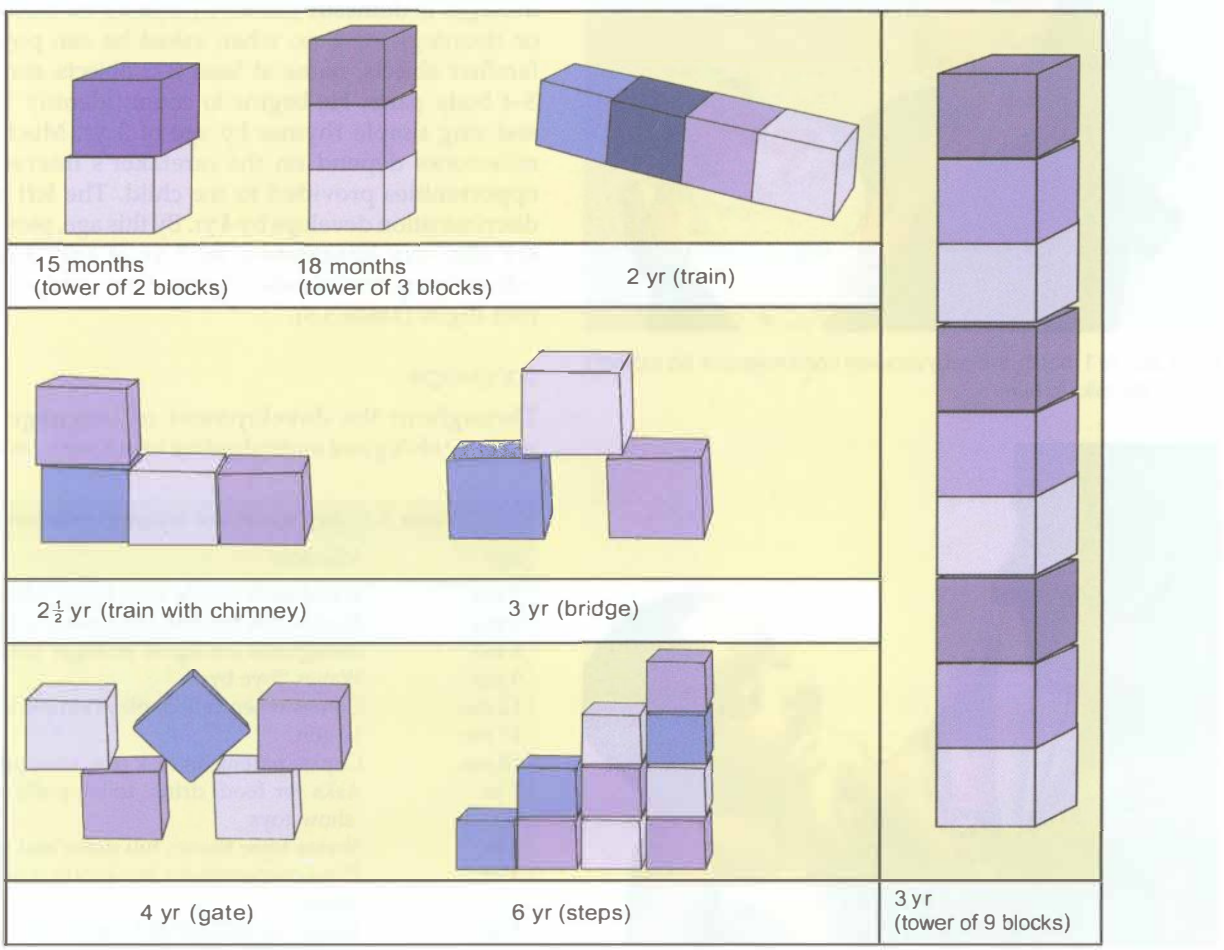


Fig. 3.35: Block skills at various ages

put on shoes or socks and can undress completely. By 3 yr, he can dress and undress fully, if helped with buttons. By 5 yr, he can tie his shoelaces as well.

Personal and Social Development and General Understanding

Much of the cognitive development and understanding is reflected by the attainment of important milestones in this sphere. Beginning at around 1 month, the child intently watches his mother when she talks to him (Fig. 3.36). He starts smiling back (social smile) when anyone talks to him or smiles at him by 6–8 weeks of age (Fig. 3.37). It is important to differentiate social smile from spontaneous smile (smile without any social interaction), which is present even in neonates. By 3 months, he enjoys looking around and recognizes his mother. By 6 months, he vocalizes and smiles at his mirror image (Fig. 3.38), and imitates acts such as cough or tongue protrusion.

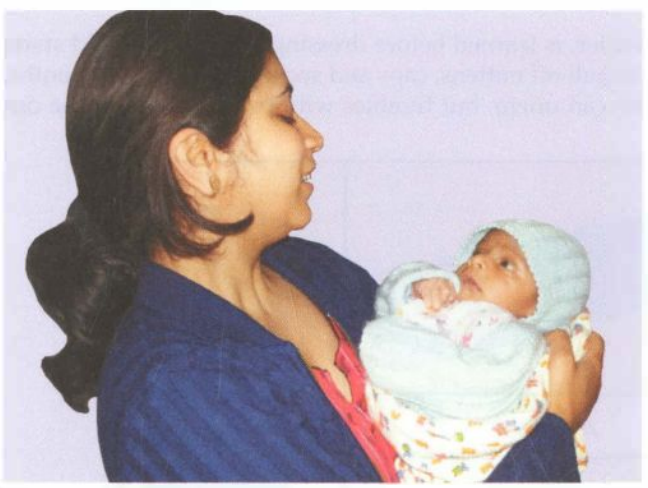


Fig. 3.36: At 1 month, the baby showing intent regard of his mother's face as she talks to him

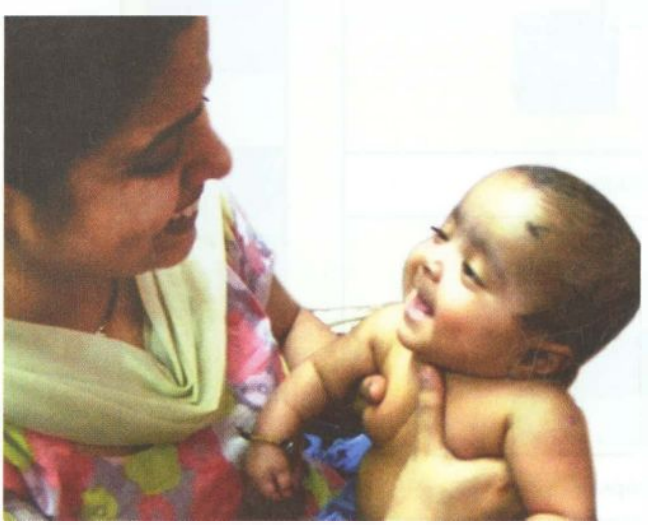


Fig. 3.37: Social smile

Fig. 3.38: A child smiles at himself in the mirror at 6 months of age

The child becomes anxious on meeting strangers (stranger anxiety) by 6–7 months of age. At this age he inhibits to "no". At 9 months, he waves "bye-bye" and also repeats any performance that evokes an appreciative response from the observers. By 1 yr, he can understand simple questions, such as "where is papa", "where is your ball", etc. By 15 months, he points to objects in which he is interested. By 18 months, he follows simple orders and indulges in domestic mimicry (imitates mother sweeping or cleaning). At 2 yr, when asked he can point to 5–6 familiar objects, name at least 2–3 objects and point to 3–4 body parts. He begins to count, identify 1–2 colors and sing simple rhymes by age of 3 yr. Much of these milestones depend on the caretaker's interaction and opportunities provided to the child. The left and right discrimination develops by 4 yr. By this age, play activities are also very imaginative. By 5 yr of age, children can follow 3 step commands, identify four colors and repeat four digits (Table 3.3).

Language

Throughout the development of language it is the *receptive ability and understanding which precedes expressive*

Table 3.3: Key social and adaptive milestones

Age	*Milestone*
2 mo	Social smile (smile after being talked to)
3 mo	Recognizes mother; anticipates feeds
6 mo	Recognizes strangers, stranger anxiety
9 mo	Waves "bye bye"
12 mo	Comes when called; plays simple ball game
15 mo	Jargon
18 mo	Copies parents in task (e.g. sweeping)
2 yr	Asks for food, drink, toilet; pulls people to show toys
3 yr	Shares toys; knows full name and gender
4 yr	Plays cooperatively in a group; goes to toilet alone
5 yr	Helps in household tasks, dresses and undresses

abilities. Soon after appearance of social smile at around 6 to 8 weeks, the child begins to vocalize with vowel sounds such as 'ah, uh'. At 3–4 months, he squeals with delight and laughs loud. He begins to say 'ah-goo', 'gaga' by 5 months of age. By 6 months, he uses monosyllables (ba, da, pa). Later, he joins consonants to form bisyllables (mama, baba, dada).

Before developing true meaningful speech, at around 9–10 months the child learns to imitate sounds derived from his native language. At his first birthday, he can usually say 1–2 words with meaning. At 18 months, he has a vocabulary of 8–10 words. Thereafter, the vocabulary increases rapidly to around 100 words by 2 yr, at which time 2–3 words are joined to form simple sentences. By 3 yr, the toddler continually asks questions and knows his full name. He can give a coherent account of recent experiences and events by the age of 4 yr (Table 3.4).

Table 3.4: Key language milestones

Age	*Milestone*
1 mo	Alerts to sound
3 mo	Coos (musical vowel sounds)
4 mo	Laugh loud
6 mo	Monosyllables (ba, da, pa), ah-goo sounds
9 mo	Bisyllables (mama, baba, dada)
12 mo	1–2 words with meaning
18 mo	8–10 word vocabulary
2 yr	2–3 word sentences, uses pronouns "I", "me", "you"
3 yr	Asks questions; knows full name and gender
4 yr	Says song or poem; tells stories
5 yr	Asks meaning of words

Vision and Hearing

Adequate sensory inputs are essential for development. Both normal vision and hearing are of paramount importance for child development. The ability to see and hear is apparent even in the newborn. Thereafter maturation of visual and hearing pathways are reflected by specific visual and auditory behaviors.

Vision The best stimulus to check visual behavior is the primary caretaker's face. At birth, a baby can fixate and follow a moving person or dangling ring held 8–10 inches away up to a range of 45°. This increases to 90° by 4 weeks and 180° by 12 weeks. At around 1 month, the baby can fixate on his mother as she talks to him (Fig. 3.39).

At about 3–4 months, the child fixates intently on an object shown to him ('grasping with the eye') as if the child wants to reach for the object (Fig. 3.40). Binocular vision begins at around 6 weeks and is well established by 4 months. By 6 months, the child adjusts his position to follow objects of interest, can follow rapidly moving objects by 1 yr. Later the child displays more maturity in vision by not only identifying smaller objects but also being able to recognize them.

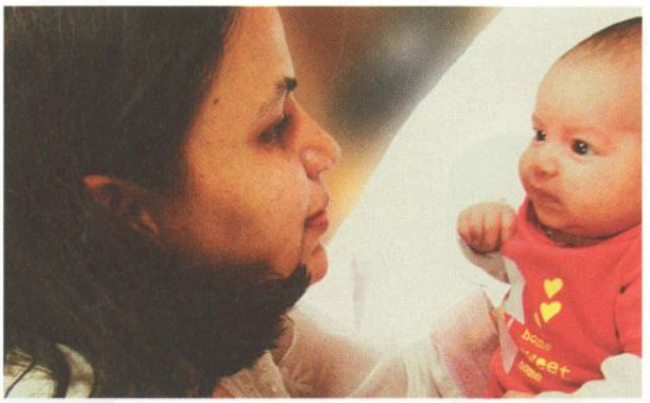


Fig. 3.39: Infant fixates on her mother as she talks to her at 1 month

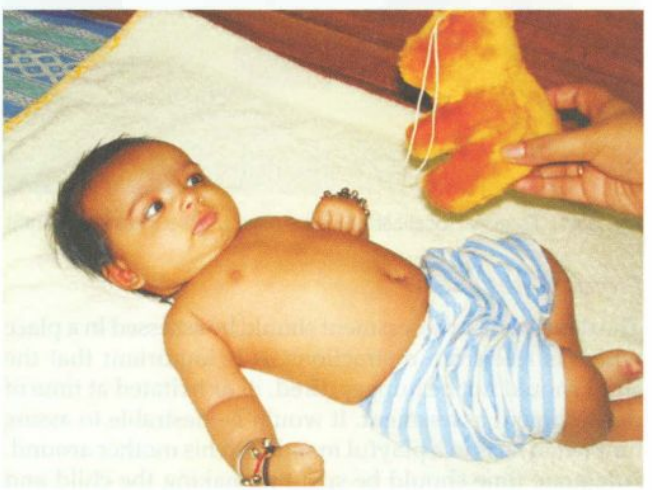


Fig. 3.40: Grasping 'with the eye' at 3 months

Hearing Newborns respond to sounds by startle, blink, cry, quieting or change in ongoing activity. By 3 to 4 months, the child turns his head towards the source of sound. Hearing, may be checked by producing sound 1½ feet away from the ear (out of field of vision), and a pattern of evolving maturity of hearing can be observed. At 5 to 6 months the child turns the head to one side and then downwards if a sound is made below the level of ears. One month later he is able to localize sounds made above the level of ears. By the age of 10 months the child directly looks at the source of sound diagonally (Fig. 3.41).

Developmental Assessment

Developmental delay is estimated to be present in about 10% of children. It is possible to recognize severe developmental disorders early in infancy. Speech impairment, hyperactivity and emotional disturbances are often not detected until the child is 3–4 yr old. Learning disabilities are not picked up until the child starts schooling.

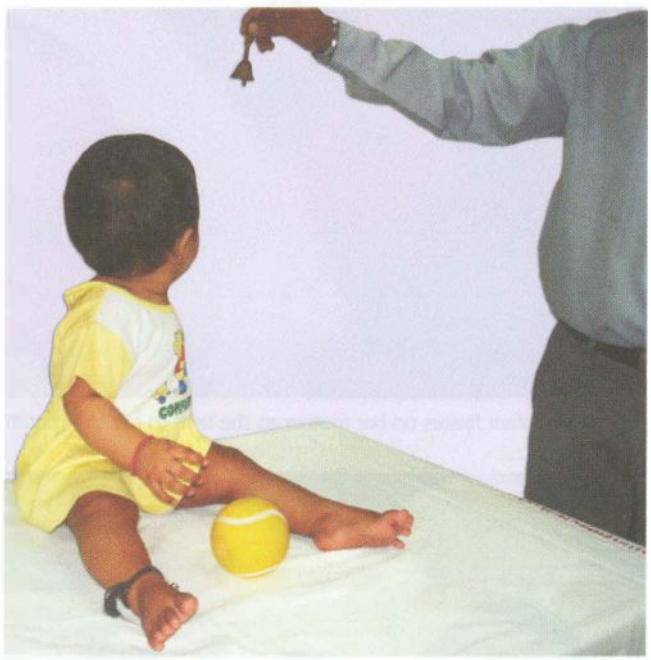


Fig. 3.41: Diagonal localization of the source of sound at 10 months

Prerequisites

The development assessment should be assessed in a place which is free from distractions. It is important that the child should not be hungry, tired, ill or irritated at time of development assessment. It would be desirable to assess him when he is in a playful mood with his mother around. Adequate time should be spent in making the child and family comfortable. Observation for alertness, concentration and skills of the child is an integral part of assessment carry a development kit (Box 3.1).

Steps

History A detailed history is the starting point for any development assessment. Observations by parents are fairly accurate. Hence, a well taken history will help in (i) determining the details of probable risk factors affecting development, (ii) evaluation of rate of acquisition of skills and differentiating between delay and regression, and (iii) forming a gross impression about the development age of the child. This helps to choose the appropriate tools for further evaluation and confirmation.

Box 3.1. Equipment for development assessment

- A red ring (diameter 6–7 cm) tied to a string
- Nine red cubes
- Paper pellets
- Spoon
- Cup with handle
- A book with thick pages
- Picture book
- Red pencil, paper
- Doll and mirror

Examination This should be done to (i) assess physical growth and head circumference, (ii) do a physical assessment, particularly for dysmorphism, stigmata of intrauterine infections and signs of hypothyroidism, (iii) screen for vision and hearing, and (iv) conduct neurological examination and examine for primitive reflexes (if required).

Adequate time should be spent in observing the baby especially social responsiveness, alertness, concentration, interest and distractibility. It would be appropriate to assess vision and hearing at the outset so that further observations are not confounded by lack of sensory stimuli. The vocal responses, particularly the nature, frequency and quality are noted. Subsequently, fine motor skills should be assessed, including the interest, alertness and rapidity of responses.

The annoying maneuvers, including assessment of reflexes, head circumference, ventral suspension and pull to sit should be done at the end. It is preferable to perform the developmental assessment before the systemic examination so that the child's cooperation is solicited.

By the end of the evaluation one should be able to arrive at a conclusion whether the neurological status and cognitive status are within normal range or not. Significant delays on screening is an indication for a detailed formal assessment of development status. By assessment, one can assign developmental quotient (DQ) for any developmental sphere. It is calculated as:

$$\frac{\text{Average age at attainment}}{\text{Observed age at attainment}} \times 100$$

A DQ below 70% is taken as delay and warrants detailed evaluation. To obtain a DQ of a child, a formal assessment by an individual trained in developmental assessment using appropriate tools/tests is needed. There are several tests to assess DQ. Each test has its own psychometric properties. They give different kinds of estimates of development like an overall score of development and subscores for gross motor, fine motor, visual perception, receptive language, expressive language, etc.

IQ tests mainly assess the cognitive/adaptive behavior part of the development. The age at which a particular test can be applied depends on the test items. However, in younger children (<5 yr), it is more meaningful to have a global assessment of abilities; hence DQ testing is more comprehensive. Specific IQ tests (Stanford-Binet intelligence scales) are available to asses IQ starting from 2 yr of age.

Interpretation

In babies born preterm, corrected age rather than postnatal age is used for determining developmental status till two years of age. For example, a child born at 32 weeks gestation (gestational age) seen at 12 weeks of age (postnatal age) should be considered as a 4-week-old (corrected age) child for development assessment.

While drawing any conclusions about development, one should remember the wide variations in normality. For example, let us consider the milestone of standing alone. The average age for attainment of this milestone in a WHO survey was 10.8 months (Fig. 3.42). However, the 3rd and 97th centiles for normal children were 7.7 and 15.2 months, respectively. The same is true for many other milestones as is shown in Fig. 3.42. The bars illustrate the age range for normal children to attain that particular milestone. This range of normalcy should always be kept in mind while assessing development.

Retardation should not be diagnosed or suggested on a single feature. Repeat examination is desirable in any child who does not have a gross delay. Factors such as recent illness, significant malnutrition, emotional deprivation, slow maturation, sensory deficits and neuromuscular disorders should always be taken into account.

One should keep in mind the opportunities provided to the child to achieve that milestone. For example, a child who has not been allowed to move around on the ground sufficiently by the apprehensive parents may have delay in gross motor skills.

At times, there can be significant variations in attainment of milestones in individual fields, this is called *dissociation*. For example, a 1-yr-old child who speaks 2–3 words with meaning and has finger thumb opposition (10–12 months), may not be able to stand with support (less than 10 months). Such children require evaluation for physical disorder affecting a particular domain of development. A child having normal development in all domains except language may have hearing deficit.

Table 3.5 gives the upper limits by which a milestone must be attained. A child who does not attain the milestone by the recommended limit should be evaluated for cause of developmental delay.

Table 3.5: Upper limit of age for attainment of milestone

Milestone	*Age*
Visual fixation or following	2 mo
Vocalization	6 mo
Sitting without support	10 mo
Standing with assistance	12 mo
Hands and knees crawling	14 mo
Standing alone	17 mo
Walking alone	18 mo
Single words	18 mo
Imaginative play	3 yr
Loss of comprehension, single words or phrases at any age	

Adapted from WHO; MGRS group, WHO motor development study. Acta Pediatrics 2006;450:86–95

The predictive value of different domains of development for subsequent intelligence is not the same. Fine motor, personal-social and linguistic milestones predict intelligence far better than gross motor skills. In particular, an advanced language predicts high intelligence in a child.

Development Screening Tests

Screening is a brief assessment procedure designed to identify children who should receive more intensive diagnosis or assessment. Such an assessment aids early intervention services, making a positive impact on development, behavior and subsequent school performance. It also provides an opportunity for early identification of comorbid developmental disabilities. Ideally,

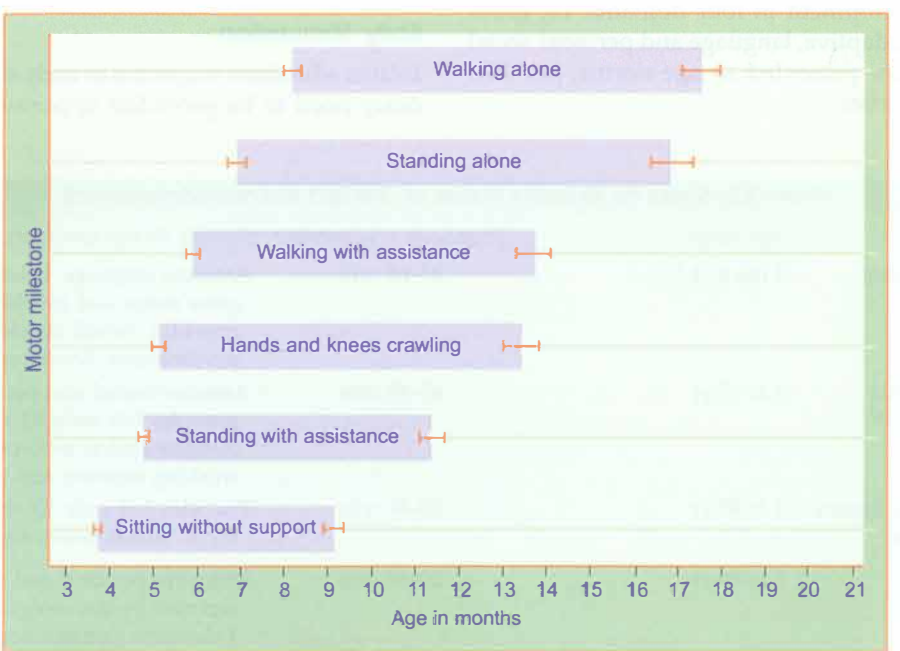


Fig. 3.42: Windows of achievement of six major motor milestones (WHO; Multicenter Growth Reference Study Group, 2006)

all children should be periodically screened but short of this, at least those with perinatal risk factors should be screened.

Developmental Surveillance

Child development is a dynamic process and difficult to quantitate by one time assessment. During surveillance repeated observations on development are made by a skilled physician over time to see the rate and pattern of development. Periodic screening helps to detect emerging disabilities as the child grows. However, using clinical judgment alone has a potential for bias and it has been suggested to use periodic screening tools for ongoing developmental surveillance. The physician should choose a standardized developmental screening tool that is practical and easy to use in office setting. Once skilled with the tool, it can be used as screening method to identify at risk children. Screening tests popular in the west include Parents' Evaluations of Development Status (PEDS) and Ages and Stages Questionnaires (ASQ). Some of the common screening tools used in India are described below.

Phatak's Baroda screening test This is India's best known development testing system that was developed by Dr Promila Phatak. It is meant to be used by child psychologists rather than physicians. It is the Indian adaptation of Bayley's development scale and is applied to children up to 30 months. It requires several testing tools and objects that are arranged according to age. The kit is available commercially.

Denver development screening test The revised Denver development screening test (DDST) or Denver II assesses child development in four domains, i.e. gross motor, fine motor adaptive, language and personal social behavior, which are presented as age norms, just like physical growth curves.

Trivandrum development screening chart This simplified adaptation of the Baroda development screening system is applicable to children up to 2 yr of age. It consists of 17 items selected from Bayley Scale of infant development (BSID) and Baroda tests. It is a simple test that can be administered in 5 min by a health worker, and is useful as a mass screening test.

Clinical adaptive test and clinical linguistic and auditory milestone scale (CAT/CLAMS) This easy to learn scale can be used to assess the child's cognitive and language skills. It uses parental report and direct testing of the child's skills. It is used at ages of 0–36 months and takes 10–20 min to apply. It is useful in discriminating children with mental retardation (i.e. both language and visual motor delay) and those with communication disorders (low language scores).

Goodenough-Harris drawing test This simple nonverbal intelligence test requires only a pencil or pen and white unlined paper. Here the child is asked to draw a man in the best possible manner and points are given for each detail that the child draws. One can determine the mental age by comparing scores obtained with normative sample. This test allows a quick but rough estimate of a child's intelligence, and is useful as a group screening tool.

Definitive Tests

These tests are required once screening tests or clinical assessment is abnormal. They are primarily aimed to accurately define the impairments in both degree and sphere. For example, by giving scores for verbal, performance abilities and personal and social skills, these can be differentially quantified. Some of the common scales used are detailed in Table 3.6.

Early Stimulation

Infants who show suspected or early signs of development delay need to be provided opportunities that promote

Table: 3.6: Scales for definitive testing of intellect and neurodevelopment

Name of the test	*Age range*	*Time taken to administer*	*Scoring details; comments*
Bayley scale for infant development II	1 mo to 3.5 yr	30–60 min	Assesses language, behavior, fine motor gross motor and problem solving skills; provides mental development index and psychomotor developmental index
Wechsler intelligence scale for children IV	6 to 17 yr	65–80 min	Assesses verbal and performance skills provides full scale IQ and indices of verbal comprehension perceptual reasoning, working memory and processing speed
Stanford-Binet intelligence scales, 5th edition	2 to 85 yr	50–60 min	Provides full scale IQ, verbal IQ, nonverbal IQ, 10 subset scores and 4 composite scores
Vineland adaptive behavior scale II	0 to 89 yr	20–60 min	Measures personal and social skills as reported by the caregiver or parent, in 4 domains (communication, daily living skills, socialization and motor skills)

body control, acquisition of motor skills, language development and psychosocial maturity. These inputs, termed early stimulation, include measures such as making additional efforts to make the child sit or walk, giving toys to manipulate, playing with the child, showing objects, speaking to the child and encouraging him to speak and prompting the child to interact with others, etc.

There is a general lack of evidence for effectiveness of these early interventions in improving neurodevelopmental outcome and motor abilities. However, studies in premature babies, cerebral palsy, institutionalized children and other children at high risk for adverse neurodevelopmental outcomes suggest that these interventions are effective if started early. Compliance to interventions is important for favorable results on neurodevelopment. Systematic reviews suggest that the effect of these interventions is sustained in later childhood. For example, play and reading were effective in early childhood in low- and middle-income countries, and kangaroo mother care was effective for low birth weight babies in resource poor settings.

Promoting Development by Effective Parenting

Comprehensive care to children requires focus on preventive efforts including child-rearing information to parents. Parenting has an immense impact on emotional, social and cognitive development and also plays a role in the later occurrence of mental illness, educational failure and criminal behavior. Creating the right conditions for early childhood development is likely to be more effective and less costly than addressing problems at a later age.

Television Viewing and Development

Television viewing in younger children has been shown to retard language development. It is a passive mode of entertainment and impairs children's ability to learn and read, and also limits creativity. Children can pick up inappropriate language and habits by watching TV shows and commercials. Violence and sexuality on television can have a lasting impact on the child's mind. Parents need to regulate both the quantity and quality of TV viewing, limiting the time to 1–2 hr per day and ensuring that the content they see is useful.

Some Useful Internet Resources

http://www.nlm.nih.gov/medlineplus/childdevelopment.html
http://kidshealth.org/parent/growth/
http://www.nichd.nih.gov/
http://www.med.umich.edu/yourchild/
http://www.bridges4kids.org/disabilities/SLI.html
http://www.zerotothree.org/

Suggested Reading

Developmental surveillance and screening of infants and young children. American Academy of Pediatrics, Committee on Children with Disabilities. Pediatrics 2001;108:192–6

Engle PL, Black MM, Behrman JR, et al. Strategies to avoid the loss of developmental potential in more than 200 million children in the developing world. Lancet 2007;369:229–42

Grantham-McGregor S, Cheung Y, Cueto S, et al. Developmental potential in the first 5 yr for children in developing countries. Lancet 2007;369:60–70

BEHAVIORAL DISORDERS

Anorexia Nervosa

This eating disorder is characterized by: (i) body weight <85% of expected weight for age and height; (ii) intense fear of becoming fat even though underweight; (iii) disturbed body image and denial that the current body weight is low; and, (iv) in postmenarcheal girls, amenorrhea. It is most common among 15–19-yr-old.

Two clinical subtypes are recognized. Some patients lose weight through excessive dietary restrictions and increased physical activity (restricting type), while others resort to vomiting and the use of laxatives or diuretics. Anorexia is commonly associated with depression, anxiety, suicidal ideation and/or obsessive compulsive disorder. Profound weight loss may result in hypothermia, hypotension, dependent edema, bradycardia and metabolic changes. Hypokalemic metabolic alkalosis may occur due to vomiting and use of diuretics or purgatives. Mortality is attributed to cachexia and suicide.

Psychotherapy, including individual and family therapy, and in some cases, group therapy, are required to establish appropriate eating patterns and restore normal perceptions of hunger and satiety. A nurturing emotional environment is essential. Severely undernourished patients require nutritional rehabilitation targeting normal weight for height. While oral supervised feeding is preferred, some patients require nasogastric or parenteral nutrition. Antidepressant and antipsychotic drugs are prescribed as required.

Bulimia

Bulimia nervosa is characterized by (i) recurrent episodes of binge eating characterized by eating in a discrete period of time an amount of food that is definitely more than what normal individuals eat during a similar time period, without control over eating during the episode; and (ii) recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, fasting, or excessive exercise. Binge eating and inappropriate compensatory behavior both occur, on average, at least twice a week for 3 months. There is undue influence of body shape and weight on self-evaluation. The disorder is more common among girls between 10–19 yr of age. Many affected patients have comorbidities like depression and other psychoses. Management includes a combination of psychotherapy (specifically, cognitive behavior therapy) and anti-depressant medications (such as fluoxetine). Active followup

needs to be maintained to ensure motivation and adherence to therapy.

Pica

Pica is the persistent ingestion of non-nutritive substances such as plaster, charcoal, paint and earth for at least 1 month in a manner that is inappropriate for the developmental level, is not part of a culturally sanctioned practice and is sufficiently severe to warrant independent clinical attention. It is a common problem in children less than 5 yr of age. Factors speculated to predispose to pica include mental retardation, psychosocial stress (maternal deprivation, parental neglect and abuse) and other behavioral disorders. Poor socioeconomic status, malnutrition and iron deficiency are commonly associated with pica but their etiologic significance has not been established. Children with pica are at an increased risk for lead poisoning, iron deficiency anemia and parasitic infestations. Management comprises behavior modification, alleviating the psychosocial stress if any, and iron supplementation if deficiency is present.

Food Fussiness

Food fussiness is a common problem in young children. It often reflects an excessive need for control on the part of the parents about what the child eats. Management involves examining the child for any nutritional deficiencies and counseling the parents regarding the normal growth pattern and dietary requirements of children. Useful behavioral strategies include establishing regular meal timings, ensuring a pleasant atmosphere, offering a variety of foods and setting an example of enjoying the same food themselves. Offering small servings at a time, reducing between meal caloric intake, not force feeding the child, presenting the food in an interesting manner and praise for good eating behavior are other helpful strategies. Parents should resist the temptation of offering sugary or fatty snacks as substitute or reward for eating healthy food.

Difficulties with Toilet Training

Refusal to defecate in the toilet with development of constipation is a common problem in children and is a cause for parental frustration and increased stress for the child. The most common setting is a power struggle between the child and parents ensuing from toilet training that is begun before the child is developmentally ready to be trained. Toilet training should be started after 2 yr of age, when the child has spontaneously started indicating bladder and bowel fullness, and is able to follow simple instructions. The general ambience should be conducive to learning and free from pressure. Use of a toddler-size seat that can be placed on top of the regular toilet seat helps the child feel more secure and not afraid of falling in. Consistency in the parents' approach and positive reinforcement help in achieving the normal pattern.

Temper Tantrums

Temper tantrums include behaviors that occur when the child responds to physical or emotional challenges by drawing attention to himself and can include yelling, biting, crying, kicking, pushing, throwing objects, hitting and head banging. Tantrums typically begin at 18–36 months of age. Inability to assert autonomy or perform a complex task on his/her own causes frustration to the child which cannot be effectively communicated due to limited verbal skills. The frustration therefore is acted out as undesired behaviors. Such behavior peaks during second and third year of life and gradually subsides by the age of 3–6 yr as the child learns to control his negativism.

Parents should be asked to list situations where disruptive behavior are likely to occur and plan strategies to avoid these. For example, they should ensure that the child is rested and fed, and should carry a snack for the child when going for an outing. During a tantrum, the parents' behavior should be calm, firm and consistent and they should not permit the child to take advantage from such behavior. The child should be protected from injuring himself or others. At an early stage, distracting his attention from the immediate cause and changing the environment can abort the tantrum. A 'time out', i.e. asking the child to stay alone in a safe and quiet place for a few minutes, is useful.

Breath Holding Spells

Breath holding spells are reflexive events typically initiated by a provocative event that causes anger, frustration or pain causing the child to cry. The crying stops at full expiration and the child becomes apneic and cyanotic or pale. In some cases the child may lose consciousness, become hypotonic and fall. If the spell lasts for more than a few seconds, brief tonic-clonic seizure may occur. Breath-holding spells always revert on their own within several seconds, with the child resuming normal activity or falling asleep for some time. Breath holding spells are rare before 6 months of age, peak at 2 yr and abate by 5 yr of age.

Diagnosis is based on the setting and the typical sequence of crying, cyanosis or pallor with or without brief loss of consciousness. The differential diagnoses include seizures, cardiac arrhythmias or brainstem malformation. The history of provoking event, stereotyped pattern of events and presence of color change preceding the loss of consciousness help in distinguishing breath holding spells from seizures. In case the spells are associated with pallor, an electrocardiogram may be done to rule out cardiac arrhythmias and long QT syndrome.

After a thorough examination of the child, the parents should be reassured. They are explained that the apneic spells are always self-limited and do not lead to brain injury or death. The family should be advised to be consistent in their behavior with the child, remaining calm

during the event, avoid picking the child up (since this decreases blood flow to the brain) and to turn him to the side so that secretions can drain. As the child recovers, they should avoid exhibiting undue concern nor give in to his demands if the spell was provoked by anger or frustration. Children with iron deficiency should receive iron supplementation.

HABIT DISORDERS AND TICS

Habit disorders include repetitive pattern of movements such as head banging, rocking of body, thumb sucking, twisting of hair and grinding of teeth. Such movements are seen frequently in normally developing children between 6 months to 2 yr and are benign and generally self limited. These movements seem to serve as a means of discharging tension in the children or providing extra self-nurturance. As these children become older, they learn to inhibit some of their rhythmic habit patterns, particularly in social situations. Undue attention from parents and forcing the child to give up the behavior often leads to reinforcement of such behavior and their persistence for a longer period.

Nail biting is a common stress-relieving habit. It includes biting the cuticle and soft tissue surrounding the nail as well as the nails. It is the most common among 'nervous' habits that include thumb-sucking, nose-picking, hair-twisting. Although seen most commonly in school-age children, it is frequent at all ages. Nail biting increases the risk for infections around the nail beds and for infections transmitted by feco-oral route. Soreness of fingertips may cause occasional bleeding from cuticles. Nail biting may interfere with normal nail growth and lead to deformed nails.

If nail biting is occasional and transient, occurring only in situations of stress (e.g. while learning something new, attending a party with many strangers), it should be ignored as this is a comforting mechanism. If nail biting is more persistent, parents should try to identify the source of persistent stress (e.g. bullying at school) and help the child in resolving it. Measures like wearing gloves or adhesive bandages and conscious substitution of nail-biting by other activities (e.g. squeezing a rubber ball) are helpful. The nails should be trimmed regularly and the child should be offered positive reinforcement or rewards for allowing the nails to grow.

Thumb sucking is normal behavior in infants and toddlers. It peaks between the ages of 18–21 months and most children spontaneously drop the habit by 4 yr of age. Its persistence in older children is socially unacceptable and can lead to dental malalignment. Parents should be reassured and asked to ignore the habit if the child is younger than 4 yr of age. If it persists beyond the age of 4–5 yr, the parents should motivate the child to stop thumb sucking and encourage him when he restrains himself from sucking the thumb. Application of noxious agents over the thumb is useful as an adjunctive second-line treatment.

Tics are involuntary and purposeless movements or utterances that are sudden, spasmodic and repetitive. They usually involve the muscles of eyes, mouth, face and neck, and can range from blinking of eyes, facial twitching, shrugging or throat clearing to extreme forms like obscene gestures and vocalization (coprolalia). The disorder is seen in 1–2% children, particularly in school-aged boys.

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in children, estimated to affect 3–5% of school-aged children, particularly boys. It is characterized by difficulty in paying attention, difficulty in controlling behavior and hyperactivity.

Etiology

For most children, no etiology is identified. Both genetic and environmental factors play a role. Studies have identified abnormalities in dopamine transporter and thyroid receptor beta genes in some patients.

Clinical Features

Examples of inattentive, hyperactive and impulsive behavior included within the criteria for diagnosis of ADHD are listed in Table 3.7. For making the diagnosis, the behavior must begin before 7 yr of age, be present for

Table 3.7: Examples of inattentive and hyperactive/ impulsive behavior included within the criteria for diagnosis of ADHD

Inattentive behavior

1. Early distraction by extraneous stimuli
2. Often makes careless mistakes in schoolwork or other activities
3. Often has difficulty sustaining attention in tasks or play
4. Often forgetful in daily activities
5. Does not seem to listen to what is being said to him
6. Often fails to finish schoolwork or other chores
7. Daydreams, becomes easily confused, and move slowly
8. Difficulty in processing information as quickly and accurately as others

Hyperactive behavior

1. Runs about or climbs excessively in situations where it is inappropriate
2. Fidgets with hands and feet and squirms in seat
3. Talks nonstop
4. Has trouble sitting still during dinner, school, and story time
5. Has difficulty doing quiet tasks or activities.

Impulsive behavior

1. Has difficulty awaiting turn in games or group situations
2. Blurts out answers to questions
3. Often interrupts conversations or others' activities

at least 6 months, be pervasive (present in at least 2 different settings) and impair the child's ability to function normally. The symptoms should not be secondary to another disorder. Three subtypes are known:

Predominantly hyperactive-impulsive. Most symptoms (6 or more) are in the hyperactivity-impulsivity categories, and less than 6 symptoms of inattention are present.

Predominantly inattentive. The majority of symptoms (6 or more) are in the inattention category and less than 6 symptoms of hyperactivity-impulsivity are present, although hyperactivity-impulsivity may still be present to some degree. Parents or teachers may not readily recognize these children as having a problem.

Combined hyperactive-impulsive and inattentive. These children have six or more symptoms each of inattention and hyperactivity-impulsivity. Most children have the combined type of ADHD.

Diagnosis is primarily clinical, using thorough clinical interview of parents and use of behavior rating scales. Physical examination includes direct observation of the child and ruling out chronic systemic illnesses that affect child's attention span. Neuropsychological evaluation using standard tests of general intelligence and educational achievement help to exclude learning disorders or mental retardation.

Management

The management of ADHD should begin with educating the parents about ADHD and helping them in setting realistic goals of treatment. The treatment involves a combination of behavioral therapy and medications.

Useful behavioral strategies include: (i) clear and explicit instructions to the child about desirable and nondesirable behavior; (ii) positive reinforcement of desirable behavior by praise or small tangible rewards; (iii) punishment strategies like verbal reprimand, nonverbal gestures or 'time out' for undesirable behaviour; and (iv) extinction technique, i.e. systematic ignoring of undesirable behavior; and (v) providing a well-structured and organized routine for the child at home as well as school. At school, giving brief and consistent instructions to the child, clear and consistent response to the child's behavior, seating in an area with few distractions, and allowing the child to change activities and move about periodically are helpful.

Stimulants, e.g. methylphenidate, amphetamine and their derivatives, are effective in ameliorating inattention, hyperactivity and impulsivity in 70–80% children. However, academic achievement or social skills do not improve. Adverse effects are mild and include abdominal discomfort, loss of appetite, headache and sleep disturbances. Atomoxetine, a selective norepinephrine reuptake inhibitor, and extended-release preparations of selective α-adrenergic agonists (e.g. guanfacine, clonidine) have also demonstrated efficacy in reducing core symptoms.

Learning Disabilities

Learning disabilities arise from specific neurodevelopmental dysfunctions that prevent expected learning in one or more academic areas. The important defining principle is that such disabilities are unexpected when considering the overall intellectual functioning of the child. These disorders are not the result of global developmental delay, major vision or hearing handicap or consequences of major social or emotional stress. Dyslexia constitutes 80% of all cases. Others are dysgraphia (difficulty in writing), reading comprehension difficulty (inability to comprehend what is read) and dyscalculia (difficulty in performing mathematical operations).

Dyslexia It is a receptive language-based learning disability that is characterized by difficulties with decoding, fluent word recognition, and/or reading comprehension skills. Word decoding is the ability to apply principles of phonetics to sound the words, i.e. understanding that each letter or letter combination in the word has a sound and by combining these, the word can be read and spelled. Secondary consequences include reduced reading experience that can impede growth of vocabulary, written expression and background knowledge. Dyslexic children read very slowly and make many mistakes in reading. They also have difficulty in spelling because of underlying problem with word decoding. The difficulty in reading impairs their ability to cope up with the academic syllabus and is often associated with low self-confidence and feeling of frustration, which increases the risk of developing psychological and emotional problems. Listening comprehension is typically normal in the affected children.

Dyslexia may co-exist with ADHD in 15–40% of children. Genetic factors are recognized to play a strong role in the etiology of dyslexia. Up to 50% of children of a dyslexic parent and 50% of siblings of a dyslexic child have dyslexia.

Diagnosis of dyslexia is clinical, based on presence of unexpected difficulties in reading at the level of phonologic processing of words. Standardized tests are used to test speed, accuracy and comprehension in reading and spelling ability, in relation to the age and school grade.

In younger children, the focus of management is on remediation. Affected children are best taught in small groups by teachers trained in the principle of phonics. The children are taught how letters are linked to sounds. The stress is on improving phonemic awareness, i.e. the ability to focus on and manipulate phonemes (speech sounds) in spoken syllables and words. Usually these programs improve the reading accuracy significantly and fluency to a lesser extent. If the child also has ADHD, this should be managed with pharmacotherapy. For older children, the management stresses more on accommodation rather than remediation, e.g. use of laptops with spell-check, recorded books, giving extra time for writing tests or use of multiple choice questions.

Stuttering

Stuttering is a defect in speech characterized by hesitation or spasmodic repetition of some syllables with pauses. There is difficulty in pronouncing the initial consonants caused by spasm of lingual and palatal muscles. It is a common problem affecting up to 5% of children between 2–5 yr of age, a period in which there is non-fluency of speech. Environmental and emotional stress or excitement may exacerbate stuttering.

Parents of a young child with primary stuttering should be reassured that stuttering between the age of 2–5 yr usually resolves on its own. Making the child conscious of his stutter or pressurizing him to repeat the word without stuttering will further increase the stress and the stutter. Children who continue to have significant stuttering require referral to a speech therapist. In older children with late onset of stuttering, the help of a child psychologist should be sought.

Suggested Reading

Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics 2011:128; 1007

Snowling MJ, Hulme C. Interventions for children's language and literacy difficulties. Int J Lang Commun Disord 2012;47:27–34

Autistic Disorder

Autistic disorder is classified as one of the pervasive developmental disorders, also called as autistic spectrum disorders, a cluster of syndromes that share marked abnormalities in the development of social and communicative skills (Table 3.8). Data from developed countries suggest that 1 in 150 children is affected by such disorders.

Children with autistic disorders (AD) show severe and pervasive impairments in reciprocal social interaction and communication and exhibit stereotyped behaviors, as well as restricted interests and activities. To meet full criteria for diagnosis, a child must demonstrate the following symptoms: (i) qualitative impairment in social interaction as manifested by two of the following: impairment in the use of multiple nonverbal behaviors (e.g. eye gaze, facial expression, body postures); failure to develop peer relationships; lack of sharing of enjoyment; and lack of social or emotional reciprocity; (ii) qualitative impairment in communication in at least one of the following areas: delay or total lack of spoken language; marked impairment in the ability to initiate or sustain a conversation with others; stereotyped or repetitive use of language; and lack of varied spontaneous play; (iii) restricted repetitive and stereotyped patterns of behaviors, interests, and activities as manifested by preoccupation with one or more restricted patterns of interests; inflexible adherence to nonfunctional routines or rituals; repetitive motor mannerisms (such as rocking, hand flapping, finger flicking); and preoccupation with parts of objects. Intelligence is variable, although most children fall in the functionally retarded category by conventional psychological testing. Some children show an isolated remarkable talent.

Table 3.8: Pervasive developmental disorders

Autistic disorder
Rett syndrome
Asperger syndrome
Childhood disintegrative disorder

Diagnosis. Diagnosis of AD is clinical, guided by the application of diagnostic tools, such as Autism Diagnostic Observational Schedule and the Autism Diagnostic Interview-Revised. Testing for associated neurological disorders such as tuberous sclerosis and fragile X is recommended. Conditions that should be differentiated from AD include mental retardation, deafness, selective mutism and ADHD.

Treatment. The primary management is through 'intensive behavioral therapy', starting before 3 yr of age, applied at home as well as school and focusing on speech and language development and good behavioral control. Older children and adolescents with relatively higher intelligence but poor social skills and psychiatric symptoms (e.g. depression, anxiety and obsessive-compulsive symptoms) may require psychotherapy and pharmacotherapy.

Prognosis. Factors associated with better prognosis are early diagnosis, intensive behavioral therapy, higher intelligence level and presence of functional speech. Children with better prognostic factors may grow up to be self-sufficient and employed, though socially isolated. On the other hand, those with poor prognosis remain dependent on family or require placement in facilities outside home.

Munchausen by Proxy

Munchausen syndrome by proxy is a disorder in which a caregiver, usually mother deliberately makes up a history of illness in her child and/or harms the child to create illness. The name is derived from the adult 'Munchausen syndrome' in which a person self-induces or acts out illness to gain medical attention. In Munchausen by proxy, the abusing caregiver gains attention from the relationships formed with health care providers, or her own family as a result of the problems created.

Most commonly, the victims are infants and young preverbal children. The child's symptoms, their pattern or response to treatment may not conform to any recognizable disease and always occurs when mother is with the child. Apnea, seizures (which may be induced by suffocating the child or injecting insulin), fever, diarrhea and skin conditions are the common symptoms. Confirmation of diagnosis needs careful history and reviewing of past and current hospital records. Monitoring

by hidden television cameras in the ward may be useful. Once the diagnosis is made, the offending caregiver should be confronted, separated from the child and provided psychotherapy.

Suggested Reading

Martínez-Pedraza F, Carter AS. Autism spectrum disorders in young children. child Adolesc Psychiatr Clin N Am 2009;18:645–63

Mitchell I, Brummet J, De Forest J. Apnea and factitious illness (Munchausen syndrome) by proxy. Pediatrics 1993;92:810–5

3

Disruptive Behavior Disorders

This term encompasses a broad range of behaviors that bring children into conflict with their environment.

Oppositional Defiant Disorder

Oppositional defiant disorder is a repetitive and persistent pattern of opposition, defiant, disobedient and disruptive behaviors towards authority figures persisting for at least 6 months. Examples of such behaviors are: (i) persistent stubbornness and refusal to comply with instructions or unwillingness to compromise with adults or peers; (ii) deliberate and persistent testing of the limits; (iii) failing to accept responsibility and blaming others for one's mistakes; (iv) deliberately annoying others; and (v) frequently losing temper. Although the disorder does not include the more aggressive aspects of conduct disorder, many children go on to be later diagnosed with conduct disorders.

Oppositional defiant disorder is thought to result from interplay of factors in the child's characteristics, parental interactions and environmental factors. Serious conflict between the parents and family history of mental health problems such as depression, ADHD or antisocial personality disorder is often present.

The management should focus on alleviating known risk factors or stresses that might be contributing to the development of oppositional behavior. Interventions are directed towards enhancing parents' skills in conflict resolution and communication and the child's skills in effective communication and anger management. Use of stimulant medication is effective in patients with ADHD.

Conduct Disorder

Conduct disorder is characterized by aggressive and destructive activities that cause disruptions in the child's natural environments such as home, school, or the neighborhood. The overriding feature is the repetitive and persistent pattern of behaviors that violate societal norms and the rights of other people, for a period of at least one year. Prevalence is estimated at 9% for boys and 2% for girls.

The specific behaviors necessary to make a diagnosis of conduct disorder are: (i) aggressive conduct that causes or threatens physical harm to other people or animals; (ii) non-aggressive behavior that causes property loss or damage; (iii) deceitfulness or theft; and (iv) serious violations of rules. The diagnosis of conduct disorder is made if three or more of the above behaviors are present, with at least one having taken place in the previous six months.

Various child behavior management techniques, such as positive reinforcement to increase desirable behavior, and extinction and time out to decrease problem behavior, are taught to the parents. The children are taught anger-coping, peer coping and problem-solving skills, so that they are able to deal better with problematic interpersonal situations. They are trained to not misjudge others' intent as hostile to avoid precipitating aggressive behavior.

Juvenile Delinquency

Children who show oppositional defiant behavior or conduct disorder and come into conflict with the juvenile justice system because of such behavior are called juvenile delinquents. The term refers to a person under 18 yr who is brought to the attention of the juvenile justice system for committing a criminal act or displaying a variety of other behaviors not allowed under the law, such as, truancy, use of alcohol or illicit drugs.

Family and parenting interventions have been shown to reduce the rate of re-incarceration and criminal behaviour by juvenile delinquents. In some cases, placement in foster care is recommended with similar interventions being administered by the foster family.

Adolescent Health and Development

4

Tushar R. Godbole, Vijayalakshmi Bhatia

Adolescence is a stage of transition from childhood to adulthood. During this stage of life, a youth undergoes rapid changes in body structure, mediated by the sex hormones. The appearance of sexual characters is coupled with changes in cognition and psychology. Whereas adolescence refers to this entire process, puberty refers to the physical aspect. The age group 10–19 yr is considered as the period of adolescence, and puberty marks the early half of adolescence. Though it is a continuous process, for convenience sake, adolescence is generally divided into three phases: early (10–13 yr), mid (14–16 yr) and late (17–19 yr) puberty.

PHYSICAL ASPECTS

The activation of the hypothalamo-pituitary-gonadal axis leads to the production of gonadotropins, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex steroids, estrogen and testosterone. Gonadal sex steroids bring about secondary sexual characters (breast development, increase in penile and testicular size and menarche), whereas adrenal androgens cause development of sexual hair, acne and underarm odor. The details of hormonal mechanisms of onset and progression of puberty are dealt with in Chapter 17.

Onset and Sequence of Puberty

Puberty in girls starts with breast development (thelarche) any time between 8 and 13 yr (Fig. 4.1). This is followed by appearance of pubic hair (pubarche) and subsequently menstruation (menarche), occurring at an average of 12.6 yr (range 10–16 yr). However, many experts believe that the normal age of menarche is advancing to as early as 9 yr in many populations. Menarche usually occurs after 2–2 ½ yr of thelarche. The breast buds may be tender and there may be asymmetry in the breast size during early phases of puberty.

In boys, the earliest change is increase in testicular size (testicular volume reaching 4 ml or length 2.5 cm) and this occurs between 9 and 14 yr (Fig. 4.2). This is followed by appearance of pubic hair and lengthening of the penis. Spermarche or the production of sperms starts during mid adolescence. Laryngeal growth, manifesting as cracking of voice, begins in boys in midpuberty under androgenic stimulus; deepening of voice is complete by the end of puberty. Mild degree of breast enlargement is normally seen in more than half of boys in early puberty which subsides spontaneously over several months. The onset of puberty is highly variable in both sexes.

Physical Growth and Nutritional Requirements

During puberty, boys gain about 20–30 cm and girls about 16–28 cm. Peak growth velocity in girls occurs before attainment of menarche (stage 3) in girls whereas boys have their peak growth velocity during later stages of puberty (stages 4–5). The growth spurt affects the distal skeleton first, hence enlargement of limb and extremities is followed by increase in trunk size.

During pubertal development there is increase in muscle mass and bone diameter, particularly in boys, and total bone mass in both the sexes. Lean body mass increases during the early stages in both the sexes; fat mass increases in girls at later stages of puberty. Rapid calcium accretion occurs during puberty. Almost 50% of adult bone mass is achieved during the adolescent period. Estrogen and androgen enhance calcium accretion by bone but favor early fusion of epiphyses. Increase in body structure is paralleled by increase in blood volume and muscle mass. With commencement of menstruation, nutritional requirements of iron are higher.

COGNITIVE AND SOCIAL DEVELOPMENT

Volumetric and functional imaging techniques show that the adolescent brain undergoes subtle structural changes and differential growth. Though the exact implications of these changes are largely unknown, these probably indicate the

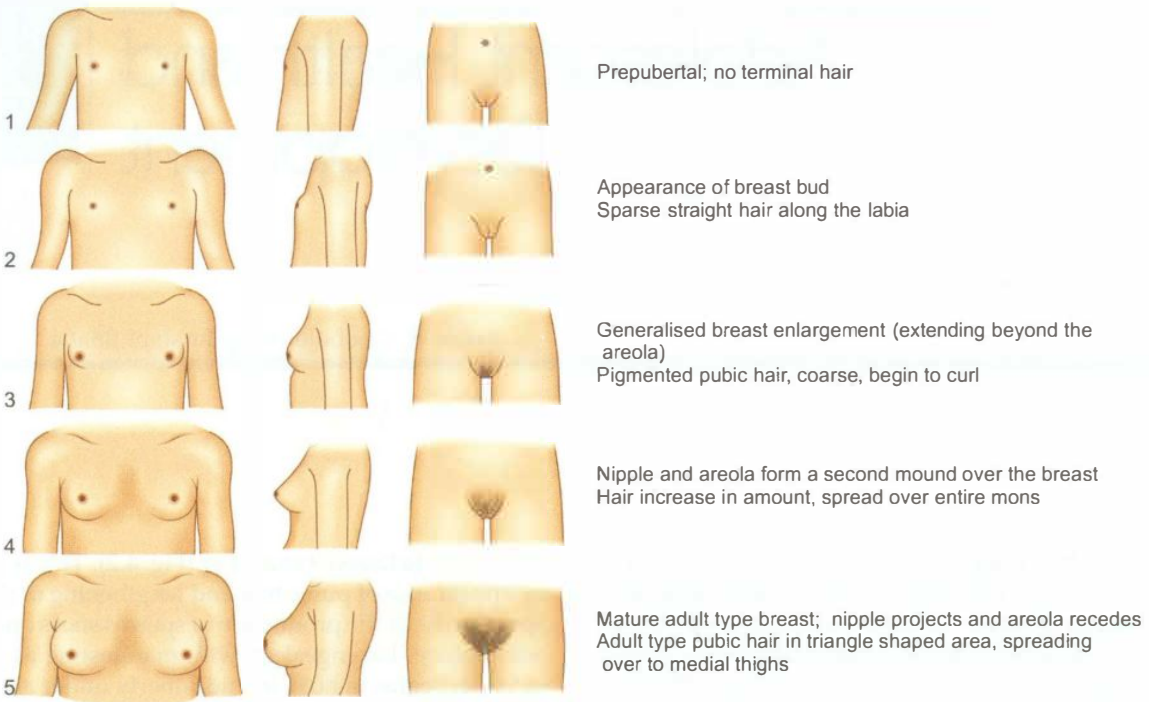


Fig. 4.1: Sexual maturity rating (1–5) in girls
(*Courtesy:* Anil Kumar, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow)

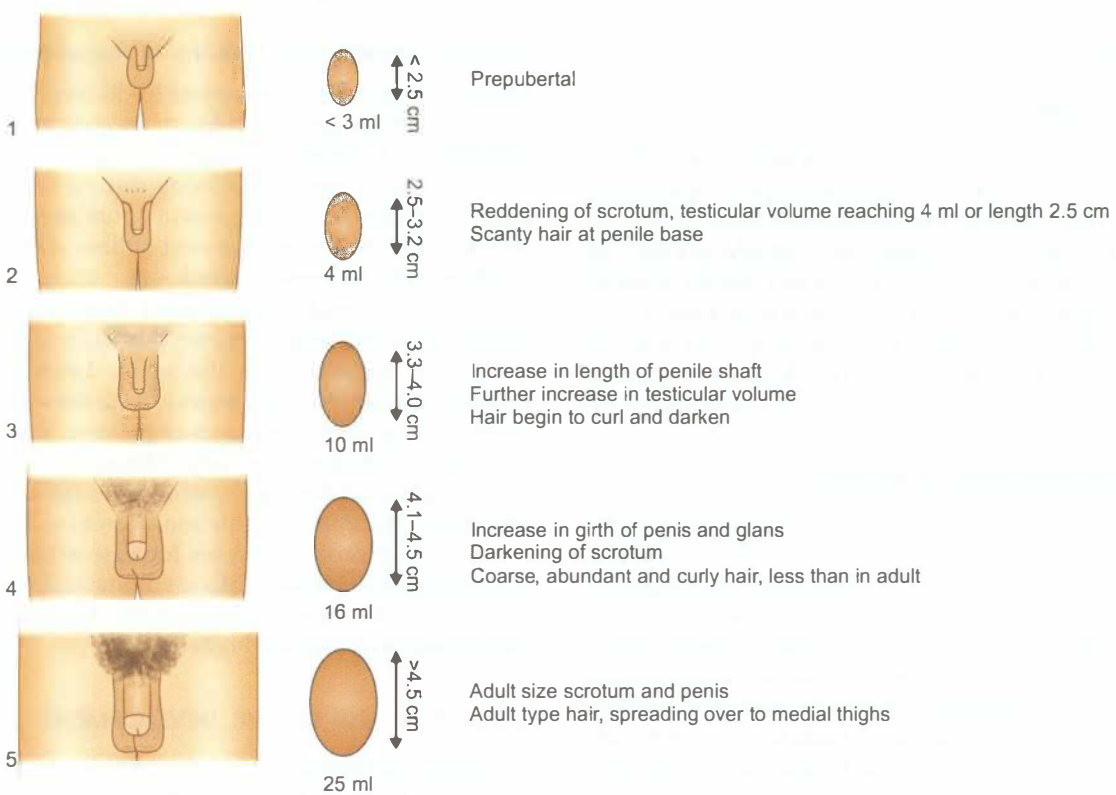


Fig. 4.2: Sexual maturity rating (1–5) in boys
(*Courtesy:* Anil Kumar, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow)

re-organizational or accommodating effort of brain paralleling the multifold increase in its functional capabilities.

Early phase. The 'concrete thinking model' of childhood persists into early adolescence, where the concepts are perceived more 'literally'. Teens are impulsive and have limited ability to perceive future implications of their current behavior. They prefer same sex peers. Many are excessively conscious of other people's concerns about their appearance and actions. Curiosity about sexual anatomy and comparison with peers is common during this stage.

Mid-phase. This phase is marked by emotional autonomy. The youth starts to think beyond self and there is beginning of abstract reasoning. They are now able to question and analyze. This is the time when they tend to have detachment from family. Acceptance by the peer group becomes very important. Sexual experimentation such as masturbation usually starts at this age.

Late phase. By this time, most of the pubertal changes are already achieved. Moral values and strong self identity are now established. They are now able to suppress impulsivity and are less affected by peer pressure. Personal relations become more important than the peer group. The youth becomes career oriented and starts short and longterm planning for his or her goals in life. Many start engaging in sexual activity.

Attitude Towards Health

Adolescents are often considered to be at the peak of their health; yet, adolescence coincides with the onset of many health disorders. High-risk behavior is common in mid-adolescent age group. The National Family Health Survey 3 (NFHS3) reported the median age of sexual debut in boys and girls to be 23 yr and 18 yr, respectively, but a significant proportion are sexually active much before that. Knowledge about contraception is improving among adolescents and most of them are aware of at least some method of contraception. Though awareness about HIV is increasing among Indian youth, most of them do not have comprehensive knowledge about it.

PROBLEMS FACED BY ADOLESCENTS

Adolescents are under immense pressure because of the rapid changes in their hormonal milieu, changing ideas and concepts about the world, having to cope up with the expectations from the society and the need to establish their own identity.

Health Problems

Nutrition or Eating disorders. There is increase in nutritional requirements during this period of rapid growth, micronutrients being as important as energy and protein (*see* Chapter 6). Data from the NFHS3 shows that 56% Indian adolescent girls are anemic and the prevalence of anemia remains unchanged over the last decade. There is lack of sun-exposure due to our modest tradition of clothing coupled with dark skin pigment. Insufficient intake of dairy products results in poor intake of calcium. The resulting low bone mineral density is more pronounced in underprivileged girls as they have low protein intake in addition to calcium and vitamin D deficiency. Vitamin A deficiency is also an important issue in economically deprived adolescents. Undernutrition often delays the onset of puberty and sexual maturation, and results in stunting, poor bone mass accrual and reduced work capacity. Anorexia nervosa and bulimia are being increasingly reported among urban Indian youth.

Mental health problems. Adjustment disorder, anxiety disorders, depression, suicide, delinquent behavior, poor body image and low self-esteem are the psychological problems faced by adolescents. Suicide rates are increasing in adolescents, with higher number of completed suicide in boys and attempted suicides in girls. Adolescents are at higher risk of committing suicide because of their cognitive immaturity and increased impulsivity.

Sleep disturbances. During the period of rapid growth, adolescents have increased sleep requirements. Many urban adolescents do not get enough sleep due to various reasons like increasing academic activity, parents working in shifts or watching television late into the night. Poor sleep habits and inadequate sleep are likely to reflect in school performance and cause daytime drowsiness, aggressive behavior, conduct disorders, anxiety, restless leg syndrome and depression. Sleep deprived teens often have periods of subconscious bouts of sleep or 'micro-sleeps' during the daytime, making them prone to injuries and accidents.

Infections. With increased outdoor activity, teens are exposed to TB, HIV, sexually transmitted infections, skin infections and parasitic infections. Early sexual activity is not uncommon in India. Various biological (immature and incompletely estrogenized mucosa) and psychosocial factors (lack of preparedness, lack of familiarity with barrier contraceptives) make an adolescent susceptible to these infections.

Genital infections and sexually transmitted infections. Vaginal discharge is common in adolescent girls and may signify physiological leucorrhea of puberty or endogenous or sexually transmitted infections. Gonorrhea can cause vulvovaginitis, urethritis or proctitis. Chlamydia can cause intermenstrual or postcoital bleeds. Both may be asymptomatic in the majority and can cause vaginal discharge. Candidal infections become common with starting of menstruation and often have a cyclic nature.

Pelvic inflammatory disease (PID) is a spectrum of inflammatory disorder of female genital tract. PID occurs commonly in sexually active young females and can present with abdominal pain with vaginal discharge. The

illness is difficult to treat with oral antibiotics and needs hospitalization and intravenous antibiotics (Table 4.1).

Lifestyle diseases. Obesity is the other end on the spectrum of malnutrition and is epidemic in the urban settings. Among Delhi school children, 5% obesity and 17–19% overweight has been reported; similar figures are available from other parts of urban India as well. The prevalence of obesity and overweight is higher in boys than girls. Obesity has strong association with asthma, sleep disorders, reflux disease, Blount disease, slipped femoral epiphysis, gallstones, fatty liver and numerous metabolic derangements like type 2 diabetes, dyslipidemia, hypertension and polycystic ovary disease. Essential hypertension is rising among Indian youth. There is a close relationship between obesity, hypertension and type 2 diabetes mellitus. Sedentary lifestyle, increased consumption of calorie dense food and decreased outdoor activity contribute to these disorders.

Problems specific to females. It is common to have anovulatory and irregular menstrual cycles during first two years after menarche. The polycystic ovary syndrome, with a combination of menstrual irregularities and ovarian cysts with androgen excess like acne or hirsutism, occurs in around 9% of Indian adolescent girls. The condition has association with other metabolic derangements like obesity, insulin resistance and type 2 diabetes.

Substance abuse. This is an issue in urban as well as rural India. Most of the tobacco and alcohol use starts during adolescence. The Global Youth Tobacco Survey 2009 showed that 14% of school youth reported using tobacco currently. Alcohol (21%), cannabis (3%) and opium (0.4%) are the most prevalent substance abuse other than tobacco in Indian youth. Addicts are more prone to accidents, injuries, violence, trading sex-for-drugs, HIV, hepatitis C, sexually transmitted diseases and tuberculosis.

Vulnerability

Abuse and violence (physical and sexual). Physical and sexual violence is common in India, with 20–30% young females suffering from domestic violence and 5–9% young females reporting sexual violence (NFHS3). Accidents are the major cause of mortality in this age group. Road traffic accidents, burns and poisoning are leading causes of traumatic mortality and disability in Indian youth. Motor vehicle and industrial accidents are common in boys whereas burns are commoner in girls.

Migration. Many adolescents migrate from rural to urban settings for labour or educational opportunities. Trafficking of youth is a serious problem in India and happens for industrial or domestic labour, forced marriages and prostitution. In states like Bihar, 70% of new HIV infections are related to outward male migration.

Table 4.1: Sexually transmitted infections: Salient features and treatment

Disease	*Salient features*	*Specific treatment*
Gonorrhea	Coinfection common	Ceftriaxone 125 mg IV or IM single dose
Chlamydia	Urethritis, vaginal discharge	Oral azithromycin 1 g single dose, or doxycycline 100 mg twice daily for 14 days
Herpes	Multiple painful vesicles and ulcers; tend to recur	Oral acyclovir 400 mg thrice daily for 7 days
Primary syphilis	Painless genital ulcer	Benzathine penicillin 2.4 MU IM (after test dose); oral doxycycline, if allergic to penicillin
Genital warts (papilloma virus)	Tend to recur	Local application of podophyllin weekly, cryotherapy or surgical removal; preventable with vaccination
Chancroid	Painful ulcer with lymphadenopathy	Oral azithromycin 1 g single dose or ciprofloxacin 500 mg twice daily for 3 days
Trichomoniasis	Malodorous yellow green discharge	Oral metronidazole or tinidazole 2 g single dose
Candidiasis	Itching, redness, white discharge	Clotrimazole cream or pessary for 7 days, miconazole pessary for 3 days or oral fluconazole 150 mg single dose
Pelvic inflammatory disease	Polymicrobial; varied disease spectrum	*Mild to moderate illness.* Oral cefixime 400 mg twice daily for 7 days, metronidazole 400 mg orally twice daily for 14 days and doxycycline 100 mg twice daily for 14 days; abstinence; symptomatic treatment *Severe disease or mild to moderate illness nonresponsive to above.* IV antibiotics
Pediculosis pubis	Pruritus	Local application of 1% permethrin, wash after 10 min
Scabies	Pruritus and rash	Local application of 5% permethrin or oral ivermectin 2 doses 14 days apart

All patients should be screened for HIV infection; partners should be treated if affected; IM intramuscular; IV intravenous

Adolescent pregnancy. Adolescent pregnancies are common in India, mainly because of early marriage. 22% of young Indian women have their first childbirth before 18 yr of age. Unmarried adolescents are likely to resort to unsafe methods of abortions, which increase the risk of complications like septicemia and also mortality. As compared to adult pregnancy, they are also at a higher risk for pre-eclampsia, preterm labor and postpartum hemorrhage. Prolonged and obstructed labor is common in adolescent pregnancies and young girls are two to four times more likely to die during childbirth as compared to adult pregnant females. Neonatal, infant and child mortality rates are higher in children delivered to adolescent mothers (NFHS3).

Lack of sex education. The majority of Indian youth do not get formal sex education in an effective way. Peers, books and magazines are their main sources of information about sex. Parents and teachers often fail to discuss issues like masturbation, safe sex, dating, abortion, HIV and sexually transmitted diseases.

Environmental and Social Challenges

Pollution. The incidence of asthma is increasing. There is ongoing research into the role of electromagnetic exposure from communication devices in disorders like childhood leukemia, brain tumors and immune dysregulation.

Media. With reduction in poverty and increased availability of electronic media, adolescents are exposed to information from all across the world. This exposure is often unsupervised because of working parents and increasing use of personal electronic gadgets. Due to inability to separate fact from fantasy, adolescents succumb to the glamorous portrayal of tobacco or alcohol consumption, unrealistic expectations, physical aggression, destructive behavior and unprotected sex. In urban areas, spending much of their spare time indoors on social networking sites, teenagers are actually deprived of sunlight and physical activity and are socially isolated.

Peer pressure. Peer formation is a part of adolescent social development. Pressure for conforming to norms drives many of their actions and decisions, including risk taking behavior and initiation of substance abuse.

Poverty. Adolescents belonging to poorer families are likely to have inadequate diets. Studies have shown that children belonging to poorer families had higher chances of having depression, antisocial behavior and engaging in drugs or sexual activity at earlier ages.

Illiteracy. Though the situation is improving over the years, still 33% of Indian youth are not able to complete their primary education. Female gender belonging to rural and poor background are risk factors for illiteracy.

Academic and emotional stress. Examinations cause significant physiological and psychological stress. Apart from rapid changes in their body structures, various other factors like peer acceptance, discrimination, academic burden, parental expectations, changing social environments cause stress among youth. Switching from vernacular to English medium schools, long hours of school and tuitions are additional stress factors that are unaddressed. While most adolescents have adequate coping skills, some may have serious adjustment problems resulting in various psychological and somatic effects.

Early marriage. Though the legal age for marriage in India is 18 yr for girls (Table 4.2), many states still have the practice of childhood and early marriage. Almost 30% of Indian girls between the ages of 15 and 19 yr are married; the proportions are higher in rural areas (Table 4.3).

Discrimination. Young people are often treated as second class citizens, under the control of adults and often not involved in any decision making. Adolescent girls are often asked to limit their outdoor or extracurricular activities and are involved in any decision making. Adolescent girls are often confined to their houses and expected to do the household work. Gender based discrimination is seen in education and even food distribution.

ROLE OF HEALTH CARE PROVIDER

A checklist for the Adolescent Clinic visit is provided in Table 4.4. During each visit, the following are important:

Table 4.2: Legal age definitions relevant to adolescence

Minimum age for marriage	Boys 21 yr; girls 18 yr
Responsibility for crime	12 yr
Juvenile criminal	12–18 yr
Compulsory free education	6–14 yr
Consumption of alcohol	Beyond 18–25 yr in different states (illegal in some states and union territories)
Employment in hazardous occupation or hotels	14 yr

Table 4.3: State of the World's Children: Adolescents in India

Adolescents (10–19 yr)	20% of population
Young people (10–24 yr)	33% of population
Girls currently married (age group 15–19 yr)	30%
Boys currently married (age group 15–19 yr)	5%
Age before 18 yr at first childbirth	22%
Net attendance in secondary school	54%
Youth literacy rates (15–24 yr)	88% boys; 74% girls
Knowledge about HIV	35% boys; 19% girls

Source: UNICEF, 2011

Table 4.4: Checklist for adolescent health visit

History from parents and adolescent	History of presenting problems Parental concerns on growth, development Academic success; school absenteeism Diet history including calcium, protein and iron intake; junk food Menstrual history; sleep problems
History on separate questioning of adolescent	Emotional problems; relationship with family and peers Outlook towards physical and sexual changes Involvement in relationship or sexual activity Awareness about safe sex and contraception Specific problems related to sex organs Tobacco or other substance use Counsel and clear doubts on sensitive topics
History on separate questioning of parents	Relationship with family Level of communication on sensitive matters
Physical examination	Anthropometry Blood pressure, markers of obesity, acanthosis Sexual maturity rating Signs of malnutrition, anemia and vitamin deficiencies Signs of skin and genital infections Level of general hygiene Signs of trauma; abuse Signs of drug abuse or tobacco use
Counseling	Nutritional intervention Hygienic practices Building rapport between parents and adolescent Providing information and sources on sex education
Investigations	Hemoglobin level Blood sugar, lipid profile Genital swabs Ultrasound of ovaries
Referrals	Counselor Dietitian Psychiatrist Gynecologist Voluntary and confidential HIV testing Social services, child protection agencies, support groups

Identifying risks. The physician needs to detect risk factors like obesity, hypertension, possible substance or drug abuse, behavioral and social problems and risky behavior. Subtle cues like sad or depressed mood, avoidance of eye contact, bruises or undue resistance to examination are the likely pointers towards physical or sexual abuse.

Establishing rapport. Being empathetic and nonjudgmental is the key to effective communication. Direct questioning of the adolescent is as important as questioning the parents. Beginning the interview with icebreakers, use of open ended nonsensitive questions and then moving to sensitive or targeted questions is helpful.

Confidentiality. One may need to interview a young patient separately, as he or she may not want to discuss sensitive topics in the presence of parents. While examining the genitalia, the doctor can ask patient's preference for presence of their parent inside the examination room. A boy may prefer his parents standing outside the exam room, whereas a girl may find it comforting if her mother accompanies her during the examination.

Consent. For a child who is less than 12 yr, consent for examination or medical or surgical procedure is obtained from the parent or guardian. While an adolescent aged 12–18 yr can give consent for examination, consent for medical or surgical procedure can be given only after 18 yr. This also includes consent for medical termination of pregnancy, blood and organ donation.

Nutritional intervention. Improving the nutritional status of an adolescent girl helps in two ways. It breaks the cycle of malnutrition and low birthweight babies and prevents the longterm complications of the latter in the future generation.

Providing health information. The adolescent health visit is an excellent opportunity to talk to the parents and their

adolescent about the pubertal changes. It is likely that they have not received any formal sex education in school and need to be provided correct educational resources for the same.

Adolescent immunization. India has low coverage for booster doses of TT at 10 and 16 yr. Papillomavirus vaccine is recommended for peripubertal girls (before initiation of sexual activity) for prevention of infection with human papillomavirus and cervical cancer. Parents need to be counseled thoroughly as the principle behind giving the vaccine might alarm them (Table 4.5).

Table 4.5: Immunization during adolescence

Vaccine	*Age; schedule*
Tetanus toxoid or Td	Booster at 10 and 16 yr
Measles, mumps, rubella	One dose; two doses 4–8 weeks apart if not given earlier
Typhoid	Vi polysaccharide vaccine; every 3 yr
Varicella	Two doses 8 weeks apart
Hepatitis B	Three doses at 0, 1 and 6 mo if not given earlier
Papillomavirus (adolescent girls, before sexual debut)	Three doses at (0, 1 and 6 mo) at 11–12 yr (may be given up to 26 yr)

Referral to social services, psychological evaluation and support. National Commission for Protection of Child Rights Act 2005 considers a person below 18 yr as a 'child'. It is mandatory for a health care provider to report all cases of child abuse (even suspected) to the Chairperson of the Commission; the complaint can be lodged online or in writing. Doctors are protected in case of erroneous reporting but punishable if they fail to report. Adolescents with special needs or victims of any kind of abuse need social and psychological support.

Adolescent friendly health services. Adolescents have diverse problems and special needs. The services include provision of reproductive health services, nutritional counseling, sex education and life skill education. Confidentiality, easy accessibility, friendly attitude and quick comprehensive health care delivery have made a positive impact on adolescent clients. Adolescent friendly clinics are functional at many centers in the country.

Management of sexual violence. This includes the following measures:

i. Forensic examination and collection of blood or body fluid samples by trained staff
ii. Care of the injuries
iii. *Prophylaxis against pregnancy:* Two doses of levonorgestrel 12 hr apart, first dose being given within 72 hr of intercourse
iv. Prophylaxis against sexually transmitted infections includes a single oral dose of azithromycin 1 g along with cefixime 400 mg and metronidazole or tinidazole 2 g. These protect against syphilis, gonorrhea, *Chlamydia* and *Trichomonas*.
v. Hepatitis B vaccination is recommended if the person is not previously immunized.
vi. Prophylaxis against HIV requires referral to the nearest integrated counseling and testing centre.
vii. Psychological support includes counseling and referral to a psychiatrist. Informing concerned authorities or social services is important as patient may need shelter and legal help. A teen may not be willing to disclose this assault to his parents. Childline (1098) is a support service provided by Government of India focussed on child care and protection.

Contraception. A pediatrician should strongly advocate for abstinence and delayed initiation of sex to adolescent patients. In case the adolescent is already sexually active, condom seems a better choice compared to other methods. Condom use is recommended in addition, even if any other method is being used, for additional protection against sexually transmitted infections. Adolescents with disabilities or mental retardation are wrongly assumed to be at low risk for STIs and pregnancy. Parents of such children need to be counseled regarding these issues. School based effective sex education is need of the hour in India.

Transition to adult care. With better medical care, a large number of chronically ill or disabled children are surviving into adulthood. As the problems of these children are diverse, they need multidisciplinary care even in their adulthood. Transition to adult care is not mere transfer of the case to a different physician. It is a gradual and planned process; keeping in mind the abilities of the child to participate in self-care, taking responsibilities and decision making. The age at transfer is not fixed; a window of age 14–18 yr is used in some countries for a gradual transfer.

Suggested Reading

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5 Fluid and Electrolyte Disturbances

Kamran Afzal

COMPOSITION OF BODY FLUIDS

The major component of body mass is water. The contribution of total body water to body weight varies with age, lean body weight and adiposity. Total body water (TBW) as a percentage of body weight declines from as high as 90% in early fetal life to nearly 75–80% at the time of birth. Thereafter it declines progressively to 60% by the end of the first year and remains so till puberty. Since adipose tissue has lower water content, therefore, adolescent females and overweight children have lower TBW as a percentage of body weight.

Total body water is distributed in two major compartments, two-thirds is intracellular fluid (ICF) and one-third is extracellular fluid (ECF). Nearly one-fourth of ECF is distributed in the intravascular space (plasma water) and the remaining in the extravascular (interstitial) space (Fig. 5.1). The relative size of the two main compartments varies with age. Increase in extracellular fluid volume contributes to the increased TBW in neonates, especially preterm babies.

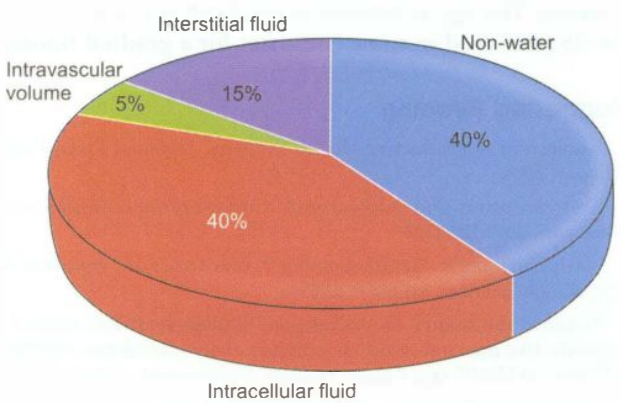

Fig. 5.1: Body composition. Nearly 60% of the body weight is water. Of this two-thirds is intracellular, while the rest is extracellular (ECF), which is distributed between the interstitial and intravascular compartment in 3:1 ratio

The interstitial fluid component of extracellular fluid is actually a matrix, a collagen/gel substance that allows the interstitium to provide structural rigidity during extracellular volume depletion. The interstitial space, especially in skin and connective tissue, is an important reservoir of extracellular fluid. The balance and appropriate distribution of fluid within these spaces is maintained by the colloid oncotic pressure, membrane permeability and hydrostatic pressure.

Water Balance

In the steady state, water balance represents the difference between water intake (including that generated from endogenous metabolism) and water losses (Fig. 5.2). Much of the water output involves obligatory losses in the urine, stool and, by evaporation from the moist surfaces of the skin and respiratory tract (insensible losses). The kidneys are the major regulators of water output with nearly two-thirds of daily water losses being urine. The obligatory renal water loss is directly related to solute excretion. The evaporative losses play an important role in thermoregulation. In contrast to these insensible losses, sweat which is hypotonic (Na^+ concentration 35 to 65 mEq/l) is actually 'sensible loss'. It also contributes to thermoregulation and may reflect the majority of total daily loss of water in presence of high ambient temperatures or when endogenous heat production is enhanced, as with exercise or fever.

The effectors for volume regulation are primarily renin-angiotensin-aldosterone system and atrial natriuretic peptide, both of which affect Na^+ excretion. Besides this regulation of body water is made possible by interplay of multiple other factors, including vasopressin, prostaglandins, dopaminergic receptors, α-adrenergic receptors, thirst mechanism and intrinsic renal properties.

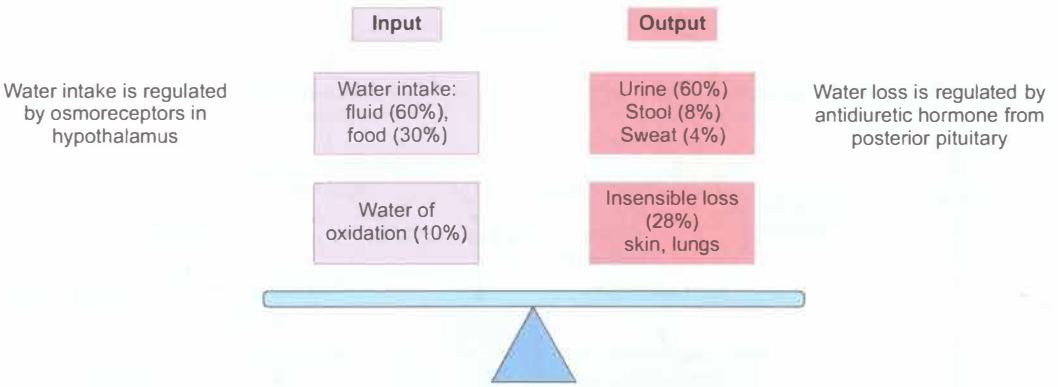

Fig. 5.2: Balance of water intake and losses maintain normal plasma osmolality. Only water intake and urinary losses can be regulated

Electrolyte Composition of Body Compartments

The extracellular fluid compartment contains high concentrations of sodium, chloride, and bicarbonate (Fig. 5.3). Potassium, organic phosphates and proteins are the predominant ICF osmoles. Because of variability in ECF and ICF distribution, the serum concentrations do not necessarily reflect the total body content of a particular electrolyte. Permeability to ions varies in each organ with the brain having the least and the liver the most permeability. However, water readily crosses cell membranes to achieve an osmotic equilibrium between the two compartments.

Osmolality

Osmolality (expressed as milliosmoles per kilogram of water, mOsm/kg) is the solute concentration of a fluid. Plasma and interstitial fluid are rich in proteins, which determine plasma colloid oncotic pressure. Changes in osmolality can produce grave neurologic consequences and even death, primarily due to water movement into and out of the brain. To prevent this, the plasma osmolality, which is primarily determined by the plasma Na^+ concentration, is normally maintained closely between 1 to 2% of the normal (285 to 295 mOsm/kg) by appropriate variations in water intake and water excretion. This regulatory system is governed by different osmo-receptors in the hypothalamus that influence both thirst and the secretion of antidiuretic hormone (ADH) (Fig. 5.4). Plasma osmolality can be measured directly using osmometers, as well as estimated indirectly as follows:

$$\text{Plasma osmolality} = 2[Na^+] + \frac{\text{glucose}}{18} + \frac{\text{blood urea nitrogen}}{2.8}$$

Measured values are generally higher than calculated values by up to 10 mOsm/kg. Increase in osmolal gap may occur due to increase in unmeasured osmoles.

Normal Maintenance Fluid and Electrolyte Requirements

The normal maintenance water requirement is equal to the insensible and urinary water losses. Holliday and Segar guidelines (1957), calculate maintenance fluid volumes to match electrolyte free water requirements from estimates of water of evaporation (heat dissipation) and caloric expenditure (heat production). They estimate a

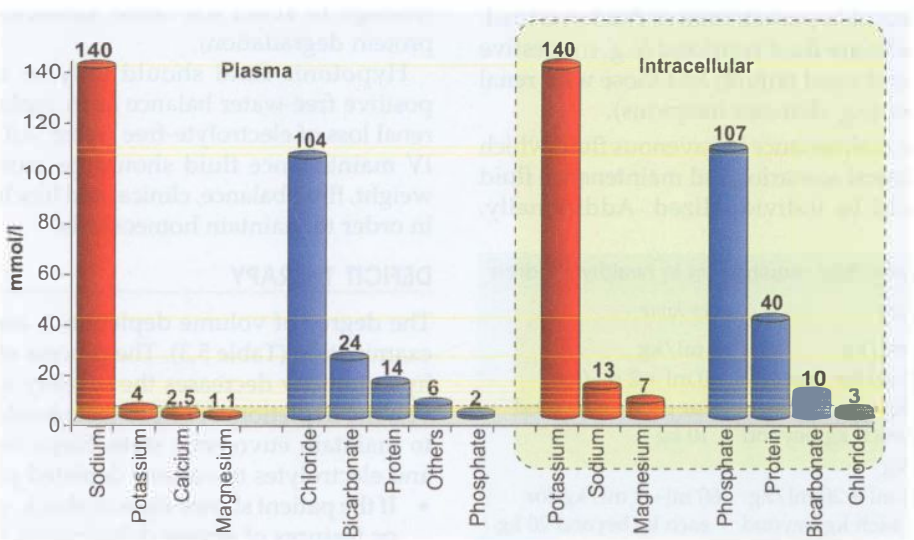

Fig. 5.3. Electrolyte composition of intracellular and extracellular fluid compartments

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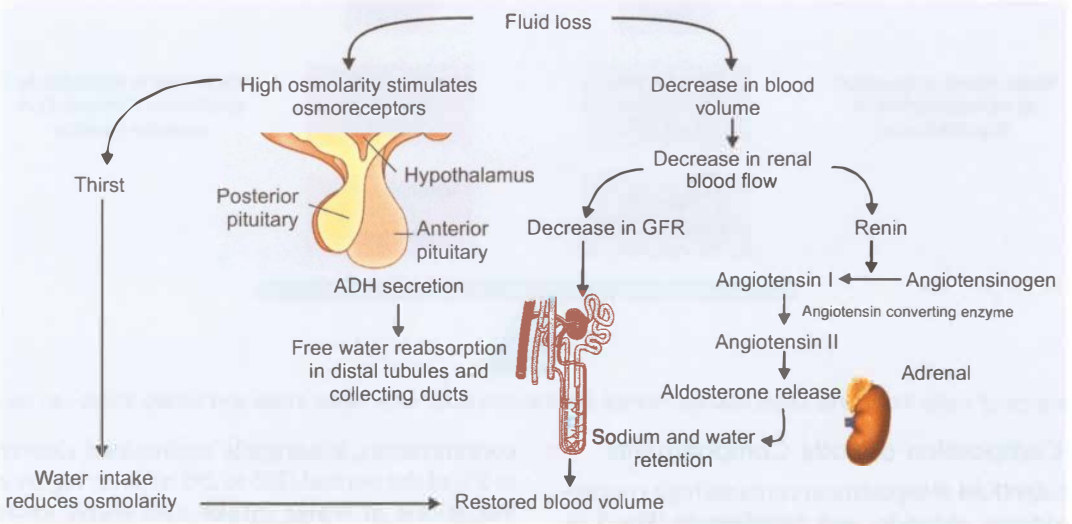

Fig. 5.4. Regulation of sodium and water balance

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daily sodium requirement of 3 mEq/kg, potassium and chloride 2 mEq/kg each and daily glucose requirement as 5 g/kg based on the electrolyte composition of human and cow milk and recommended 30 mEq/l sodium chloride (saline) for maintenance fluid in children. These requirements translate to use of a hypotonic saline solution for maintenance fluids, equivalent to 0.2% saline in 5% dextrose in water and form the basis for the use of hypotonic fluids traditionally used in children. The guidelines for maintenance volume (Table 5.1) assume average calorie expenditure in a healthy child. Fluid requirements change considerably in different clinical conditions (Table 5.2).

However, there is considerable evidence that use of hypotonic fluids in sick hospitalized patients increases the risk of hyponatremia several fold. Normal saline (0.9%) can be safely administered in standard maintenance volume without risks of hypernatremia or fluid overload, except in patients who are fluid restricted (e.g. congestive heart failure, liver and renal failure) and those with renal concentrating defect (e.g. diabetes insipidus).

There is no single maintenance intravenous fluid which is suitable for all clinical scenarios and maintenance fluid prescriptions should be individualized. Additionally, maintenance IV fluids do not replace daily nutrient requirements and provide only 20% of daily calories (enough to avoid starvation ketoacidosis and diminish protein degradation).

Hypotonic fluid should only be used to achieve a positive free-water balance as in replacing renal or non-renal loss of electrolyte-free water. All children receiving IV maintenance fluid should be monitored with daily weight, fluid balance, clinical and biochemical parameters in order to maintain homeostasis.

Table 5.1: Maintenance fluid requirement in healthy children

Body weight	*Per day*	*Per hour*
0–10 kg	100 ml/kg	4 ml/kg
10–20 kg	1000 ml for first 10 kg + 50 ml/kg for each kg beyond 10 kg	40 ml + 2 ml/kg for each kg beyond 10 kg
>20 kg	1500 ml + 20 ml/kg for each kg beyond 20 kg	60 ml+ 1 ml/kg for each kg beyond 20 kg

Table 5.2: Conditions that alter maintenance fluid needs

Increased fluid requirement	*Decreased fluid requirement*
Fever (10–15% per °C above 38°C)	Oliguria or anuria
Radiant warmer, phototherapy	Humidified ventilator or incubator
Burns, sweating	Hypothyroidism
Physical activity; hyperventilation	
Diarrhea, vomiting	
Polyuria, renal concentrating defects	
Very low birth weight babies (large surface area)	

DEFICIT THERAPY

The degree of volume depletion is assessed by physical examination (Table 5.3). The process of hypernatremia or hypertonicity decreases the severity of physical signs of volume depletion. All fluid lost should be replaced daily to maintain euvolemic state. Steps for providing fluids and electrolytes to volume depleted patients are:

- If the patient shows signs of shock, compensated shock or features of severe dehydration (Table 5.3), rapidly infuse isotonic fluids to restore intravascular volume.

Table 5.3: Clinical assessment of dehydration

	No dehydration	*Some dehydration*	*Severe dehydration*
Decrease in body weight	<5% in infants; <3% in older children	5–10% in infants; 3–6% in older children	>10% in infants; >6% in older children
Mental status	Normal	Irritable	Lethargic to comatose
Thirst	Normal	Increased	Unable to drink
Skin color and elasticity (turgor)	Normal	Cool, pale; mild delay in turgor	Cold, mottled; tenting
Sunken eyes	Normal	Sunken	Very sunken
Mucous membrane	Normal	Dry	Very dry
Pulse rate	Normal	Slightly increased	Tachycardia
Capillary refill	2–3 sec	3–4 sec	>4 sec
Blood pressure	Normal	Normal	Normal or low
Urine output	Slightly decreased	Decreased	Oliguria, anuria

This is done by infusing 1 to 3 fluid boluses of isotonic saline or Ringer lactate, 20 ml/kg body weight.

- Provide fluids to replace calculated/observed volume deficit. This is calculated as volume at the rate of 10 ml for each percentage weight loss. For example, in patients with moderate (some) dehydration, which is on an average 7.5% weight loss, the replacement volume is 75 ml/kg body weight. If the pre-dehydration weight is known the volume of fluid needed is 1 litre for every kg of weight loss.
- Provide fluid and electrolytes to replace the amounts lost in normal daily metabolism (maintenance fluids).
- Provide enough fluid to replace ongoing losses of various body fluids (Table 5.4).

Table 5.4: Electrolyte composition of body fluids

Losses	*Na^+ (mEq/l)*	*K^+ (mEq/l)*	*Cl^- (mEq/l)*	*HCO_3^- (mEq/l)*
Gastric	60–100	5–20	90–130	0
Small intestine	80–140	5–15	90–140	40
Colon	60	30	40	15
Pancreas	135–145	5–10	70–90	95–120
Diarrhea	10–90	10–80	90–130	40

SODIUM

Physiology

Sodium is the most abundant ion of the extracellular fluid compartment and is critical in determining extracellular and intracellular osmolality. Normal serum sodium concentration varies between 135 and 145 mEq/l. Extracellular sodium balance is determined by sodium intake relative to sodium excretion. Daily sodium requirement is 2 to 3 mEq/kg body weight although intakes are generally well in excess. The requirement varies with age. It is nearly two- to three-folds higher in term and very low birthweight preterm babies, a reflection of immaturity of renal tubular function and higher requirements for growth. Adult requirements decrease to 1.5 mEq/kg/d. Urinary sodium excretion represents the majority of sodium losses and approximately equals the daily intake of sodium. Fractional excretion of sodium is generally less than 1% of filtered load. Extrarenal sodium losses can be significant *via* profuse sweating, burns, severe vomiting or diarrhea.

A fall in blood pressure, decrease in sodium delivery to the macula densa, or sympathetic stimulation may activate the renin-angiotensin axis, generating angiotensin II. This results in increase in blood pressure and sodium retention caused by enhanced aldosterone secretion. The effective circulating volume refers to that part of the extracellular fluid that is in the arterial system and is effectively perfusing the tissues. The effective circulating volume usually varies directly with the extracellular fluid volume, and both are proportional to total body Na^+ stores. As a result, the regulation of Na^+ balance (by alteration in its urinary excretion) and maintenance of effective circulating volume are closely related. Sodium loading tends to produce volume expansion, whereas loss leads to volume depletion.

Hyponatremia

Hyponatremia, defined as plasma sodium less than 135 mEq/l, can result from excessive loss of sodium from excessive sweating, vomiting, diarrhea, burns and the administration of diuretics (Table 5.5). The most common cause of hyponatremia, however, is not a deficiency of total body sodium, but an excess of total body water, as in the syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

SIADH is seen in association with pulmonary and cranial disorders and postoperatively. High levels of vasopressin or antidiuretic hormone (ADH) are secreted at a low threshold or continuously despite low osmolality. The presence of hyponatremia plus a urine osmolality higher than maximal dilution confirms the diagnosis. SIADH should be differentiated from cerebral salt wasting which is also associated with central nervous system disorders. In the latter there is hypovolemic hyponatremia and high urinary sodium (>80 mEq/l) due to increase in blood levels of natriuretic factor(s). SIADH is characterized by euvolemia or mild volume expansion, relatively low

Table 5.5: Causes of hyponatremia

Hypovolemic hyponatremia (sodium loss in excess of free water)	*Renal loss:* Diuretic use, osmotic diuresis, renal salt-wasting, adrenal insufficiency, pseudohypoaldosteronism
	Extra-renal loss: Diarrhea, vomiting, drains, fistula sweat (cystic fibrosis), cerebral salt wasting syndrome, third-spacing (effusions, ascites)
Normovolemic hyponatremia (conditions that predispose to SIADH)	Inflammatory central nervous system disease (meningitis, encephalitis), tumors
	Pulmonary diseases (severe asthma, pneumonia)
	Drugs (cyclophosphamide, vincristine)
	Nausea, postoperative
Hypervolemic hyponatremia (excess free water retention)	Congestive heart failure, cirrhosis, nephrotic syndrome, acute or chronic renal failure

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urine output and high urine sodium. The treatments are different, as cerebral salt wasting requires replacement of urinary salt-water losses while SIADH is managed by fluid restriction.

Hyperosmolality resulting from non-sodium molecules (hyperglycemia, mannitol overdose) draws water from the intracellular space to dilute the extracellular sodium concentration. Factitious hyponatremia, reported when hyperlipidemia (chylomicronemia) or hyperproteinemia coexist, is uncommon due to use of ion-selective electrodes.

Patients are generally symptomatic when serum sodium concentration falls below 125 mEq/l or the decline is acute (<24 hr). Early features include headache, nausea, vomiting, lethargy and confusion. Advanced manifestations are seizures, coma, decorticate posturing, dilated pupils, anisocoria, papilledema, cardiac arrhythmias, myocardial ischemia and central diabetes insipidus. Cerebral edema occurs at levels of 125 mEq/l or less.

Hypo-osmolality causes influx of water into the intracellular space, which results in cytotoxic cerebral edema and increased intracranial pressure and can lead to brain ischemia, herniation and death. The brain's primary mechanism in adapting to hyponatremia is the extrusion of intracellular electrolytes and organic osmolytes. Some of these organic osmolytes are excitatory amino acids, such as glutamate and aspartate that can produce seizures in the absence of detectable cerebral edema. Major risk factors for developing hyponatremic encephalopathy are young age, hypoxemia and neurological disease. Children are at significantly higher risk than are adults for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio compared with adults. Hyponatremia in association with increased intravascular volume can result in pulmonary edema, hypertension and heart failure. Asymptomatic hyponatremia in preterm neonates is associated with poor growth and development, sensorineural hearing loss and a risk factor for mortality in neonates who suffered perinatal birth asphyxia.

Treatment

The first step is to determine whether hyponatremia is acute (<48 hr) or chronic (>48 hr), symptomatic or asymptomatic and evaluate the volume status (hypervolemic, euvolemic, hypovolemic) (Box 5.1). The underlying cause should be corrected, where possible. Losses due to renal or adrenocortical disease are suggested by urinary sodium concentration of more than 20 mEq/l in presence of clinically evident volume depletion (Fig. 5.5).

In case of hypovolemic hyponatremia the fluid and sodium deficit is estimated and replaced over 24 to 48 hr. The dose of sodium required is calculated using the formula:

Sodium deficit (mEq) =
0.6 × body wt (kg) × [(desired Na^+) – (observed Na^+)] mEq/l

The optimal rate of correction is 0.6 to 1 mEq/l/hr until the sodium concentration is 125 mEq/l and then at a

Box 5.1: Treatment of hyponatremia

- Treat hypotension first, regardless of serum sodium (normal saline bolus, Ringer lactate, 5% albumin). WHO oral rehydration solution is preferable for asymptomatic cases with hypovolemia
- Correct deficit over 48 to 72 hr for chronic hyponatremia. Rapid decline is associated with risk of central pontine myelinosis. Recommended rate of increase is 0.5 mEq/l/hr (8–10 mEq/l/day). Correction in the first 48 hr should not exceed 15–20 mEq/l
- Acute and symptomatic hyponatremia may be corrected rapidly. For symptomatic cases, immediate increase in serum sodium level by 5–6 mEq/l with hypertonic saline (3% saline) is recommended. IV infusion at a dose of 3–5 ml/kg over 1–2 hr will raise serum sodium by 5–6 mEq/l. Alternatively, 3% saline may be given as 1–3 boluses at 2 ml/kg/bolus over 10 min (maximum 100 ml/bolus)
- Stop further therapy with 3% saline when patient is either symptom free and/or acute rise in sodium of 10 mEq/l is noted in first 5 hr.
- Increase of serum Na^+ can be estimated using Adrogue Madias formula (Box 5.2)
- Hypotonic infusates (0.45% dextrose normal saline) are used as maintenance fluid. Normal saline should be avoided except for correction of hypovolemia; can aggravate cerebral edema in those with impaired free water clearance.
- Fluid restriction alone is needed for SIADH; sodium and water restriction is required in hypervolemic hyponatremia. Diuretics may be added in refractory cases.

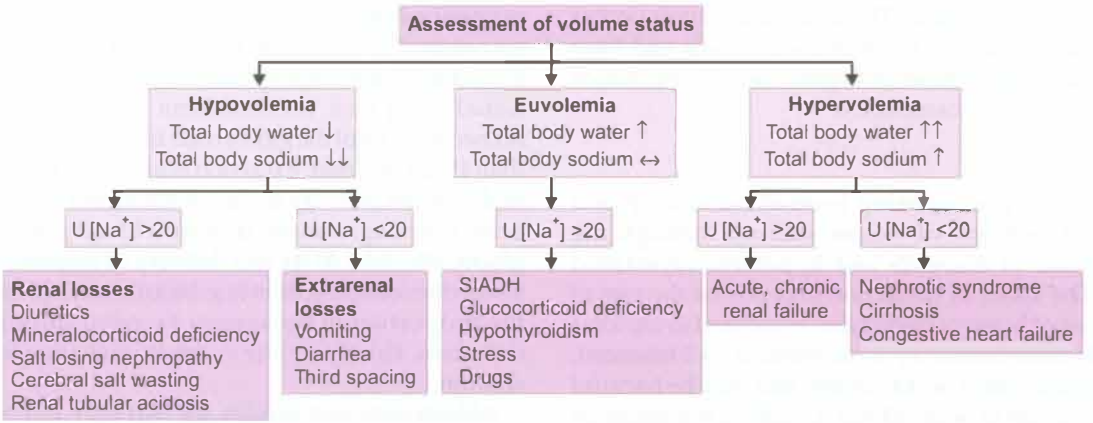

Fig. 5.5: Diagnostic approach to hyponatremia. U(Na+) urinary sodium, mEq/l; ↑ increased; ↓decreased

slower rate. For symptomatic patients a combination of intravenous infusion of hypertonic saline (3% sodium chloride) and fluid restriction rapidly increase serum sodium by 5–6 mEq/l and ameliorates the symptoms. Thereafter, if the symptoms remit, the remaining deficit can be corrected slowly over the next 1 to 3 days. When slow correction of hyponatremia in a volume-expanded patient is indicated, water restriction alone, or if this is unsuccessful, in combination with a loop-diuretic such as furosemide is preferred. Serum sodium concentration should be monitored every 2 to 4 hr and appropriate adjustments made.

Aggressive therapy with hypertonic saline in patients with chronic hyponatremia (where brain adaptation to hypo-osmolality has set in by extrusion of intracellular electrolytes and organic osmoles) can lead to osmotic demyelination called central pontine myelinolysis. This condition, which is often irreversible is reported in patients with liver disease, severe malnutrition and hypoxia. Patients generally become symptomatic 2 to 7 days following rapid correction (>25 mEq/l in the first 24–48 hr) of chronic hyponatremia. Clinical features include mutism, dysarthria, spastic quadriplegia, ataxia, pseudobulbar palsy, altered mental status, seizures and hypotension.

Fluid restriction alone has no role in the management of symptomatic hyponatremia. Normal saline is also inappropriate for treating hyponatremic encephalopathy due to non-hemodynamic states of vasopressin excess, such as SIADH and postoperative hyponatremia, as it is not sufficiently hypertonic to induce reduction in cerebral edema. In presence of elevated ADH levels there is impaired ability to excrete free water with the urine osmolality exceeding that of plasma. V2–receptor antagonists or vaptans that block the binding of ADH to its V2 receptor, are yet not recommended for treatment of hyponatremic encephalopathy. These agents may have a role in treating euvolemic hyponatremia from SIADH and hypervolemic hyponatremia in congestive heart failure.

Hypernatremia

Hypernatremia is defined as increase in serum sodium concentration to levels more than 150 mEq/l. It may be accompanied by the presence of low, normal or high total body sodium content. The major cause of hypernatremia is loss of body water, inadequate intake of water, a lack of antidiuretic hormone (ADH), or excessive intake of sodium (e.g. solutions with high sodium such as sodium bicarbonate) (Table 5.6). Diabetes insipidus may result from a deficiency of ADH or its end organ unresponsiveness.

In the presence of an intact thirst mechanism, a slight increase in serum sodium concentration (3 to 4 mEq/l) above normal elicits intense thirst. The lack of thirst in the presence of hypernatremia in a mentally alert child indicates a defect in either the osmoreceptors or the cortical thirst center. The most objective sign of hypernatremia is lethargy or mental status changes, which proceeds to coma and convulsions. With acute and severe hypernatremia, the osmotic shift of water from neurons leads to shrinkage of the brain and tearing of the meningeal vessels and intracranial hemorrhage; slowly developing hypernatremia

Table 5.6: Causes of hypernatremia

Net water loss
Pure water loss
Insensible losses
Diabetes insipidus
Inadequate breastfeeding
Hypotonic fluid loss
Renal: Loop, osmotic diuretics, postobstructive, polyuric phase of acute tubular necrosis
Gastrointestinal: Vomiting, nasogastric drainage, diarrhea; lactulose
Hypertonic sodium gain
Excess sodium intake
Sodium bicarbonate, saline infusion
Hypertonic feeds, boiled skimmed milk
Ingestion of sodium chloride
Hypertonic dialysis
Endocrine: Primary hyperaldosteronism, Cushing syndrome

is generally well tolerated. The latter adaptation occurs initially by movement of electrolytes into cells and later by intracellular generation of organic osmolytes, which counter plasma hyperosmolarity.

Treatment

Treatment involves restoring normal osmolality and volume and removal of excess sodium through the administration of diuretics and hypotonic crystalloid solutions. The speed of correction depends on the rate of development of hypernatremia and associated symptoms (Box 5.2). Because chronic hypernatremia is well tolerated, rapid correction offers no advantage and may be harmful since it may result in brain edema. Usually a maximum of 10% of the serum sodium concentration or about 0.5 mEq/l/hr should be the goal rate of correction. Seizures due to hypernatremia are treated using 5–6 ml/kg infusion of 3% saline over 1–2 hr.

POTASSIUM

5

Physiology

Potassium being a predominantly intracellular cation, its blood levels are unsatisfactory indicator of total body stores. Normal serum concentration of potassium ranges between 3.5 and 5 mEq/l. Common potassium-rich foods include meats, beans, fruits and potatoes. Gastrointestinal absorption is complete and potassium homeostasis is maintained predominantly through the regulation of renal excretion. The fractional excretion of potassium is about 10%, chiefly regulated by aldosterone at the collecting duct. Renal adaptive mechanisms maintain potassium homeostasis until the glomerular filtration rate drops to less than 15–20 ml/min. Excretion is increased by aldosterone, high sodium delivery to the collecting duct (e.g. diuretics), urine flow (e.g. osmotic diuresis), blood potassium level, glucocorticoids, ADH and delivery of negatively charged ions to the collecting duct (e.g. bicarbonate). In renal failure, the proportion of potassium excreted through the gut increases, chiefly by the colon in exchange for luminal sodium.

Aldosterone and insulin are two play important roles in potassium homeostasis. Insulin stimulated by potassium ingestion increases uptake of potassium in muscle cells, through increased activity of the sodium pump. High potassium levels stimulate its renal secretion *via* aldosterone-mediated enhancement of distal expression of secretory potassium channels (ROMK). Insulin, beta-adrenergic stimuli and alkalosis enhance potassium entry into cells. The reverse happens with glucagon, α-adrenergic stimuli and acidosis.

Hypokalemia

Hypokalemia is defined as a serum potassium level below 3.5 mEq/l. The primary pathogenetic mechanisms resulting in hypokalemia include increased losses, decreased intake or transcellular shift (Table 5.7). Vomiting, a

Box 5.2: Treatment of hypernatremia

- Treat hypotension first, regardless of serum sodium (normal saline bolus, Ringer lactate, 5% albumin)
- Correct deficit over 48 to 72 hr. Rapid decline of chronic (>48 hr) hypernatremia is associated with risk of cerebral edema. Recommended rate of drop in serum sodium is 0.5 mEq/l/hr (10–12 mEq/l/day)
- Oral solutions preferred to parenteral correction
- Generally hypotonic infusates are used (infusate sodium of ~ 40 mEq/l, as N/4 or N/5 saline). Sodium free fluids should be avoided (except in acute onset hypernatremia, e.g. sodium overload)
- Decline of serum Na^+ can be estimated using Adrogue-Madias Formula:

$$D[Na^+] = \frac{\{[Na^+]_{inf} + [K^+]_{inf} - [Na^+]_s\}}{(TBW + 1)}$$

Where $\Delta[Na^+]$ expected change in serum sodium; $[Na^+]_{inf}$ sodium and $[K^+]_{inf}$ potassium in 1 liter of the infusate, $[Na^+]_s$ serum sodium; TBW or total body water = 0.6 × body weight

- Seizures due to hypernatremia are treated using hypertonic (3%) saline at 5–6 ml/kg infusion over 1–2 hr.
- Renal replacement therapy (peritoneal or hemodialysis, hemofiltration) is indicated for significant hypernatremia (>180–200 mEq/l) with concurrent renal failure and/or volume overload.
- Ensure correction of ongoing fluid losses; frequent biochemical and clinical reassessment is needed.

Table 5.7: Causes of hypokalemia

Increased losses
Renal
Renal tubular acidosis (proximal or distal)
Drugs (loop and thiazide diuretics, amphotericin B, aminoglycosides, corticosteroids)
Cystic fibrosis
Gitelman syndrome, Bartter syndrome, Liddle syndrome
Ureterosigmoidostomy
Mineralocorticoid excess (Cushing syndrome, hyperaldosteronism, congenital adrenal hyperplasia (11 β-hydroxylase, 17 α-hydroxylase deficiency)
High renin conditions (renin secreting tumors, renal artery stenosis)
Extrarenal
Diarrhea, vomiting, nasogastric suction, sweating
Potassium binding resins (sodium polystyrene sulfonate)
Decreased intake or stores
Malnutrition, anorexia nervosa
Potassium-poor parenteral nutrition
Intracellular shift
Alkalosis, high insulin state, medications (β_2-adrenergic agonists, theophylline, barium, hydroxychloroquine), refeeding syndrome, hypokalemic periodic paralysis, malignant hyperthermia, thyrotoxic periodic paralysis

common cause of hypokalemia, produces volume depletion and metabolic alkalosis. Volume depletion leads to secondary hyperaldosteronism, which enhances sodium resorption and potassium secretion in the cortical collecting tubules. Metabolic alkalosis also increases potassium secretion due to the decreased availability of hydrogen ions for secretion in response to sodium resorption.

Regardless of the cause, hypokalemia produces similar signs and symptoms. Symptoms are nonspecific and predominantly are related to muscular or cardiac function. Severe hypokalemia (<2.5 mEq/l) may cause muscle weakness (neck flop, abdominal distension, ileus) and produce cardiac arrhythmias. Chronic hypokalemia is associated with interstitial renal disease of uncertain pathogenesis. Hypokalemia increases the risk of digoxin toxicity by promoting its binding to myocytes, potentiating its action and decreasing clearance.

The transtubular potassium gradient (TTKG) accounts for the confounding effect of urine concentration on interpretation of urine potassium excretion.

$$\text{TTKG} = \frac{(\text{urine potassium} \times \text{serum osmolality})}{(\text{serum potassium} \times \text{urine osmolality})}$$

This test cannot be applied when the urine osmolality is less than the serum osmolality. TTKG less than 4 suggests that the kidney is not wasting excessive potassium, while a value greater than or equal to 4 indicates significant renal loss.

Treatment

Patients should be evaluated to determine the underlying causes and determine whether it is associated with hypertension and acidosis or alkalosis (Fig. 5.6). Hypertension may be a clue to primary hyperaldosteronism, renal artery stenosis, or the rarer forms of genetically inherited hypertension such as congenital adrenal hyperplasia, glucocorticoid remediable hypertension or Liddle syndrome. Relative hypotension and alkalosis suggests diuretic use, or a tubular disorder such as Bartter or Gitelman syndrome.

Therapy involves decreasing ongoing losses (e.g. discontinuation of diuretics, α_2-agonists), replenishing potassium stores (oral or intravenous administration of potassium chloride) and disease-specific therapy for the conditions such as Bartter and Gitelman syndrome (e.g. indomethacin, angiotensin-converting enzyme inhibitors) (Box 5.3). Potassium is generally replaced orally at a dose of 2–4 mEq/kg/day in 3 or 4 divided doses. Intravenous

Box 5.3: Treatment of hypokalemia

- Deficit is corrected over 24 hr
- Identify and stop ongoing losses of potassium: use of potassium sparing diuretics, intravascular volume restoration with normal saline, correction of coexisting hypomagnesemia
- Take ongoing potassium losses into consideration while replacing deficit, by measuring the volume and potassium concentration of body fluid losses
- *Replace the deficit*: Oral route is safer than IV. Dose is 2–4 mEq/kg/day (maximum 120–240 mEq/day) in 3 or 4 divided doses. Liquid preparations are bitter and may be diluted with juice or water. Potassium chloride preferred; potassium citrate or acetate in concurrent acidosis
- *IV correction* is used cautiously preferably under ECG monitoring in patients unable to take oral preparation, severe hypokalemia (≤ 2.5 mEq/l), or associated arrhythmias. For rapid correction: 0.5 to 1.0 mEq/kg (maximum 40 mEq) over 1 hr. Infusate potassium should not exceed 40–60 mEq/l
- Disease specific therapy for specific conditions

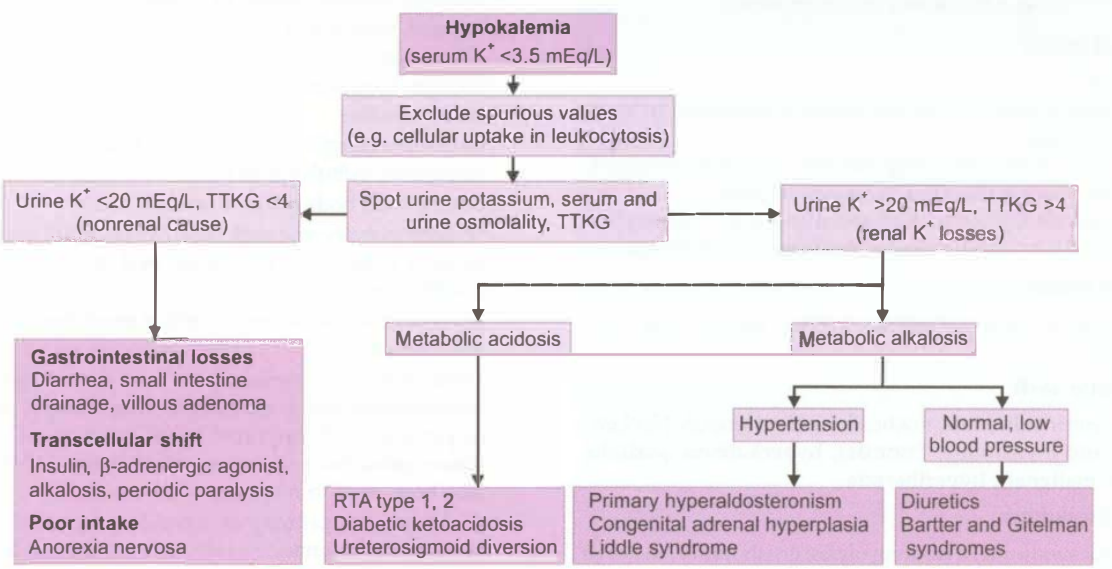

Fig. 5.6: Diagnostic approach to hypokalemia. K^+ potassium; RTA renal tubular acidosis; TTKG transtubular potassium gradient

potassium chloride may be used for correction in cases unable to take orally or those with severe hypokalemia (≤2.5 mEq/l) or associated arrhythmias.

Hyperkalemia

Hyperkalemia, defined as serum potassium level exceeding 5.5 mEq/l, is most commonly associated with renal insufficiency, acidosis and diseases that involve defects in mineralocorticoid, aldosterone and insulin function. Sudden and rapid onset of hyperkalemia is one of the most serious electrolyte disturbances and result in severe cardiac arrhythmia.

Factitious or pseudohyperkalemia can occur because of the practice of squeezing of extremities during phlebotomy or blood sampled from a limb being infused with potassium-containing fluid or hemolysis of a standing sample. Thrombocytosis and leukocytosis can also lead to false elevation of serum potassium levels. True hyperkalemia is caused by one or more of 3 mechanisms: increased potassium intake, extracellular potassium shifts or decreased excretion (Table 5.8). Increased potassium intake may result from inappropriate intravenous or oral potassium supplementation. Packed red blood cells have high concentrations of potassium that can lead to hyperkalemia. Acidosis results in transcellular potassium shift, but any cellular injury that disrupts the cell membrane (e.g. tumor lysis syndrome, rhabdomyolysis, crush injury, massive hemolysis) can cause hyperkalemia.

Patients may report nausea, vomiting and paresthesias or nonspecific findings of muscle weakness (skeletal, respiratory), fatigue and ileus. Clinical manifestations are related to the effects of elevated potassium levels on cardiac conduction since they interfere with repolarization of the cellular membrane. ECG changes appear progressively with rising serum potassium and include tall, peaked T waves (5.5 to 6.5 mEq/l), prolonged PR interval, flat P waves, wide QRS complex (6.5 to 8.0 mEq/l), absent P waves, bundle branch blocks and eventually sine waves (>8.0 mEq/l).

Table 5.8: Causes of hyperkalemia

Decreased losses
Renal failure
Renal tubular disorders: Pseudohypoaldosteronism, urinary tract obstruction
Drugs: ACE inhibitors, angiotensin receptor blockers, potassium sparing diuretics, NSAIDS, heparin
Mineralocorticoid deficiency: Addison disease, 21-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency
Increased intake
Intravenous or oral potassium intake; packed red cells transfusion
Extracellular shift
Acidosis, low insulin state, medications (β-adrenergic blockers, digitalis, succinylcholine, fluoride), hyperkalemic periodic paralysis, malignant hyperthermia
Cellular breakdown
Tumor lysis syndrome, rhabdomyolysis, crush injury, massive hemolysis

Treatment

Hyperkalemia is a medical emergency, requiring prompt discontinuation of potassium-containing fluids and administration of medications that ensure stability of myocardial membrane, intracellular shift of potassium and enhance its elimination (Box 5.4). Continuous ECG monitoring should be performed. Treatment should be individualized based upon the presentation, potassium level, and ECG changes. If the hyperkalemia is severe (potassium >7.0 mEq/l) or the patient is symptomatic with ECG changes, therapy should be initiated promptly with intravenous calcium gluconate, followed by sodium bicarbonate, insulin-glucose infusion and/or nebulized β_2-agonists. Hemodialysis may be needed in the more refractory patients. Milder elevations (5.5–6.5 mEq/l) are managed with elimination of potassium intake, discontinuation of potassium sparing drugs and treatment of the underlying etiology. Children with primary or secondary hypoaldosteronism require stress-dose steroid supplements and mineralocorticoids.

Box 5.4: Treatment of hyperkalemia

- Prompt discontinuation of potassium-containing fluids and medications that lead to hyperkalemia
- Stabilize the myocardial cell membrane to prevent lethal cardiac arrhythmia. Use intravenous (IV) 10% calcium gluconate (or calcium chloride), at 0.5 ml/kg over 5–10 minutes under cardiac monitoring. Discontinue if bradycardia develops
- Enhance cellular uptake of potassium
  Regular insulin and glucose IV: (0.3 Ü regular insulin/g glucose over 2 hr)
  Sodium bicarbonate IV: 1–2 mEq/kg body weight over 20–30 minutes
  Beta-adrenergic agonists, such as salbutamol and terbutaline nebulized or IV
- Ensure total body potassium elimination
  Sodium polystyrene sulfonate (Kayexalate) oral/per rectal: 1 g/kg (max. 15 g/dose) oral or as rectal enema in 20–30% sorbitol
  Loop or thiazide diuretics (only if renal function is maintained)
- Hemodialysis is necessary to treat severe symptomatic hyperkalemia that is resistant to drug therapy, particularly in patients with impaired renal functions. Continuous veno-venous hemofiltration with dialysis (CVVHDF) have also been used to remove potassium
- Children with primary or secondary hypoaldosteronism require maintenance steroids and mineralocorticoid supplements

CALCIUM

Physiology

Ninety-eight percent of body calcium is found in the skeleton which is in equilibrium with the extracellular concentration of calcium. Approximately 1 to 2% of body calcium exists in the ECF for physiological functions like blood coagulation, cellular communication, exocytosis, endocytosis, muscle contraction and neuromuscular transmission. Calcium affects the intracellular processes, through its calcium-binding regulatory protein, calmodulin.

Most of the filtered calcium is reabsorbed in the proximal tubule (70%), ascending loop of Henle (20%) and the distal tubule and collecting duct (5–10%). Factors that promote calcium reabsorption include parathormone (PTH), calcitonin, vitamin D, thiazide diuretics and volume depletion. Volume expansion, increased sodium intake and diuretics such as mannitol and frusemide promote calcium excretion.

The intestine serves as a longterm homeostatic mechanism for calcium. Although the major source of calcium is dietary, less than 15% of dietary calcium is absorbed, primarily in the ileum and jejunum by means of active transport and facilitated diffusion. Calcium is controlled primarily by major regulatory hormones, PTH, calcitonin and vitamin D. Additionally thyroid hormones, growth hormone, adrenal and gonadal steroids also have minor influences on calcium metabolism.

Role of the calcium-sensing receptor. The calcium-sensing receptor (CaSR) is a G protein-coupled receptor, which allows the parathyroid chief cells, the thyroidal C cells and the ascending limb of the loop of Henle (renal tubular epithelial cells) to respond to changes in the extracellular calcium concentration. The ability of the CaSR to sense the serum calcium is essential for the appropriate regulation of PTH secretion by the parathyroid glands and for the regulation of passive paracellular calcium absorption in the loop of Henle. Calcitonin secretion and renal tubular calcium reabsorption are directly regulated by the action of calcium ion on its receptor. Ionized calcium acts through calcitonin, to inhibit its release from bones. Decrease in extracellular calcium concentration, stimulates the CaSR in parathyroid glands, resulting in an increase in PTH secretion (Fig. 5.7). PTH increases distal renal tubular reabsorption of calcium within minutes and stimulates osteoclast activity, with release of calcium from the skeleton within 1–2 hr. More prolonged PTH elevation stimulates 1α-hydroxylase activity in the proximal tubular cells, which leads to 1, 25-dihydroxy-vitamin D production. In the kidney, vitamin D and PTH stimulate the activity of the epithelial calcium channel and the calcium-binding protein (i.e. calbindin) to increase active transcellular

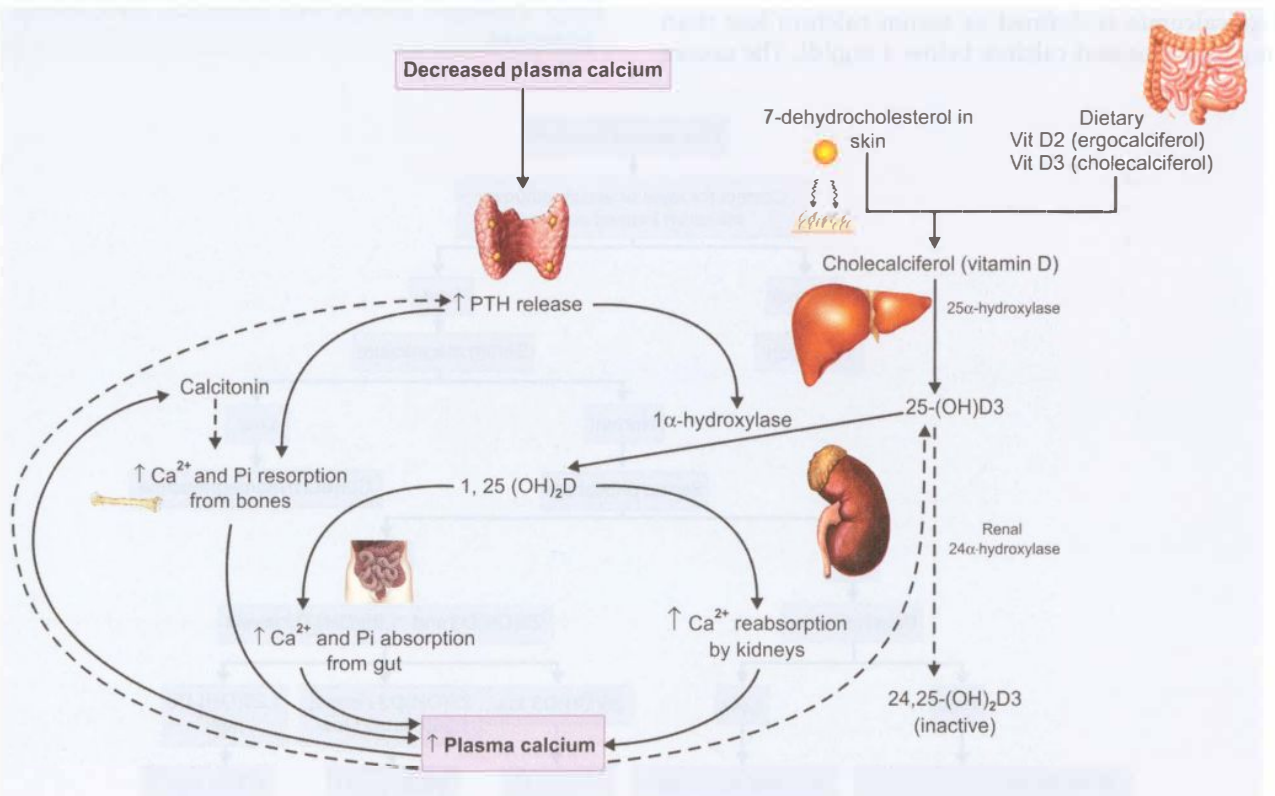

Fig. 5.7: Regulation of plasma calcium. Reduction in ionized calcium results in parathormone secretion, which through direct and indirect actions on the bones, intestine and the kidneys results in positive calcium balance. Calcitonin results in accretion of bone mass. Discontinuous lines indicate inhibitory control

calcium absorption in the distal convoluted tubule. These mechanisms help to maintain normal levels of serum calcium.

Plasma calcium exists in 3 different forms: 50% as biologically active ionized form, 45% bound to plasma proteins (mainly albumin) and 5% complexed to phosphate and citrate. In the absence of alkalosis or acidosis, the proportion of albumin-bound calcium remains relatively constant. Metabolic acidosis leads to increased ionized calcium from reduced protein binding and alkalosis has the opposite effect. Plasma calcium is tightly regulated despite its large movements across the gut, bone, kidney and cells in the normal range of 9–11 mg/dl.

Because calcium binds to albumin and only the unbound (free or ionized) calcium is biologically active, the serum level must be adjusted for abnormal albumin levels. For every 1 g/dl drop in serum albumin below 4 g/dl, measured serum calcium decreases by 0.8 mg/dl. Corrected calcium can be calculated using the following formula:

Corrected Ca =
[4 – plasma albumin in g/dl] × 0.8 + measured serum calcium

Alternatively, serum free (ionized) calcium levels can be directly measured, negating the need for correction for albumin.

Hypocalcemia

Hypocalcemia is defined as serum calcium less than 8 mg/dl or ionized calcium below 4 mg/dl. The causes and algorithm for investigating the etiology are shown in Table 5.9 and Fig. 5.8. Hypocalcemia manifests as central nervous system irritability and poor muscular contractility. Newborns present with nonspecific symptoms such as lethargy, poor feeding, jitteriness, vomiting, abdominal distension and seizures. Children may develop seizures, twitching, cramps and rarely laryngospasm (Box 5.5). Tetany and signs of nerve irritability may manifest as muscular twitching, carpopedal spasm and stridor. Latent tetany can be diagnosed clinically by clinical maneuvers such as Chvostek sign (twitching of the orbicularis oculi

Table 5.9: Causes of hypocalcemia

Neonatal:	Early (within 48–72 hr after birth) or late (3–7 days after birth) neonatal hypocalcemia; prematurity; infant of diabetic mother; neonates fed high phosphate milk
Parathyroid:	Aplasia or hypoplasia of parathyroid glands, DiGeorge syndrome, idiopathic; pseudohypoparathyroidism; autoimmune parathyroiditis; activating mutations of calcium sensing receptors
Vitamin D:	Deficiency; resistance to vitamin D action; acquired or inherited disorders of vitamin D metabolism
Others:	Hypomagnesemia; hyperphosphatemia (excess intake, renal failure); malabsorption syndromes; idiopathic hypercalciuria; renal tubular acidosis; metabolic alkalosis; hypoproteinemia; acute pancreatitis
Drugs:	Prolonged therapy with frusemide, corticosteroid or phenytoin

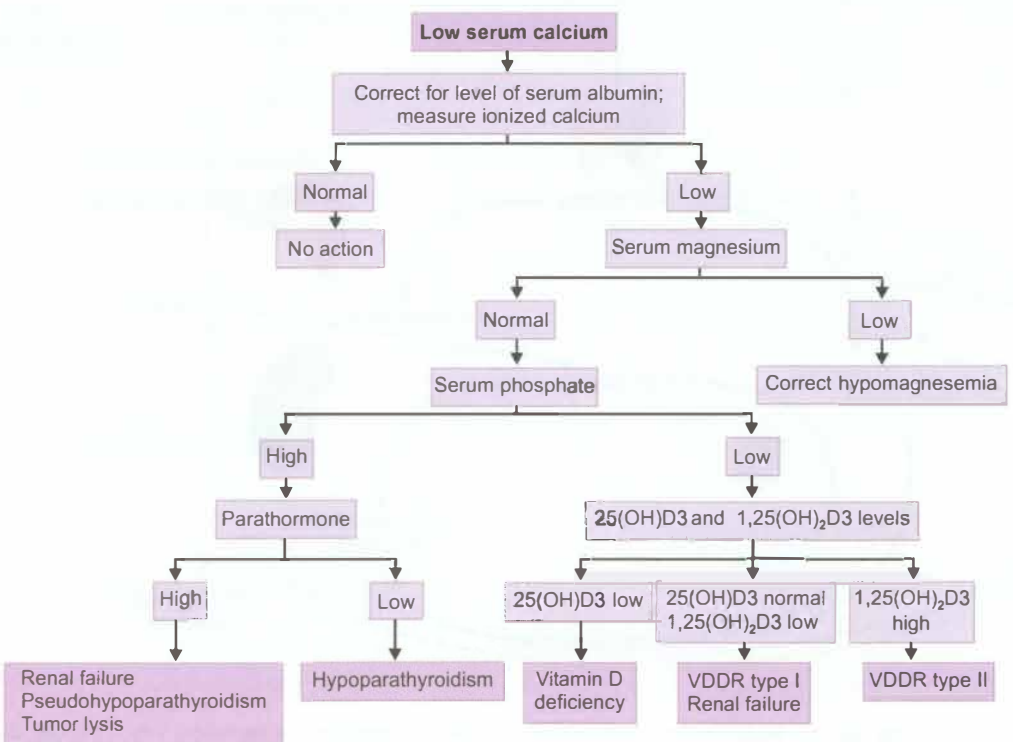

Fig. 5.8: Algorithm for evaluation of hypocalcemia. VDDR vitamin D dependent rickets

Box. 5.5: Clinical features of hypocalcemia

- Carpopedal and muscle spasms
- Tetany
- Laryngospasm
- Paresthesias
- Seizures
- Irritability, depression, psychosis
- Intracranial hypertension
- Prolonged QTc interval

and mouth elicited by tapping the facial nerve anterior to the external auditory meatus) and the Trousseau sign (carpopedal spasm elicited by inflating a blood pressure cuff on the arm to a pressure above the systolic pressure for 3 min). ECG shows prolonged corrected QT interval (QTc) to more than 0.45 seconds. Cardiac function may be impaired because of poor muscle contractility. Prolonged hypocalcemia can present with features of rickets.

Management

Tetany, laryngospasm and seizures must be treated immediately with 2 ml/kg of 10% calcium gluconate, administered IV slowly under cardiac monitoring. Calcium gluconate 10% (100 mg/ml) IV solution contains 9.8 mg/ml (0.45 mEq/ml) elemental calcium; calcium chloride 10% (100 mg/ml) contains 27 mg/ml (1.4 mEq/ml). Initially IV calcium boluses are given every 6 hr. Thereafter, oral calcium supplementation is provided at 40–80 mg/kg/day. Oral calcium therapy is used in asymptomatic patients and as followup to intravenous (IV) calcium therapy. Intravenous infusion with calcium-containing solutions can cause severe tissue necrosis; therefore integrity of the IV site should be ascertained before administering calcium through a peripheral vein. Rapid infusion of calcium-containing solutions through arterial lines can cause arterial spasm and if administered *via* an umbilical artery catheter, intestinal necrosis. Magnesium administration is necessary to correct any hypomagnesemia because hypocalcemia does not respond until the low magnesium level is corrected. In patients with concurrent acidemia, hypocalcemia should be corrected first. Acidemia increases the ionized calcium levels by displacing calcium from albumin. If acidemia is corrected first, ionized calcium levels decrease.

Calcium carbonate is an oral supplement providing 40% elemental calcium. Therapy with cholecalciferol is used in patients with vitamin D deficiency. Calcitriol, an active metabolic form of vitamin D (i.e. 1,25-dihydroxycholecalciferol) is administered in liver or renal disease.

Hypercalcemia

Hypercalcemia is defined as a serum calcium level greater than 11 mg/dl. Because calcium metabolism normally is tightly controlled by the body, even mild persistent elevations should be investigated. Etiologies of hypercalcemia vary by age and other factors (Table 5.10). Hypercalcemia is often asymptomatic, although it can cause symptoms at levels as low as 12 mg/dl and consistently at values above 15 mg/dl. Such high values are however, rarely encountered and present as stupor and coma. Neonates may be asymptomatic or may have vomiting, hypotonia, hypertension or seizures. Clinical features in older children are summarized in Box 5.6 and include irritability,

Box 5.6: Clinical features of hypercalcemia

Lethargy, confusion, depression, coma	Bradycardia, systemic hypertension, headache
Hyporeflexia	Nephrocalcinosis, nephrolithiasis
Muscle weakness	Polyuria
Constipation	Reduced QTc interval

malaise, headache, confusion, unsteady gait and proximal muscle weakness. Abdominal pain with paralytic ileus, nausea and vomiting and constipation are often observed. Ectopic calcification can lead to symptoms of pancreatitis, with epigastric pain and vomiting. Ectopic calcification can manifest as conjunctivitis or band keratopathy. Renal manifestations due to renal stones and nephrocalcinosis can progress to renal failure, and polyuria and polydipsia occur due to nephrogenic diabetes insipidus.

Treatment

The initial treatment of hypercalcemia involves hydration to improve urinary calcium excretion. Rapid lowering of serum calcium can be expected with isotonic sodium

Table 5.10: Causes of hypercalcemia

Neonates
Neonatal primary hyperparathyroidism, secondary hyperparathyroidism
Familial hypocalciuric hypercalcemia
Excessive supplementation of calcium
William syndrome, hypophosphatasia, idiopathic infantile hypercalcemia
Older children
Hyperparathyroidism (parathyroid adenoma, autosomal dominant hereditary hyperparathyroidism, multiple endocrine neoplasia type 1)
Malignancies: Non-Hodgkin or Hodgkin lymphoma, Ewing sarcoma, neuroblastoma, Langerhans cell histiocytosis, rhabdomyosarcoma
Granulomatous disease: Sarcoidosis, tuberculosis, Wegener disease, berylliosis
Others: Vitamin D or A intoxication; thiazide diuretics; milk-alkali syndrome; dietary phosphate deficiency; subcutaneous fat necrosis; thyrotoxicosis; prolonged immobilization

chloride solution, because increasing sodium excretion increases calcium excretion. Addition of a loop diuretic inhibits tubular reabsorption of calcium but attention should be paid to other electrolytes (e.g. magnesium, potassium) during saline diuresis. Bisphosphonates serve to block bone resorption and decrease serum calcium within a couple of days but have not been used extensively in children. Pamidronate and etidronate have been used in the treatment of hypercalcemia due to malignancy, immobilization and hyperparathyroidism but may cause mineralization defects.

Peritoneal dialysis or hemodialysis can be used in extreme situations, particularly in patients with renal failure. Calcimimetics (cinacalcet hydrochloride) change the configuration of the CaSR in a manner that makes it more sensitive to serum calcium. Its safety and efficacy in pediatric population has yet to be substantiated. Surgical intervention may be needed in patients with hyperparathyroidism, particularly with recurrent renal stones or persistent serum calcium levels higher than 12.5 mg/dl. Subtotal parathyroidectomy can be performed, or complete parathyroidectomy can be chosen with reimplantation of a small amount of tissue in the forearm.

5

MAGNESIUM

Physiology

Magnesium is the third-most abundant intracellular cation predominantly located in muscle and liver cells. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable.

Magnesium plays a fundamental role in many functions of the cell, including energy transfer and storage and nerve conduction. Magnesium also plays important role in protein, carbohydrate, and fat metabolism, maintenance of normal cell membrane function and regulation of PTH secretion.

Dietary sources include green leafy vegetables, cereals, nuts and meats. Absorption of magnesium takes place primarily in the small intestine and is inversely related to the amount of magnesium, calcium, phosphate and fat. PTH and glucocorticoids increase magnesium absorption. Absorption is diminished in presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and PTH enhance absorption. Renal excretion is the principal regulator of magnesium balance. Reabsorption occurs chiefly in the thick ascending loop of Henle (70%) and to a smaller extent in the proximal (15%) and distal (5–10%) tubules. Fractional excretion of magnesium exceeding 4% indicates renal magnesium wasting.

Hypomagnesemia

Hypomagnesemia develops from decreased intake or more commonly increased losses which could be gastrointestinal (diarrhea, vomiting, nasogastric suction) or renal (chronic use of thiazide diuretics, recovery phase of acute tubular necrosis, Gitelman syndrome, familial hypomagnesemia-hypercalciuria-nephrocalcinosis). Symptomatic magnesium depletion (occurs at levels below 1.2 mg/dl) is often associated with multiple biochemical abnormalities, including hypokalemia, hypocalcemia and metabolic acidosis. As a result, hypomagnesemia is sometimes difficult to attribute solely to specific clinical manifestations. Hypomagnesemia often leads to hypocalcemia, possibly by inhibition of PTH activity. Neuromuscular manifestations of hypomagnesemia include muscle weakness, tremors, seizures, paresthesias, tetany, positive Chvostek sign, Trousseau signs and nystagmus. Cardiovascular manifestations include nonspecific T-wave changes, U-waves and prolonged QT interval and arrhythmias.

Treatment

Therapy can be oral for patients with mild symptoms or intravenous for patients with severe symptoms or those unable to tolerate oral administration. Severe hypomagnesemia is treated with slow intravenous infusion of magnesium sulfate (50% solution) at a dose of 25–50 mg/kg (2.5–5.0 mg/kg of elemental magnesium). The dose is repeated every 6 hr, for a total of 2–3 doses. Doses need to be reduced in children with renal insufficiency. Oral replacement should be given in the asymptomatic patient, or those requiring longterm replacement, preferably with a sustained-release preparation to avoid diarrhea. Oral magnesium preparation provide 5–7 mEq of magnesium per tablet. Two to four tablets may be sufficient for mild, asymptomatic disease while severe cases require up to six to eight tablets, to be taken daily in divided doses. Patients with renal magnesium wasting may benefit from diuretics with magnesium-sparing properties, such as spironolactone and amiloride.

Hypermagnesemia

Serum magnesium >2.5 mg/dl is uncommon in children and may be seen in the setting of renal insufficiency, prolonged use of magnesium containing antacids or in neonates born to mothers given magnesium sulfate as a treatment for eclampsia. Symptoms of hypermagnesemia are nonspecific at lower levels: nausea, vomiting, flushing, lethargy, weakness and dizziness. At higher levels, deep tendon reflexes are depressed which may progress to coma and respiratory depression. Effects on the heart may result in prolongation of intervals on ECG or manifest as arrhythmias, complete heart block and asystole.

Treatment

In patients with mildly increased levels, the source of magnesium may simply be removed. Intravenous calcium directly antagonizes the cardiac and neuromuscular effects of excess extracellular magnesium. Dialysis may be used

for patients with severe hypermagnesemia and renal impairment, or those with serious cardiovascular or neuromuscular symptoms.

ACID-BASE DISORDERS

Regulation of Acid-Base Equilibrium

The body is sensitive to changes in blood pH level, as disturbances in acid-base homeostasis can result in denaturation of proteins and inactivation of enzymes that may be potentially fatal. Strong mechanisms exist to regulate acid-base balance and maintain arterial pH (7.35 to 7.45), pCO_2 (35 to 45 mm Hg) and HCO_3^- (20 to 28 mEq/l) within a narrow range.

Acidemia is defined as H^+concentration exceeding 45 nmol/l (pH <7.35); values below 35 nmol/l (pH>7.45) define alkalemia. The disorders that cause acidemia or alkalemia are termed as acidosis and alkalosis respectively. Metabolic activity results in production of two types of acids, carbonic acid (a volatile acid, derived from carbon dioxide) and nonvolatile acids (including sulfuric acid, organic acids, uric acid and inorganic phosphates). Accumulation of H^+ ions of nonvolatile acids due to excess production or inadequate buffering, failure to excrete H^+ or loss of bicarbonate results in metabolic acidosis. If the reverse occurs, it results in metabolic alkalosis. The principle mechanism for carbon dioxide handling is by the lungs. Hyperventilation results its CO_2 washout and drop in arterial pCO_2 (respiratory alkalosis), hypoventilation has the opposite effect (respiratory acidosis). When only one primary acid-base abnormality occurs and its compensatory mechanisms are activated, the disorder is classified as simple acid-base disorder. A simple algorithm for defining simple acid-base disorders is shown in Fig. 5.9. When a combination of disturbances occurs, the disorder is classified as a mixed acid-base disorder. The latter are suspected when the compensation in a given patient differs from the predicted values in Table 5.11.

In order to maintain body homeostasis, changes in pH are resisted by a complex system of intracellular and extracellular buffers. The first line of defense, are the chemical buffers. In metabolic disorders the extracellular buffers rapidly titrate the addition of strong acids or bases. Intracellular buffers chiefly accomplish the buffering of respiratory disorders. Secondary respiratory compensations to metabolic acid-base disorders occur within minutes and is completed by 12 to 24 hr. In contrast secondary metabolic compensation of respiratory

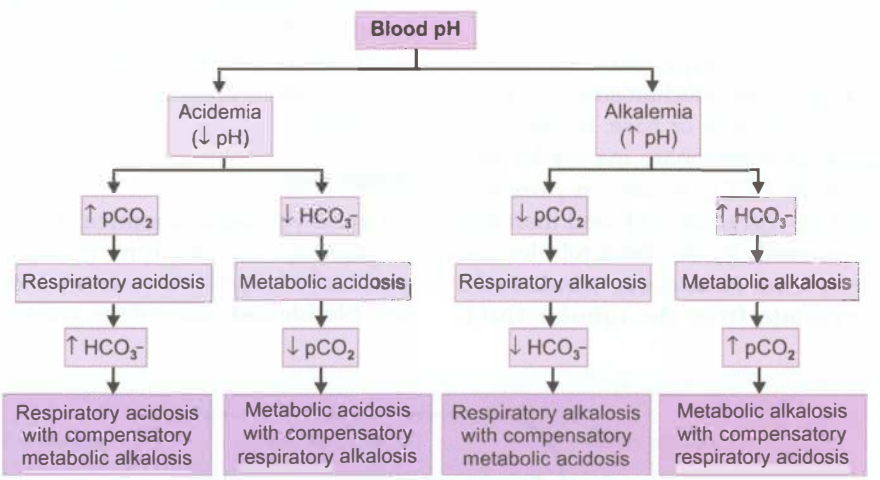

Fig. 5.9: Algorithm for simple acid-base disorders

Table 5.11: Compensation for primary acid-base disorders

Disorder	*Primary event*	*Compensation*	*Expected Compensation*
Metabolic acidosis	↓ [HCO_3^-]	↓ pCO_2	pCO_2 ↓ by 1–1.5 mm Hg for 1 mEq/l ↓[HCO_3^-]
Metabolic alkalosis	↑ [HCO_3^-]	↑ pCO_2	pCO_2 ↑ by 0.5–1 mm Hg for 1 mEq/l ↑ [HCO_3^-]
Respiratory acidosis			
Acute (<24 hr)	↑pCO_2	↑[HCO_3^-]	[HCO_3^-] ↑ by 1 mEq/l for 10 mm Hg ↑ pCO_2
Chronic (3–5 days)	↑pCO_2	↑↑ [HCO_3^-]	[HCO_3^-] ↑ by 4 mEq/l for 10 mm Hg ↑ pCO_2
Respiratory alkalosis			
Acute (<24 hr)	↓pCO_2	↓[HCO_3^-]	[HCO_3^-] ↓ by 1–3 mEq/l for 10 mm Hg ↓ pCO_2
Chronic (3–5 days)	↓pCO_2	↓↓[HCO_3^-]	[HCO_3^-] ↓ by 2–5 mEq/l for 10 mm Hg ↓ pCO_2

disorders begins more slowly and takes 2 to 5 days for completion. The compensatory mechanisms do not return the pH to normal until the underlying disease process has been appropriately treated. Several buffering agents reversibly bind hydrogen ions and impede any change in body pH. Extracellular buffers include bicarbonate and ammonia, whereas proteins and phosphate act as intracellular buffers.

Bicarbonate-carbonic acid buffer in the extracellular fluid, is the key buffer as carbon dioxide (CO_2) can be shifted through carbonic acid (H_2CO_3) to hydrogen ions and bicarbonate (HCO_3^-):

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3.$$

Acid-base imbalances that overcome the buffer system can be compensated in the short-term by altering the rate of ventilation, which alters the pCO_2. While this is a relatively weak buffer, it accounts for 55% of the buffering capacity because of its sheer abundance. When H^+ concentration increases the above reaction shifts to the left, more CO_2 is generated and exhaled from the lungs, moderating the change in pH. Hemoglobin is a powerful intracellular buffer because its negatively charged histidine moieties accept H^+, normalizing the pH. Other proteins also have negative charges that can accept H^+.

5

Renal Regulation of Acid-base Balance

The kidneys are slower to compensate, but renal physiology has several powerful mechanisms to control pH by the excretion of excess acid or base. Kidneys are the principal regulators of bicarbonate mainly by two methods: (i) resorption of HCO_3^- mostly in proximal convoluted tubules and (ii) excretion of H^+ and therefore generation of HCO_3^-, primarily by the distal tubules and collecting ducts. In responses to acidosis, tubular cells reabsorb more bicarbonate from the tubular fluid, collecting duct cells secrete more hydrogen and generate more bicarbonate, and ammoniagenesis leads to increased formation of renal ammonia (Fig. 5.10). In responses to alkalosis, the kidneys excrete more bicarbonate by decreasing hydrogen ion secretion from the tubular epithelial cells, and lowering rates of glutamine metabolism and ammonia excretion.

Bicarbonate-carbonic acid in the kidney tubules: H^+ ions secreted from the tubular cells combines with luminal HCO_3^- to form water and CO_2. The CO_2 enters the tubular cell and combines with water, in presence of carbonic anhydrase, to regenerate HCO_3^- that is reabsorbed into the bloodstream, thus conserving the filtered HCO_3^-.

Monohydrogen phosphate-dihydrogen phosphate buffer: This luminal buffer system buffers H^+ ions secreted from the tubular cells, as follows:

$H^+ + Na_2HPO_4 \rightarrow NaH_2PO_4 + Na^+$. The weakly acidic sodium dehydrogen phosphate is excreted in the urine.

Ammonia-ammonium buffer: In tubular cells glutamine is converted to glutamic acid and ammonia, the reaction catalyzed by glutaminase. Ammonia is secreted in the lumen and combines with H^+ to form ammonium ions, which are excreted in urine.

Sodium-hydrogen exchange in the distal tubule: The distal tubular cells actively reabsorb Na^+; to maintain electroneutrality H^+ ions are exchanged. The latter combine with either monohydrogen phosphate or ammonia and are excreted.

Anion Gap

To achieve electrochemical balance, the number of negatively charged ions (anions) should equal the positively charged ions (cations). Measured plasma anions are chloride and bicarbonate, and the unmeasured anions

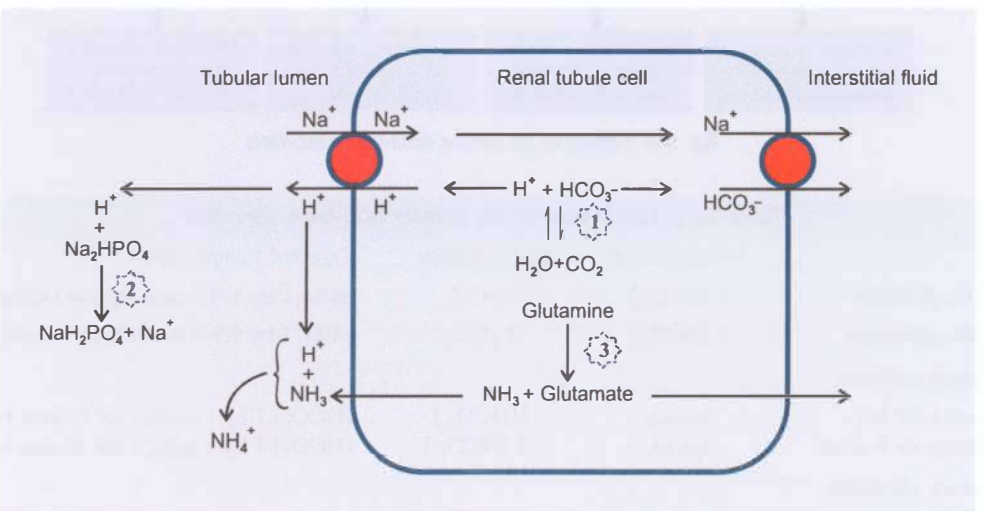

Fig. 5.10: Renal regulation of acid-base disorders. 1 = bicarbonate-carbonic acid buffer; 2 = monohydrogen phosphate-dihydrogen phosphate buffer; 3 = ammonia-ammonium buffer

include phosphates, sulfates and proteins (e.g. albumin). Under typical conditions, unmeasured anions exceed unmeasured cations; this is referred to as the anion gap and can be represented by the following formula:

$$\text{Anion gap} = (Na^+) - (Cl^- + HCO_3^-)$$

The anion gap is normally 8 to 16 mEq/l. When a strong acid is added to or produced in the body, hydrogen ions are neutralized by bicarbonate, resulting in a fall in bicarbonate. These acids include inorganic (e.g. phosphate or sulfate), organic (e.g. ketoacids or lactate) or exogenous (e.g. salicylate) acids incompletely neutralized by bicarbonate. The accompanying unmeasured anion results in increased anion gap proportional to the fall in bicarbonate. In contrast, when the bicarbonate is lost from the body, no new anion is generated; therefore there is a reciprocal increase in chloride ions (proportional to the fall in bicarbonate) resulting in normal anion gap. Hypoalbuminemia is the most common cause of a low anion gap. Albumin represents about half of the total unmeasured anion pool; for every decrease of 1 g/dl of plasma albumin, the plasma anion gap decreases by 2.5 mEq/l.

Metabolic Acidosis

Metabolic acidosis is an acid-base disorder characterized by a decrease in serum pH that results from either a loss in plasma bicarbonate concentration or an increase in hydrogen ion concentration (Table 5.12). Primary metabolic acidosis is characterized by an arterial pH of less than 7.35 due to a decrease in plasma bicarbonate in the absence of an elevated $PaCO_2$. If the measured $PaCO_2$ is higher than the expected $PaCO_2$, a concomitant respiratory acidosis is also present (caused by a depressed mental state, airway obstruction or fatigue). Acutely, medullary chemoreceptors compensate for metabolic acidosis through increase in alveolar ventilation, which results in tachypnea and hyperpnea that washes off CO_2 and corrects pH.

Table 5.12: Causes of metabolic acidosis

Normal anion gap (hyperchloremic acidosis)
Renal loss of bicarbonate
Proximal (type 2) renal tubular acidosis, carbonic anhydrase inhibitors (e.g. acetazolamide), tubular damage due to drugs or toxins
Gastrointestinal bicarbonate loss
Diarrhea, ureteral sigmoidostomy, rectourethral fistula, fistula or drainage of small bowel or pancreas
Decreased renal hydrogen ion excretion
Renal tubular acidosis type 1 and type 4 (aldosterone deficiency)
Potassium sparing diuretics
Increased hydrogen chloride production
Parenteral alimentation, increased catabolism of lysine and arginine
Ammonium chloride ingestion
Elevated anion gap
Increased acid production/accumulation: Sepsis, shock, poisonings (ethanol, methanol, ethylene glycol); inborn errors of metabolism
Ketoacidosis: Diabetic ketoacidosis, starvation
Exogenous acids: salicylates, iron, isoniazid, paraldehyde
Failure of acid excretion: Acute or chronic renal failure

Calculation of plasma anion gap helps to classify metabolic acidosis into those with elevated anion gap (i.e. >12 mEq/l as in increased acid production or decreased losses) and those with normal anion gap (i.e. 8–12 mEq/l as in gastrointestinal or renal loss of bicarbonate or when hydrogen ions cannot be secreted because of renal failure) (Table 5.12).

Another useful tool in the evaluation of metabolic acidosis with normal anion gap is urinary anion gap.

$$\text{Urinary anion gap} = \text{urinary } [Na^+] + [K^+] - [Cl^-]$$

Urinary anion gap is negative in patients with diarrhea regardless of urinary pH, and urinary anion gap is positive in renal tubular acidosis. An elevated osmolal gap (>20 mOsm/kg) with metabolic acidosis suggests the presence of osmotically active agents such as methanol, ethylene glycol or ethanol.

Clinical Features

Initially, patients with a metabolic acidosis develop a compensatory tachypnea and hyperpnea, which may progress if the acidemia is severe, and the child can present with significant work of breathing and distress (Kussmaul breathing). An increase in H^+ concentration results in pulmonary vasoconstriction, which raises pulmonary artery pressure and pulmonary vascular resistance. Tachycardia is the most common cardiovascular effect seen with mild metabolic acidosis. Cerebral vasodilation occurs as a result of metabolic acidosis and may contribute to an increase in intracranial pressure. Acidosis shifts the oxygen-hemoglobin dissociation curve to the right, decreasing hemoglobin's affinity for oxygen. During metabolic acidosis, excess hydrogen ions move toward the intracellular compartment and potassium moves out of the cell into the extracellular space. Untreated severe metabolic acidosis may be associated with life-threatening arrhythmias, myocardial depression, respiratory muscle fatigue, seizures, shock and multiorgan failure.

Treatment

It is important to identify the cause of metabolic acidosis as most cases resolve with correction of the underlying disorder. The role of alkali therapy in acute metabolic acidosis is limited. It is definitely indicated in some situations, e.g. salicylate poisoning, inborn errors of metabolism, or in those with pH below or equal to 7.0 or $[HCO_3^-]$ less than 5 mEq/l, as severe acidosis can produce myocardial dysfunction. The amount of bicarbonate required is: Body weight (kg) × base deficit × 0.3.

One ml of 7.5% sodium bicarbonate provides 0.9 mEq bicarbonate. The recommendation is to replace only half of the total bicarbonate deficit during the first few hours of therapy. This amount is given as continuous infusion over two hours. Rapid correction of acidosis with sodium bicarbonate can lead to extracellular volume expansion, exacerbating pulmonary edema in patients with cardiac failure. In the latter, the rate of infusion should be slower or sodium bicarbonate replaced by THAM [dose (ml) = weight (kg) × base deficit] which is infused over 3–6 hr. If hypernatremia is a concern, sodium bicarbonate may be used as part of the maintenance intravenous solution.

During correction of acute metabolic acidosis, the effect of sodium bicarbonate in lowering serum potassium and ionized calcium concentrations must also be considered and monitored. Since bicarbonate therapy generates large amount of CO_2, ventilation should increase proportionately otherwise this might worsen intracellular acidosis. The inability to compensate may be especially important in patients with diabetic ketoacidosis who are at risk for cerebral edema. In diabetic ketoacidosis, insulin therapy generally corrects the acidosis.

In newborns, frequent administration of hypertonic solutions such as sodium bicarbonate have led to intracranial hemorrhage resulting from hyperosmolality and resultant fluid shifts from the intracellular space. Children with inherited metabolic abnormalities, poisoning, or renal failure may require hemodialysis.

Mild to moderate acidosis in renal failure or renal tubular acidosis improves on oral alkali therapy, the dose being 0.5 to 2 mEq/kg/day of bicarbonate in 3–4 divided doses. In cases of acidosis due to volume depletion, the volume deficit should be corrected.

Metabolic Alkalosis

Metabolic alkalosis (pH >7.45) is an acid-base disturbance caused by elevation in the plasma bicarbonate (HCO_3^-) concentration in the extracellular fluid that results from a net loss of acid, net gain of base or loss of fluid with more chloride than bicarbonate. There are 2 types of metabolic alkalosis classified based on the amount of chloride in the urine, i.e. chloride-responsive or chloride resistant (Table 5.13). Chloride-responsive metabolic alkalosis shows urine chloride levels of less than 10 mEq/l and is characterized by decreased ECF volume and low serum chloride levels, such as occurs with vomiting or use of diuretics. This type responds to administration of chloride salt (usually as normal saline). Chloride resistant metabolic alkalosis is characterized by urine chloride levels of more than 20 mEq/l. Primary aldosteronism is an example of chloride-resistant metabolic alkalosis and this type resists administration of therapy with chloride.

The body compensates for metabolic alkalosis through buffering of excess bicarbonate and hypoventilation. Intracellular buffering occurs through sodium-hydrogen and potassium-hydrogen ion exchange, with eventual formation of CO_2 and water from HCO_3^-. Within several hours, elevated levels of HCO_3^- and metabolic alkalosis inhibit the respiratory center, resulting in hypoventilation and increased pCO_2 levels. This mechanism produces a rise in pCO_2 of as much as 0.7 to 1 mm Hg for each 1 mEq/l increase in HCO_3^-.

Table 5.13: Causes of metabolic alkalosis

Chloride responsive
Gastric fluid loss (e.g. vomiting, nasogastric drainage)
Volume contraction (e.g. loop or thiazide diuretics, metolazone)
Congenital chloride diarrhea, villous adenoma
Cystic fibrosis
Post-hypercapnia syndrome (mechanically ventilated patients with chronic lung disease)
Chloride resistant
Primary aldosteronism (adenoma, hyperplasia)
Renovascular hypertension, renin secreting tumor
Bartter and Gitelman syndromes
Apparent mineralocorticoid excess
Glucocorticoid remediable aldosteronism
Congenital adrenal hyperplasia (11β- and 17α-hydroxylase deficiency)
Liddle syndrome
Excess bicarbonate ingestion

Clinical Features

Signs and symptoms observed with metabolic alkalosis usually relate to the specific disease process that caused the acid-base disorder. Increased neuromuscular excitability (e.g. from hypocalcemia), sometimes causes tetany or seizures. Generalized weakness may be noted if the patient also has hypokalemia. Patients who develop metabolic alkalosis from vomiting can have symptoms related to severe volume contraction, with signs of dehydration. Although diarrhea typically produces a hyperchloremic metabolic acidosis, diarrheal stools may rarely contain significant amounts of chloride, as in the case of congenital chloride diarrhea. Children with this condition present at birth with watery diarrhea, metabolic alkalosis, and hypovolemia. Weight gain and hypertension may accompany metabolic alkalosis that results from a hypermineralocorticoid state.

Treatment

The overall prognosis in patients with metabolic alkalosis depends on the underlying etiology. Prognosis is good with prompt treatment and avoidance of hypoxemia. Mild or moderate metabolic alkalosis or alkalemia rarely requires correction. For severe metabolic alkalosis, therapy should address the underlying disease state, in addition to moderating the alkalemia. The initial target pH and bicarbonate level in correcting severe alkalemia are approximately 7.55 and 40 mEq/l, respectively.

Therapy with diuretics (e.g. furosemide, thiazides) should be discontinued. Chloride-responsive metabolic alkalosis responds to volume resuscitation and chloride

repletion. Chloride-resistant metabolic alkalosis may be more difficult to control. As with correction of any electrolyte or acid-base imbalance, the goal is to prevent life-threatening complications with the least amount of correction.

For persistent severe metabolic alkalosis in the setting of fluid overload, wherein saline cannot be given, cautious use of HCl or ammonium chloride may be considered. Acetazolamide may help patients with chloride-resistant metabolic alkalosis provided GFR is adequate. Correction of metabolic alkalosis in patients with renal failure may require hemodialysis or continuous renal replacement therapy with a dialysate that contains high levels of chloride and low HCO_3^-.

Respiratory Acidosis

Respiratory acidosis occurs when the alveolar ventilation falls or when carbon dioxide production is increased, so that the arterial partial pressure of carbon dioxide ($PaCO_2$) is elevated above the normal range (>44 mm Hg) leading to a blood pH lower than 7.35 (Table 5.14). pCO_2 is directly proportional to carbon dioxide production and inversely proportional to alveolar ventilation. The kidneys compensate for respiratory acidosis by increasing HCO_3^- reabsorption, a process that begins in 6–12 hr but takes 3–5 days for maximal compensation.

The kidneys increase excretion of hydrogen ions (predominantly in the form of ammonium) that increases the plasma bicarbonate concentration by approximately 3.5–4 mEq/l for every 10 mm Hg increase in CO_2.

Clinical Features

Patients with acute respiratory acidosis frequently demonstrate air-hunger with retractions and use of accessory muscles. Neurologic findings include anxiety, disorientation, confusion and lethargy followed by tremors, somnolence or coma at higher pCO_2. Hypercapnic neurologic changes are reversible with no residual effect. Cardiovascular findings include tachycardia, bounding arterial pulses and in severe cases hypotension.

Treatment

The goal of therapy is to correct or compensate for the underlying pathologic process. Failure to consider a mixed acidosis can lead to missed therapies and diagnosis. Assisted ventilation is required in many cases.

Table 5.14: Causes of respiratory acidosis

Decrease in alveolar ventilation
Depressed central respiratory drive
Acute paralysis of the respiratory muscles
Acute or chronic parenchymal lung and airway diseases
Progressive neuromuscular disease
Worsening scoliosis (restrictive lung disease)
High carbon dioxide production and inability to increase minute ventilation
Extensive burn injury
Malignant hyperthermia
Fever

Respiratory Alkalosis

Respiratory alkalosis occurs in the setting of a primary decrease in pCO_2 as a consequence of hyperventilation (Table 5.15). In a child this may result from high fever, sepsis, mild bronchial asthma, central nervous system disorders or overventilation of an intubated child in intensive care setting. In acute respiratory alkalosis, titration is done by intracellular buffers. Renal compensation begins within several hours and takes several days for the maximal response.

Table 5.15: Causes of respiratory alkalosis

Hypoxia and hypoxemia
High altitude or low fraction of inspired oxygen, anemia, hypotension or lung disease
Pulmonary disorders
Pulmonary edema, embolism, airway obstruction, pneumonia, intersititial lung disease
Mechanical ventilation (ventilatory rate or tidal volume too high)
Extrapulmonary disorders (severe respiratory alkalosis)
Stress, neurologic disease (stroke, infection, trauma, tumor)
Medications: Catecholamines, progesterone, methylxanthines, salicylates, doxapram, nicotine
Hyperthermia, hepatic encephalopathy, sepsis, recovery from metabolic acidosis

Clinical Features

Patients primarily have clinical manifestations of the underlying disorder. Alkalosis, by promoting the binding of calcium to albumin, can reduce the fraction of ionized calcium in blood which may manifest as feeling of tingling, paresthesias, dizziness, palpitations, tetany and seizures. Therapy is directed towards the causal process.

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6 Nutrition

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Nutrition, also called nourishment, is the provision to cells and organisms of the materials necessary in the form of food to support life. Our food is made up of essential, natural substances called *nutrients*. There are seven major classes of nutrients: carbohydrates, fats, fiber, minerals, proteins, vitamins and water. These nutrients can be grouped as macronutrients and micronutrients. The *macronutrients* are needed in large quantities, e.g. carbohydrates, fats and proteins and are building blocks of the body. The *micronutrients*, e.g. minerals and vitamins are needed in tiny quantities and are crucial for their role in metabolic pathways and in enhancing immunity. Micronutrients are discussed in Chapter 7.

MACRONUTRIENTS

Carbohydrates

Carbohydrates are the main source of energy in the Indian diet contributing to 55–60% of total energy intake. Carbohydrates contribute taste, texture and bulk to the diet. Lack of carbohydrates (less than 30%) in the diet may produce ketosis, loss of weight and breakdown of proteins. Carbohydrates are divided into *simple carbohydrates* (monosaccharide and disaccharides such as glucose and fructose in fruits, vegetables and honey, sucrose in sugar and lactose in milk) and *complex carbohydrates* (oligosaccharides and polysaccharides such as starch in cereals, millets, pulses and root vegetables). The main source of energy in the body is glucose derived from starch and sugars present in the diet. Glucose is used as a fuel by the cells and is converted to glycogen by liver and muscles. Excess carbohydrates are converted to fat. *Carbohydrates provide 4 kcal of energy per gram.*

Fiber

Dietary fibers include polysaccharides such as cellulose, hemicelluloses, pectin, gums, mucilage and lignin. They have little nutritional value as they are not digested by the enzymes in the gut. Fibers are essential for the normal functioning of the gut, elimination of waste, bile acid binding capacity and for maintaining the growth of normal intestinal microflora.

Proteins

Proteins are the second most abundant substance in the body, after water. They are required for the growth and synthesis of tissues in the body; formation of digestive juices, hormones, plasma proteins, enzymes and hemoglobin; as buffers to maintain acid-base equilibrium in the body; and as alternate source of energy for the body. Amino acids that can be synthesized in the body are called nonessential, while essential amino acids require to be supplied in the diet.

Essential amino acids include leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Histidine and arginine are essential during infancy because the rate of their synthesis is inadequate for sustaining growth.

Protein Quality

Food proteins differ in their nutritional quality depending on their amino acid profile and digestibility. Cereal grains are deficient in the essential amino acids like lysine, threonine or tryptophan, whereas pulses are rich in lysine but are limited in sulfur containing amino acids, mainly methionine. When cereals are taken in combination with the pulses, the deficiency in one is made good by an excess in other. *Proteins provide 4 kcal energy per gram.*

The following terms are used to describe protein quality:

$$\text{True digestibility (TD)} = \frac{\text{Nitrogen absorbed}}{\text{Nitrogen intake}} \times 100$$

$$\text{Biological value (BV)} = \frac{\text{Nitrogen retained}}{\text{Nitrogen absorbed}} \times 100$$

$$\text{Net protein utilization (NPU)} = \frac{TD}{100} \times BV$$

Egg protein has the highest values for BV and NPU and is therefore taken as the reference protein, and the value of others is expressed as relative to egg (taken as 100%). Generally, animal proteins have a higher BV than the plant proteins. The nutritive value of a mixture of two proteins may be higher than the mean of the two because of mutual complementary effects.

Requirements The protein allowances shown in Table 6.1 are given in terms of the mixed vegetable proteins contained in Indian diets, the NPU of which is assumed to be 65. Nearly 8–12% of the total energy should be provided from protein sources. An intake of 8% proteins may be sufficient for those having a higher content of animal proteins or high value proteins in the diet.

Fats

Fats comprise a diverse group of saponifiable esters of long chain fatty acids. Fats function as structural elements of the cell membranes, are a major source of energy, carry fat soluble vitamins (A, D, E and K) and are precursors of prostaglandins and hormones.

Fats are present in the diet or the human body in the form of fatty acids (triglycerides), phospholipids and cholesterol. Fatty acids have varying carbon chain length and may be saturated or unsaturated (Fig. 6.1) depending on the predominating fatty acids. The degree of saturation determines whether the fat is solid or liquid at room temperature.

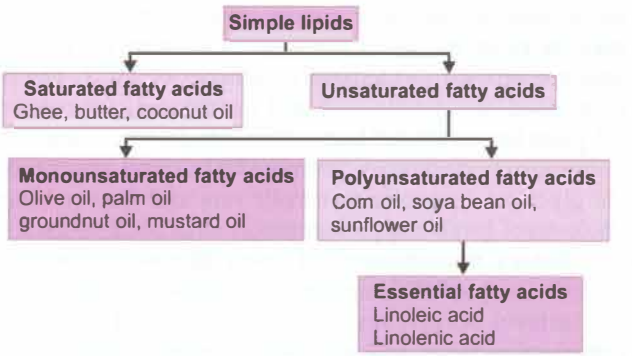


Fig. 6.1: Classification of fats

Fats provide 9 kcal of energy per gram. About 25–30% of energy intake should be from fat. However, in malnourished children, up to 45% of calories can be provided from fat safely. In India, almost 10–15% of fat is derived from invisible fat; therefore, visible fat intake should be restricted to below 20%. Saturated fat should not exceed 7% of the total fat intake; polyunsaturated fat should be restricted to 10% and rest should be derived from monounsaturated fats. A minimum of 3% energy should be derived from linoleic and 0.3% from linolenic acid.

Triglycerides

Triglycerides are divided on the basis of chain length into *medium chain triglycerides* (MCT; 6–12 carbon length) or *long chain triglycerides* (LCT; >12 carbon length). MCTs are

Table 6.1: Daily nutrient requirements and recommended dietary allowances for Indian children

Age	*Energy, kcal*	*Protein, g*	*Visible fat, g*	*Calcium, mg*	*Iron, mg*	*Zinc, mg*	*Magnesium, mg*
<6 mo	92 kcal/kg	1.16 g/kg	–	500	46 µg/kg	–	30
6–12 mo	80 kcal/kg	1.69 g/kg	19	500	05	–	45
1–3 yr	1060	16.7	27	600	09	5	50
4–6 yr	1350	20.1	25	600	13	7	70
7–9 yr	1690	29.5	30	600	16	8	100
Boys, 10–12 yr	2190	39.9	35	800	21	9	120
Girls, 10–12 yr	2010	40.4	35	800	27	9	160
Boys, 13–15 yr	2750	54.3	45	800	32	11	165
Girls, 13–15 yr	2330	51.9	40	800	27	11	210
Boys, 16–17 yr	3020	61.5	50	800	28	12	195
Girls, 16–17 yr	2440	55.5	35	800	26	12	235

Age	*Vitamin A, µg*		*Vitamin*	*Vitamin*	*Vitamin*	*Vitamin*	*Folate*	*Vitamin*	*Vitamin*
	Retinol	*β-carotene*	*B1, mg*	*B2, mg*	*B3, mg*	*B6, mg*	*µg*	*B12, µg*	*C, mg*
<6 mo	350	–	0.2	0.3	710 µg/kg	0.1	25	0.2	25
6–12 mo	350	2800	0.3	0.4	650 µg/kg	0.4	25	0.2	25
1–3 yr	400	3200	0.5	0.6	8	0.9	80	0.2–1.0	40
4–6 yr	400	3200	0.7	0.8	11	0.9	100	0.2–1.0	40
7–9 yr	600	4800	0.8	1.0	13	1.6	120	0.2–1.0	40
Boys, 10– 12 yr	600	4800	1.1	1.3	15	1.6	140	0.2–1.0	40
Girls, 10–12 yr	600	4800	1.0	1.2	13	1.6	140	0.2–1.0	40
Boys, 13–15 yr	600	4800	1.4	1.6	16	2.0	150	0.2–1.0	40
Girls, 13–15 yr	600	4800	1.2	1.4	14	2.0	150	0.2–1.0	40
Boys, 16–17 yr	600	4800	1.5	1.8	17	2.0	200	0.2–1.0	40
Girls, 16–17 yr	600	4800	1.0	1.2	14	2.0	200	0.2–1.0	40

Based on the 2010 recommendations of Indian Council of Medical Research

an immediate source of energy as they are transported directly from the small intestine to liver by portal vein and are burned immediately. Sources of MCT, chiefly comprised of caprylic acid and capric acid, are coconut oil, palm kernel oil and butter (15% MCT). MCTs improve endurance performance, promote fat burning, spare muscle glycogen, increase metabolic rate and lowers blood cholesterol level. Supplementation with MCT is used in the dietary management of cystic fibrosis, pancreatic insufficiency, AIDS, epilepsy, gallstones, high blood cholesterol levels, fat malabsorption and intestinal lymphangiectasia, and are used as energy supplements in athletes. LCT provide essential fatty acids (EFAs) and requires carnitine to produce energy. Prolonged use of MCTs alone leads to EFA deficiency.

Essential Fatty Acids (EFAs)

EFA cannot be synthesized in the body and have to be supplied through dietary fat. Linolenic acid, eicosapentanoic acid and docosahexanoic acid are omega-3 type of fatty acids. They are important components of gray matter of the brain and improve intellectual performance. It is recommended that omega-3 fatty acid content of the diet should be about 0.5% of the total calories or 1.0–1.5 g/day. Most omega-6 fatty acids are consumed in the diet in the form of linoleic acid, which gets converted in the body to γ-linolenic acid and is further broken down to arachidonic acid. Deficiency of EFAs leads to cessation of growth, alopecia, diarrhea, impaired wound healing, decreased calcium absorption, decreased calcium deposits in bones and decreased bone strength.

Cholesterol

Cholesterol is a component of the cell membranes, helps the body produce steroid hormones and bile acids.

Dietary Standards

Infants and children have higher requirements of nutrients than adults. While adults need nutrients for maintaining constant body weight and functions, infants and children require nutrients not only for maintenance but also for promoting and supporting their rapid rate of growth and development. A range of acceptable or safe intake levels have been established for almost all the important nutrients at different ages, which are recognized as Recommended Dietary Allowances (RDA), Recommended Nutrient Intakes (RNI), recommended daily amount of nutrients or safe intakes of nutrients. These terms refer to the average daily amounts of essential nutrients estimated to be sufficiently high to meet the physiological needs of practically all healthy persons in the group.

The RDA of a nutrient accounts for the variability in nutrient requirements and refers to the daily requirement of given nutrient to meet the needs of most (97.5%) individuals in a given population, as estimated from the requirements of two standard deviations above the mean. Hence, the RDA determines the satisfactory level of intake of a nutrient, since only 2.5% individuals are expected to have requirements above the RDA. However, RDA is not meant to be used as standard to determine the requirement of a given individual since it exceeds the requirement of most individuals in a given population. The principle of advising intakes by RDA is used for all nutrients except energy.

Energy

Energy requirements in of children are computed keeping in mind the constant and rapid increase in body size, high metabolic rate that regulates body temperature and maintains high level of activities, and marked developmental changes in organ function and composition. Energy requirements vary through childhood because of variations in growth rate and physical activity. Although growth rate slows in toddlers, their activity levels are high and appetite and food intake tends to be erratic. In older children, growth is more constant but energy needs vary within and between individuals. During adolescence, energy needs increase due to rapid growth and development. There are 3 critical periods in early life of a young child with regards to energy requirements: around 6 months when complementary feeding is initiated, between 1 and 2 yr when physical activity is increased, and between 10 and 12 yr for girls and 15–18 yr for boys when puberty is attained.

In case of energy, advising intakes in excess or below the actual requirements is not safe. Calculation of energy requirement should account for the level of physical activity and the energy required to allow for optimal growth. For children with normal body weights, the energy requirements are calculating roughly as 100 kcal/kg for the first 10 kg of body weight; between 10 and 20 kg, the requirement is 1000 kcal plus 50 kcal/kg added for weight above 10 kg (e.g. for a 15 kg child, the requirement will be 1250 kcal); and for weight more than 20 kg, 20 kcal/kg is added to 1500 kcal to estimate the requirements (e.g. for a 30 kg child the requirement is approximately 1700 kcal).

NORMAL DIET

Breastfeeding

An infant should be exclusively breastfed till six months of age (Box 6.1). During this phase, additional food or fluid is not required as breast milk is nutritionally complete for

Box 6.1: Cardinal principles of breastfeeding practice

- Initiation of breastfeeding within an hour afterbirth
- Exclusive breastfeeding up to 6 mo of age
- Continuation of breastfeeding along with complementary feeding for up to 2 yr of age

the child's growth and development and it protects from infections and strengthens immune system. Breastfeeding issues are discussed in Chapter 8.

Complementary Feeding

After six months of age, breast milk alone is not enough to make an infant grow well. Complementary feeding refers to food which complements breast milk and ensures that the child continues to have enough energy, protein and other nutrients to grow normally. *Complementary feeding is started at six months of age, while continuing breastfeeding,* Breastfeeding is encouraged up to two years of age in addition to normal food. Key recommendations for breastfeeding and complementary feeding are given in Table 6.2.

Balanced Diet

Balanced diet is defined as nutritionally adequate and appropriate intake of food items that provide all the nutrients in required amounts and proper proportions. Even at 9 months, infants need small portions of a mix of food groups to be included in their diet to ensure intakes of all macronutrients and micronutrients. A combination of carbohydrate rich food (any cereal, fruit and/or vegetable), a protein source (milk and milk products, pulse, egg, meat, fish, nuts) and a fat (visible oil or ghee) and/or sugar or salt should be used to make nutritionally adequate complementary food or feed. A balanced diet should be consumed by children and adolescents to ensure proper growth and development and to stay healthy and disease free. A balanced diet contains 55–60% calories from carbohydrates, 10–12% proteins and 25–30% fat. Tables 6.3 and 6.4 describe the quality and content of important nutrients of common food items. Table 6.5 lists food exchanges useful in planning diet for children.

Foods are grouped conventionally as: (i) cereals, millets and pulses; (ii) vegetables and fruits; (iii) milk and milk products; (iv) egg, meat, fish; and (v) oils and fats.

Cereals, millets and pulses are the major source of most nutrients in Indian diets. Milk provides good quality protein and calcium and hence, is an essential item of our diet. Eggs, flesh foods and fish enhance the quality of diet but Indians are predominantly a vegetarian society and most of our nutrients are derived from cereals, pulse and milk based diets. Oils and nuts are calorie rich foods and are useful in increasing the calorie density. Vegetables and fruits provide protective substances such as vitamins, minerals, fiber and antioxidants.

Table 6.2: Counseling for feeding of infants and children

Age (months)	*Food*
Up to 6 mo	Breastfeed as often as the child wants, day and night, at least 8 times in 24 hr Do not give any other foods *or* fluids, not even water *Remember:* Continue breastfeeding even if the child is sick
6–12 mo	Breastfeed as often as the child wants *Complementary feedings:* Give at least one katori serving at a time of mashed roti/bread/biscuit mixed in sweetened undiluted milk; *or* mashed roti, rice, bread mixed in thick dal with added ghee/oil; *or* khichri with added oil or ghee Add cooked vegetables in these servings *or* use sevian, dalia, halwa, kheer prepared in milk *or* any cereal porridge cooked in milk, *or* mashed boiled or fried potatoes Offer banana, biscuit, cheeku, mango or papaya as snacks in between the serving *Frequency:* 3 times per day if breastfed; 5 times per day if not breastfed *Remember:* Keep the child in your lap and feed with your own hands; wash your own and child's hands with soap and water every time before feeding
12 mo to 2 yr	Breastfeed as often as the child wants; offer food from the family pot Give at least 1½ katori serving at a time of mashed roti/rice bread mixed in thick dal *or* khichri with added ghee or oil Add cooked vegetables in the servings, *or* mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk, *or* sevian, dalia, halwa or kheer prepared in milk *or* any cereal porridge cooked in milk, *or* mashed boiled/fried potatoes *Frequency:* 5 times a day Offer banana, biscuit, cheeku, mango or papaya as snacks in between the servings *Remember:* Sit by the side of child and help him to finish the serving; wash your child's hands with soap and water every time before feeding
2 yr and older	Give family food as 3 meals each day Twice daily, also give nutritious snacks between meals, e.g. banana, biscuit, cheeku, mango, or papaya *Remember:* Ensure that the child finishes the serving; teach your child to wash his hands with soap and water every time before feeding

Table 6.3: Nutritive value of common food items

Foods	*Quantity*	*Household measure (cooked amount)*	*Calories kcal*	*CHO g*	*Protein g*	*Fats g*	*Na mg*	*K mg*
Milk and milk products								
Milk (cow)	250 ml	1 glass	166	11	8	10	40	350
Milk buffalo	250 ml	1 glass	238	12.5	11	16	47	225
Full cream milk (Mother dairy)	250 ml	1 glass	215	12	8	15	?	?
Toned milk (Mother dairy)	250 ml	1 glass	144	11	8	7.5		
Double toned milk	250 ml	1 glass	110	11	8	3.75		
Curd (cow milk)	125 ml	1 katori (medium)	77	4	4	5	40	165
Paneer (cow milk)	25 g	1 small piece	64	3	4	4	60	29
Butter milk (cow milk)	250 ml	1 glass	39	1	2	3	–	–
Skimmed milk (fresh)	250 ml	1 glass	75	12	6	0.3	–	–
Skimmed milk (dry)	25 g	–	93	13	9.5	0.3	40	350
Cream	25 ml	–	35	1	1	3	10	25
Processed cheese	25 g	1 small piece	84	1.5	6	6	175	21
Meat and poultry								
Meat (muscle)	100 g	4 pieces	191	–	18.5	13	33	270
Chicken	100 g	1 portion	136	–	25	4	7	50
Fish (rohu)	100 g	2–3 pieces	106	5	17	2	101	288
Egg (hen)	50 g	1	77	0.90	6.0	5.35	52	63
Egg white (hen)	25 g	1 Egg white	13	0.18	2.73	0.04	42	41
Egg yolk (hen)	20 g	1 Egg yolk	64	0.72	3.17	5.31	10	22
Bacon	25 g	1 slice	188	–	2	20	170	32
Ham	25 g	1 slice	29	–	5	1	275	85
Cereal and pulses								
Wheat flour	25 g	1 medium roti	84	17	3	0.4	5	80
Rice	25 g (raw)	3/4 katori (75 g)	86	19	2	0.2	2	17
Bread	25 g	1 slice	61	13	2	0.1	120	20
Corn flakes	25 g	½ cup	94	21	2	0.2	251	30
Wheat dalia	25 g	½ cup	87	18	3	0.3	1	87
Green gram	25 g	1 katori	87	15	6	0.3	7	211
Lentils	25 g	1 katori	86	15	6	0.2	10	157
Rajmah	25 g	1 katori	87	15	6	0.3	–	–
Bengal gram	25 g	1 katori	89	15	4	1.4	9	202
Soya beans	25 g	1 katori	109	5	11	5	–	–
Khichri (rice + dal 4:1)	25 g	1 katori (cooked)	89	18.2	3	1.5	3.2	33.6
Vegetables								
Leafy (spinach, bathua, amaranth)	125 g	1 katori	42	7.5	1.2	0.8	100	182
Seasonal (cauliflower, bhindi, and peas, brinjal)	100 g	1 katori	51	10	2.5	0.1	15	96
Roots and tubers (potato, arbi and zimkand)	100 g	1 katori	93	21	2	0.1	10	345
Fruits								
Papaya	100 g	1 slice	32	7	1	–	6	69
Grapes	100 g	8–10 nos.	71	16.5	0.5	0.3	–	70
Apricots	100 g	2 nos.	55	12	1	0.3	–	430
Lichi	100 g	4–5 nos.	61	13	1.5	0.3	104	159
Pears	100 g	1 medium	52	12	0.5	0.2	6	96
Watermelon	100 g	1 small size	16	3.3	0.2	0.2	27	160
Musk melon	100 g	1 slice	17	3.5	0.3	0.2	104	341

Contd.

Table 6.3: Nutritive value of common food items *(Contd.)*

Foods	*Quantity*	*Household measure (cooked amount)*	*Calories kcal*	*Carbohydrate g*	*Protein g*	*Fats g*	*Na mg*	*K mg*
Tomato ripe	100 g	2 nos	20	3.4	1	0.2	12	146
Apple	100 g	1 medium	58	13	0.2	0.5	28	75
Orange	100 g	1 medium	46	10.5	0.5	0.2	5	93
Banana	100 g	1 medium	116	27	1.2	0.3	37	88
Guava	100 g	1 medium	51	11	1	0.3	6	91
Mussambi	100 g	1 medium	43	9	1	0.3	–	490
Mango	100 g	1 small	72	16	1	0.4	26	205
Lemon	100 g	1 medium	14	3	–	0.2	–	70
Dried fruits and nuts								
Raisin (kishmish)	25 g	1½ tsp.	78	19	0.5	–	8	216
Apricot (dried)	25 g	4–6 nos.	76	18	0.5	0.2	8	215
Dates (fresh)	25 g	4 nos.	35	8	0.5	0.1	1	–
Almonds	25 g	8–10 nos.	163	3	5	14.5	1	170
Cashewnut	25 g	8–10 nos.	150	5.5	5	12	1	113
Walnuts	25 g	8–10 nos.	172	3	4	16	1	120
Ground nuts	25 g	15–20 nos.	142	6.5	6.5	10	–	–
Coconut (fresh)	100 g	–	444	13	4.5	41.6	–	–
Coconut (dry)	25 g	–	165	4.6	1.7	15.5	–	–
Fats and oils								
Oil	10 g	2 teaspoon	90	–	–	10	–	–
Ghee	10 g	1 teaspoon	90	–	–	10	–	–
Butter	10 g	1 teaspoon	72	–	–	8	–	–
Miscellaneous								
Sponge cake	–	1 small piece	114	21	3	2	145	22
Ice cream plain	100 g	1 cup	203	21	5	11	63	181
Burfi	40 g	1 piece	135	13	5	7	–	–
Rasgulla	35 g	1 piece	163	32	2	3	30	15
Pakora or samosa	40 g	1 piece	132	14	1	8	–	–
Puri	40 g	1 piece	187	19	3	11	–	–
Biscuit salt	25 g	8–10 nos.	132	14	1	8	3	20
Biscuit sweet	25 g	5–6 nos.	112	18	1	4	–	–
Arrowroot powder	25 g	5 tablespoons	84	21	–	–	1	7
Pastry	25 g	1 small piece	265	35	2	13	–	–
Sugar cane juice	250 ml	1 glass	88	22	–	–	15	750
Honey	25 ml	5 teaspoons	80	20	–	–	6	60
Sago	25 g	2 tablespoons	88	22	–	–	–	–
Jaggery	25 g	–	96	24	–	–	–	–
Sugar	25 g	5 teaspoons	100	25	–	–	–	–
Mushrooms	100 g	–	33	1	5	1	4	103
Macaroni	25 g	¼ cup	88	19	3	–	2	221
Marmlade	10 g	1 teaspoon	28	7	–	–	7	2
Milk chocolate	40 g	1 slab	221	23	3	13	–	37
Horlicks and Viva	25 g	5 teaspoons	88	19	3	–	–	–
Protinex	30 g	–	88	5	17	–	–	–
Soya nuggets	25 g	8– 10 nos.	80	7	13	–	–	80
Custard powder	25 g	5 teaspoons	25	–	–	–	–	100
Coffee	5 g	1 teaspoon	–	–	–	–	–	–
Ovaltin/Bournvita	5 g	1 teaspoon	25	3	1	1	–	–
Cornstarch	25 g	5 teaspoons	100	25	–	–	–	–
Dalmoth	25 g	–	190	12	4	14	150	157
Sev	25 g	–	105	3	5	105	150	157
Fried moong dal	25 g	–	170	15	5	10	400	157

Adapted from the 2004 recommendations of the National Institute of Nutrition (ICMR), Hyderabad on the Nutritive Value of Indian Foods. Contents of some miscellaneous food items have been standardized at All India Institute of Medical Sciences, New Delhi. K potassium; Na sodium

Table 6.4: Nutritional characteristics of common food items

Foods	*Main nutrients*	*Other characteristics*
Milk and milk products	Protein, fat, calcium, phosphorus, vitamin B2	Provide high quality protein lactose and saturated fats; lack in iron and vitamin C
Egg (hen)	Protein, fat, phosphorus, riboflavin	Provide high quality protein and vitamin B12; lacks in carbohydrates and vitamin C; contains saturated fats and is rich in cholesterol
Chicken	Protein, phosphorus	Provides high quality protein and all B vitamins; does not provide carbohydrate, fat and iron
Fish	Protein, fat, calcium, vitamin B12	Lacks in carbohydrates; good source of high quality protein and fat containing omega-3 fatty acids
Cereals grains and products	Carbohydrate, fiber, folic acid, vitamins B1 and B2, phytates, iron	Good source of energy; has poor quality protein that lacks in lysine; provides negligible amounts of unsaturated fat; phytates hinder the absorption of iron
Pulses, peas, beans	Carbohydrate, protein, folic acid, calcium, fiber, vitamins B1 and B2, iron, phosphorus	Good source of energy; contain proteins of lower quality that lack in methionine; provides negligible amount of unsaturated fat; absorption of iron is hindered by phytates
Soya bean	Protein (35%), fiber, fat (40%), calcium, iron, zinc, copper, magnesium, selenium, folic acid, potassium, all B vitamins, carotenoids, fiber, isoflavones	Source of high quality protein (twice of that in pulses) and fat (three times that in pulses); contains polyunsaturated, monounsaturated and saturated fats; vegetarian source of omega-3 fatty acids; deficient in sodium and vitamin C and B12; phytates hinder the absorption of iron and calcium
Seasonal vegetables	Carotenoids, folic acid, calcium, fiber, vitamin C	Good source of carbohydrates in the form of roughage and fiber that provide bulk in diet; deficient in proteins and fat
Green leafy vegetables	Carotenoids, folic acid, calcium	Good source of soluble fiber; deficient in protein and fat fiber, vitamin C, iron, riboflavin
Root vegetables	Carbohydrate (chiefly starch)	Good source of energy; deficient in protein, fat and folic acid; carrots are a rich source of carotene, potatoes provide vitamin C; tapioca is rich in calcium
Fruits	Carbohydrate, potassium	Good source of fiber and roughage; deficient in proteins, fat and folic acid; juicy fruits have high potassium content; banana is a good source of energy but poor source of potassium
Nuts	Energy, protein, fat and B vitamins	Groundnuts are particularly rich in thiamine and nicotinic acid

Adapted from the 2010 recommendations of the National Institute of Nutrition (ICMR), Hyderabad on the Nutritive Value of Indian Foods

Table 6.5: Food exchanges

Foods	*Amounts*	*Household measure*	*Calorie, kcal*	*Carbohydrate, g*	*Protein, g*	*Fats, g*
Cow milk	100 ml	½ cup	67	4.4	3.2	4.1
Human milk			65	7.4	1.1	3.4
Buffalo milk			96	5.0	4.4	6.5
Full cream milk			91	4.8	4.4	6.0
Egg	100 g	2 nos.	169	–	13	13
Meat	100 g	4 pcs.	191	–	18.5	13
Fish	100 g	2–3 pcs	106	5	17	2
Chicken	100 g	1 portion	136	–	25	4
Wheat flour	1 katori raw	4 chapatis	336	68	12	1.6
Rice	1 katori raw	3 katoris	345	76	8	1.0
Pulses	100 g raw	4 katoris	345	60	24	1.0
Green leafy veg	100 g raw	1/3 katori	33	6	1	0.6
Seasonal veg	100 g raw	½ katori	51	10	2.5	1.0
Root veg	100 g raw	½ cup	93	21	2	0.1
Fruits	100 g	1 portion	54	12	1	0.2
Banana	100 g	1 portion	116	27	1.2	0.3
Nuts	100 g	Handful	568	26	26	40
Sugar	100 g	–	400	100	–	–
Fat	100 g	–	900	–	–	100

Factors to be Considered while Planning Food for the Child

There are six cardinal factors to be considered while feeding the child:

1. *Energy density.* Most of our traditional foods are bulky and a child cannot eat large quantities at a time. Hence, it is important to give small energy dense feeds at frequent intervals to ensure adequate energy intakes by the child. Energy density of foods given to infants and young children can be increased without increasing the bulk by adding a *teaspoon of oil or ghee in every feed*. Fat is a concentrated source of energy and increases energy content of food without increasing the bulk. Sugar and jaggery can be added in infant foods. *Amylase rich foods* such as malted foods reduce the viscosity of the foods and therefore, the child can eat more quantities at a time (malting is germinating whole grain cereal or pulse, drying and then grinding). Thin gruels do not provide enough energy; a young infant particularly during 6–9 months requires thick but smooth mixtures.
2. *Amount of feed.* At 6 months of age, feed should be started with small amount as much as 1–2 teaspoons and the quantity is increased gradually as the child gets older and starts to accept food better. Child should be given time to adapt gradually to larger quantities from teaspoon to tablespoon and then to a katori.
3. *Consistency of feed.* Infants can eat pureed, mashed and semisolid foods beginning at six months. By 8 months, most infants can also eat finger foods (snacks that can be eaten by children alone). By 12 months, most children can eat the same types of foods as consumed by the rest of the family. As the child grows older, he should be shifted to more appropriate foods suitable for his age. Foods that can cause choking such as nuts, grapes, raw carrots should be avoided. For small children, the food should not contain particulate matter that may trigger gag reflex or vomiting.
4. *Frequency of feeding.* An average healthy breastfed infant needs complementary foods 2–3 times per day at 6–8 months of age and 3–4 times per day at 9–24 months. For children 12–24 months of age, additional nutritious snacks such as a piece of fruit should also be offered 1–2 times per day. Snacks are defined as foods eaten between meals that are convenient and easy to prepare. If energy density or amount of food per meal is low, or the child is no longer breastfed, more frequent meals should be provided.
5. *Hygiene.* Good hygiene and proper food handling should be practiced to prevent children from infections and malnutrition. Simple practices include: (i) washing hands before food preparation and eating, (ii) serving freshly cooked foods (cooked food should not be kept for more than 2–3 hr), (iii) using clean utensils, (iv) covering food properly, and (v) avoiding use of feeding bottles.
6. *Helping the child.* Feeding the infants and children should be an active, engaging and interactive affair. Often the food is left in front of the child to eat. This approach is not appropriate. Parents should actively engage with the child in feeding, making the child sit in the lap and feeding him affectionately in small portions with spoon or with small morsels. The older child is coaxed and encouraged to finish the desired amount of food.

UNDERNUTRITION

Undernutrition is a condition in which there is inadequate consumption, poor absorption or excessive loss of nutrients. *Overnutrition* is caused by overindulgence or excessive intake of specific nutrients. The term *malnutrition* refers to both undernutrition as well as overnutrition. However, sometimes the terms malnutrition and *protein energy malnutrition* (PEM) are used interchangeably with undernutrition.

Malnourished children may suffer from numerous associated complications. They are more susceptible to infections, especially sepsis, pneumonia and gastro-enteritis. Vitamin deficiencies and deficiencies of minerals and trace elements can also be seen. Malnutrition in young children is conventionally determined through measurement of height, weight, skinfold thickness (or subcutaneous fat) and age. The commonly used indices derived from these measurements are given in Table 6.6.

Epidemiology

Childhood undernutrition is an underlying cause in an estimated 35% of all deaths among children under five and 21% of total global disability adjusted life years (DALYs) lost among under 5 children. According to the National Family Health Survey (NFHS) 3, carried out in 2005–06, 40% of India's children under the age of three are underweight, 45% are stunted and 23% are wasted (Fig. 6.2). Comparable figures for NFHS 2 (1998–99) are 43%, 51% and 20%, respectively. There has been a slow reduction in undernutrition in the country over the years, but we continue to have the highest burden of childhood undernutrition in the world.

Overall, both girls and boys have similar prevalence of undernutrition. Prevalence of undernutrition is higher in rural areas (46%) than in urban populations (33%). Levels

Table 6.6: Indicators of undernutrition

Indicator	*Interpretation*	*Comment*
Stunting	Low height-for-age	Indicator of chronic malnutrition, the result of prolonged food deprivation and/or disease or illness
Wasting	Low weight-for-height	Suggests acute malnutrition, the result of more recent food deficit or illness
Underweight	Low weight-for-age	Combined indicator to reflect both acute and chronic malnutrition

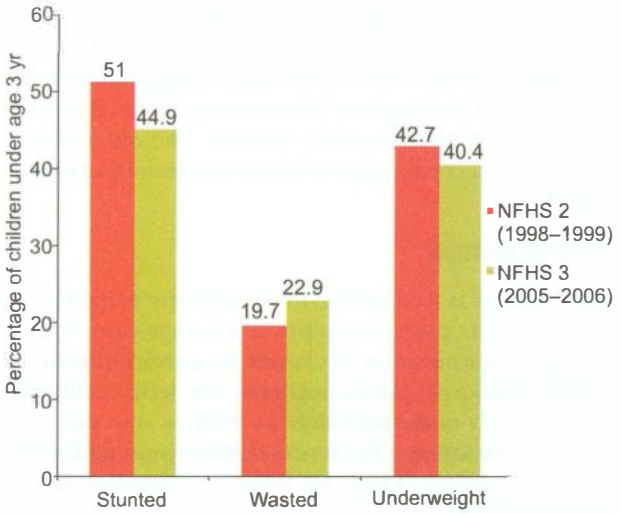


Fig. 6.2: Trends in nutritional status of children under 3 yr in India, Source: National Family Health Survey (NFHS) 2 and 3

of malnutrition vary widely across Indian states. Punjab, Kerala, Jammu and Kashmir and Tamil Nadu account for the lowest proportions (27–33%) of underweight children; while Chhattisgarh, Bihar, Jharkhand and Madhya Pradesh report the maximum (52–60%) levels of underweight children.

During the first six months of life, 20–30% of children are already malnourished, often because they were born low birthweight. The proportion of undernutrition starts rising after 4–6 months of age because of the introduction of unhygienic foods that cause infections such as diarrhea. Late introduction of complementary feeding and inadequate food intake leads to increasing predisposition to undernutrition. The proportion of children who are stunted or underweight increases rapidly with the child's age until about 18–24 months of age (Fig. 6.3).

Undernutrition is strongly associated with shorter adult height, less schooling, reduced economic productivity and, for women, lower offspring birthweight. Low birthweight and undernutrition in childhood are risk factors for diabetes, hypertension and dyslipidemias in adulthood.

Classification of Undernutrition

Undernutrition is classified in different ways.

Basic Groupings: Undernourished, Stunted and Wasted

An undernourished child has low weight-for-age (Table 6.6). Stunting means being short or low height-for-age. This indicates chronic undernutrition. Wasting on the other hand means low weight-for-height indicating acute undernutrition. A wasted child has an emaciated look.

WHO Classification

The assessment of nutritional status is done according to weight-for-height (or length), height (or length)-for-age and presence of edema. The WHO recommends the use of Z scores or standard deviation scores (SDS) for evaluating anthropometric data, so as to accurately classify individuals with indices below the extreme percentiles. The SD score is defined as the deviation of the value for an individual from the median value of the reference population, divided by the standard deviation of the reference population.

$$\text{SD score} = \frac{\text{Observed value} - \text{Median reference value}}{\text{Standard deviation of reference population}}$$

The calculation of the SDS gives a numerical score indicating how far away from the 50th centile for age the child's measurements falls. A score of –2 to –3 indicates moderate malnutrition and a score of +2 to +3 SDS indicates overweight. A score of less than –3 SDS indicates

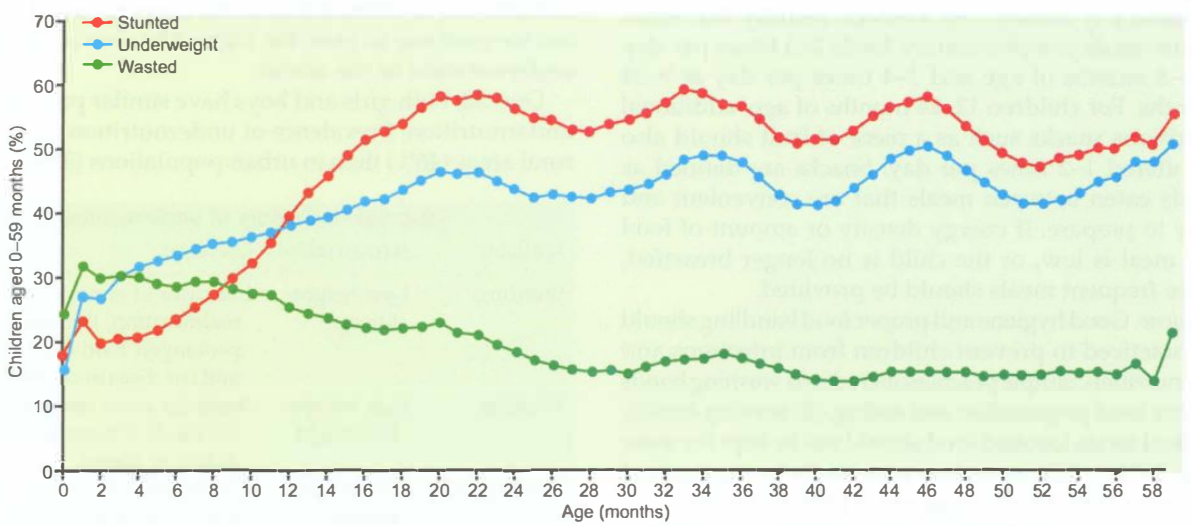


Fig. 6.3: Proportions of malnourished children according to age (National Family Health Survey 3)

severe malnutrition and a score of more than +3 indicates obesity. WHO growth charts are provided in Chapter 2.

The term 'edematous malnutrition' is used if edema is also present. Clinical classification of undernutrition as marasmus, kwashiorkor and marasmic kwashiorkor is helpful (discussed below).

IAP Classification

This classification proposed by the Indian Academy of Pediatrics is based on weight for age values (Table 6.7). The standard used in this classification for reference population was the 50th centile of the old Harvard standards.

Table 6.7: IAP classification of malnutrition

Grade of malnutrition	*Weight-for-age of the standard (%)*
Normal	>80
Grade I	71–80 (mild malnutrition)
Grade II	61–70 (moderate malnutrition)
Grade III	51–60 (severe malnutrition)
Grade IV	<50 (very severe malnutrition)

Marasmus, Kwashiorkor, Marasmic Kwashiorkor

Based on the appearance, undernourished child may have marasmus or kwashiorkor or marasmic kwashiorkor. These severe forms of malnutrition are described later in this chapter.

Age Independent Indices to Diagnose Undernutrition

In many situations the child's age is not known, e.g. children from orphanages, street children, during natural disasters, etc. This has prompted many attempts to devise methods of interpreting anthropometric data, which do not require knowledge of precise age. Various variables change slowly over certain broad age ranges and thus are regarded as independent of age over these ranges (Table 6.8). Certain tools have been developed to simplify the measurement for field workers and give a visible indicator of the degree of malnutrition.

Mid upper arm circumference (MUAC) It is a widely used measurement and requires minimum equipment. It increases rapidly in the first year (11–16 cm) and then been found to be relatively stable between the ages 1 and 5 yr at a value of between 16 and 17 cm. Any value below 13.5 cm is abnormal and suggestive of malnutrition. A value below 11.5 cm is suggestive of severe malnutrition. Recently, it has been shown that MUAC may not be age independent and therefore, the WHO recommends MUAC-for-age reference data to be used in girls and boys 6–59 month old where possible.

Shakir tape method This special tape has colored zones: red, yellow and green corresponding to <12.5 cm (wasted), 12.5 to 13.5 cm (borderline) and over 13.5 cm (normal) MUAC respectively.

Bangle test A bangle with internal diameter of 4 cm is passed above the elbow. In severe malnutrition it can be passed above the elbow, in normal children it cannot.

Skinfold thickness It is an indication of the subcutaneous fat. Triceps skin fold is the most representative of the total subcutaneous fat up to sixteen years of age. It is usually above 10 mm in normal children whereas in severely malnourished it may fall below 6 mm.

Severe Acute Malnutrition

Severe acute malnutrition (SAM) among children 6–59 months of age is defined by World Health Organization (WHO) and UNICEF as *any* of the following: (i) weight-for-height below –3 standard deviation (SD or Z scores) of the median WHO growth reference; (ii) visible severe wasting; (iii) presence of bipedal edema; or (iv) mid upper arm circumference below 11.5 cm. This classification is used to identify children at high-risk of death. *Children having SAM require urgent attention and management in the hospital*. In a child below 6 months of age, the MUAC cannot be used, and SAM should be diagnosed in the presence of (i), (ii) or (iii).

Etiology

The causes of malnutrition could be viewed as immediate, underlying and basic as depicted in Fig. 6.4.

Immediate determinants The immediate determinants of a child's nutritional status work at the individual level. They include low birthweight, illnesses (particularly infections such as diarrhea and pneumonia) and inadequate dietary intake (Box 6.2).

Underlying determinants The immediate determinants are in turn influenced by three household determinants namely food, health and care.

Table 6.8: Age independent indices

Name of index	*Calculation*	*Normal value*	*Value in malnutrition*
Kanawati and McLaren	Mid-arm circumference/head circumference (cm)	0.32–0.33	Severely malnourished <0.25
Rao and Singh	Weight (in kg) × 100/height^2 (in cm)	0.14	0.12–0.14
Dugdale	Weight (in kg)/height$^{1.6}$ (in cm)	0.88–0.97	< 0.79
Quaker arm circumference measuring stick (Quac stick)	Mid-arm circumference that would be expected for a given height		75–85% malnourished; <75% severely malnourished
Jeliffe ratio	Head circumference/chest circumference		Ratio <1 in a child >1 yr suggests malnutrition

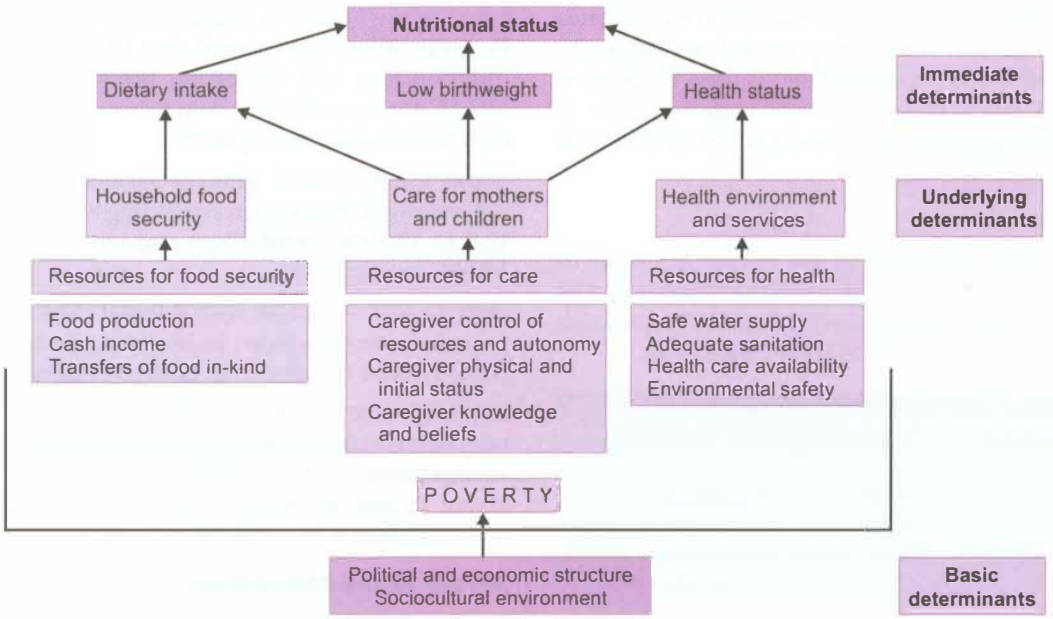


Fig. 6.4: Determinants of a child's nutrition status

Box 6.2: Three immediate causes of undernutrition

- *Low dietary intake*: Delayed complementary feeding and inadequate intake of food means less nutrients available for growth
- *Low birthweight*: Infants born small, often remain small
- *Infection*: Diarrhea, pneumonia and other infections consume energy and hamper growth. Diarrhea causes nutrition loss in stool

Food refers to food security at the household level. It is the sustainable access to safe food of sufficient quality and quantity, paying attention to energy, protein and micronutrients. This in-turn depends on having financial, physical and social access as distinct from mere availability.

Care refers to a process taking place between a caregiver and the receiver of care. It translates food availability at the household level and presence of health services into growth and development of the child. Households may have an abundance of food but still have malnourished children attributed to absence of care. Care includes care for women, breastfeeding and complementary feeding, home health practices, hygiene practices, psychosocial care and food preparation. The factors that determine adequate household food security, care and health are related to resources, their control and a host of political, cultural and social factors that affect their utilization.

Health includes access to curative and preventive health services to all community members as well as a hygienic and sanitary environment and access to water.

Basic Determinants

Finally, the underlying determinants are influenced by the basic determinants. These include the socioeconomic status and education level of the families, women's empowerment, cultural taboos regarding food and health, access to water and sanitation, etc.

Pathological Features

Malnutrition affects almost all organ systems. The salient findings in various organs or tissues are elucidated in Table 6.9.

Clinical Features of Malnutrition

Mild Malnutrition

It is most common between the ages of 9 months and 2 yr. Main features are as follows:

Growth failure. This is manifested by slowing or cessation of linear growth; static or decline in weight; decrease in mid-arm circumference; delayed bone maturation; normal or diminished weight for height Z scores; and normal or diminished skin fold thickness.

Infection. A high rate of infection involving various organ systems may be seen, e.g. gastroenteritis, pneumonia and tuberculosis.

Anemia. May be mild to moderate and any morphological type may be seen.

Activity. This may be diminished

Skin and hair changes. These may occur rarely.

Moderate to Severe Malnutrition

Moderate to severe malnutrition is associated with one of classical syndromes, namely, marasmus, kwashiorkor, or with manifestations of both (Table 6.10).

Table 6.9: Pathological changes in malnutrition in various organ systems

Upper gastrointestinal tract	Mucosa shiny and atrophic, papillae of tongue flattened
Small and large intestine	Mucosa and villi atrophic; brush border enzymes reduced; hypotonic, rectal prolapse
Liver	Fatty liver, deposition of triglycerides
Pancreas	Exocrine secretion depressed; endocrine function less severely affected; glucagon production reduced; insulin levels low; atrophy and degranulation or hypertrophy of islets seen
Endocrine system	Elevated growth hormone; thyroid involution and fibrosis; adrenal glands atrophic and cortex thinned; increased cortisol; catecholamine activity unaltered
Lymphoreticular system	Thymus involuted; loss of distinction between cortex and medulla; depletion of lymphocytes; paracortical areas of lymph nodes depleted of lymphocytes; germinal centers smaller and fewer
Central nervous system	Head circumference and brain growth retarded; changes seen in the dendritic arborization and morphology of dendritic spines; cerebral atrophy on CT/MRI; abnormalities in auditory brainstem potentials and visual evoked potentials
Cardiovascular system	Changes in cardiac volume, muscle mass and electrical properties of the myocardium; systolic function affected more than diastolic function

Table 6.10: Differences between kwashiorkor and marasmus

Clinical finding	*Marasmus*	*Kwashiorkor*
Occurrence	More common	Less common
Edema	Absent	Present
Activity	Active	Apathetic
Appetite	Good	Poor
Liver enlargement	Absent	Present
Mortality	Less than kwashiorkor	High in early stage
Recovery	Recover early	Slow recovery
Infections	Less prone	More prone

Marasmus

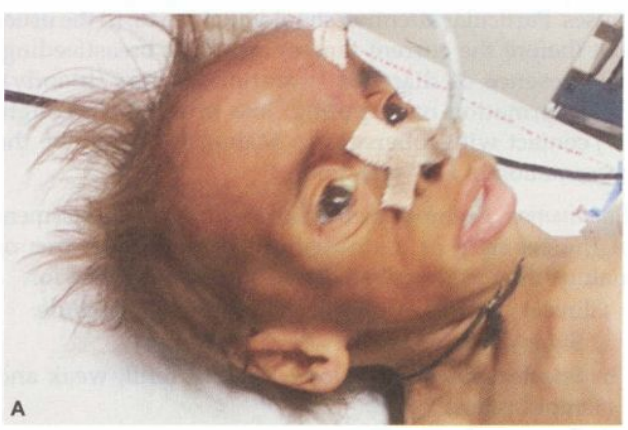
It results from rapid deterioration in nutritional status. Acute starvation or acute illness over a borderline nutritional status could precipitate this form of undernutrition. It is characterized by marked *wasting of fat and muscle* as these tissues are consumed to make energy.

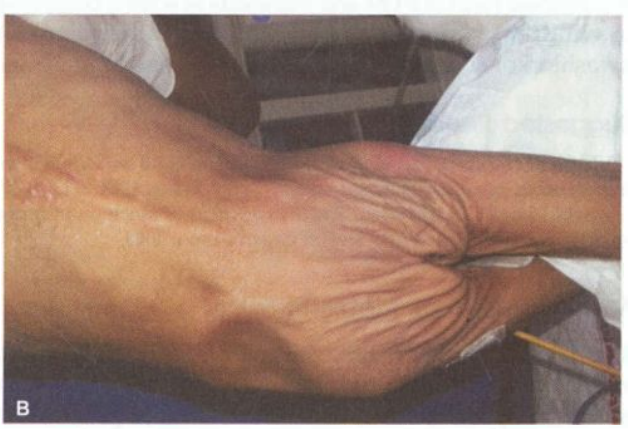
i. The main sign is *severe wasting*. The child appears very thin (skin and bones) and has no fat. There is severe wasting of the shoulders, arms, buttocks and thighs (Figs 6.5A and B).
ii. The loss of buccal pad of fat creates the aged or wrinkled appearance that has been referred to as *monkey facies* (Fig. 6.5A). *Baggy pants* appearance refers to loose skin of the buttocks hanging down (Fig. 6.5B). Axillary pad of fat may also be diminished
iii. Affected children may appear to be alert in spite of their condition
iv. There is no edema

Kwashiorkor

It usually affects children aged 1–4 yr. The main sign is *pitting edema*, usually starting in the legs and feet and spreading, in more advanced cases, to the hands and face. Because of edema, children with kwashiorkor may look healthy so that their parents view them as well fed.

i. *General appearance.* Child may have a fat *sugar baby* appearance.
ii. *Edema.* It ranges from mild to gross and may represent up to 5–20% of the body weight.
iii. *Muscle wasting.* It is always present. The child is often weak, hypotonic and unable to stand or walk.





Figs 6.5A and B: An 8-yr-old child with severe acute malnutrition. Note the (A) dull, lustreless, sparse hair; temporal hollowing; loss of buccal pad of fat; anxious look; (B) loose folds of skin in the gluteal region giving a 'baggy pant' appearance

iv. *Skin changes.* The skin lesions consist of increased pigmentation, desquamation and dyspigmentation. Pigmentation may be confluent resembling *flaky paint* or in individual *enamel spots*. The distribution is typically on buttocks, perineum and upper thigh. Petechiae may be seen over abdomen. Outer layers of skin may peel off and ulceration may occur. The lesions may sometimes resemble burns.

v. *Mucous membrane lesions.* Smooth tongue, cheilosis and angular stomatitis are common. Herpes simplex stomatitis may also be seen.

vi. *Hair.* Changes include dyspigmentation, loss of characteristic curls and sparseness over temple and occipital regions. Hairs also lose their lustre and are easily pluckable. A *flag sign* which is the alternate bands of hypopigmented and normally pigmented hair pattern is seen when the growth of child occurs in spurts.

vii. *Mental changes.* Includes unhappiness, apathy or irritability with sad, intermittent cry. They show no signs of hunger and it is difficult to feed them.

viii. *Neurological changes.* These are seen during recovery.

ix. *Gastrointestinal system.* Anorexia, sometimes with vomiting, is the rule. Abdominal distension is characteristic. Stools may be watery or semisolid, bulky with a low pH and may contain unabsorbed sugars.

x. *Anemia.* It may also be seen, as in mild PEM, but with greater severity.

xi. *Cardiovascular system.* The findings include cold, pale extremities due to circulatory insufficiency and are associated with prolonged circulation time, bradycardia, diminished cardiac output and hypotension.

xii. *Renal function.* Glomerular filtration and renal plasma flow are diminished. There is aminoaciduria and inefficient excretion of acid load.

Marasmic Kwashiorkor

It is a mixed form of PEM and manifests as edema occurring in children who may or may not have other signs of kwashiorkor and have varied manifestations of marasmus.

Suggested Reading

Victora C, Adair L, Fall C, et al. Maternal and child undernutrition: consequences for adult health and human capital. Lancet 2008; 371;340–57

World Health Organization. The management of nutrition in major emergencies. Geneva: World Health Organization; 2000

MANAGEMENT OF MALNUTRITION

The management of malnutrition depends on its severity. While mild to moderate malnutrition can be managed on ambulatory basis, severe malnutrition is preferably managed in hospital. The management of low birthweight infants is discussed in Chapter 8.

Mild and Moderate Malnutrition

Mild and moderate malnutrition make up the greatest portion of malnourished children and account for >80% of malnutrition associated deaths. It is, therefore, vital to intervene in children with mild and moderate malnutrition at the community level before they develop complications.

The mainstay of treatment is provision of adequate amounts of protein and energy; at least 150 kcal/kg/day should be given. In order to achieve these high energy intakes, frequent feeding (up to seven times a day) is often necessary. Because energy is so important and because carbohydrate energy sources are bulky, oil is usually used to increase the energy in therapeutic diets.

It is recognized increasingly that a relatively small increase over normal protein requirements is sufficient for rapid catchup growth, provided energy intake is high. A protein intake of 3 g/kg/day is sufficient. Milk is the most frequent source of the protein used in therapeutic diets, though other sources, including vegetable protein mixtures, have been used successfully. Adequate minerals and vitamins should be provided for the appropriate duration. The best measure of the efficacy of treatment of mild and moderate malnutrition is weight gain.

Severe Acute Malnutrition (SAM)

The World Health Organization has developed guidelines for the management of severe acute malnutrition and these have been adapted by the Indian Academy of Pediatrics. At the community level, the four criteria listed previously should be used to diagnose severe acute malnutrition. *WHO recommends exclusive inpatient management of children with severe acute malnutrition.*

Assessment of the Severely Malnourished Child

History. The child with severe malnutrition has a complex backdrop with dietary, infective, social and economic factors underlying the malnutrition. A history of events leading to the child's admission should be obtained. Socioeconomic history and family circumstances should be explored to understand the underlying and basic causes. Particular attention should be given to: (i) the usual diet (before the current illness) including breastfeeding; (ii) presence of diarrhea (duration, watery/bloody); (iii) information on vomiting, loss of appetite, cough; (iv) contact with tuberculosis. Malnutrition may be the presentation of HIV infection.

Examination. Anthropometry provides the main assessment of the severity of malnutrition. Physical features of malnutrition as described above should be looked for.

Clinical features of prognostic significance include:

i. Signs of dehydration
ii. Shock (cold hands, slow capillary refill, weak and rapid pulse)
iii. Severe palmar pallor
iv. Eye signs of vitamin A deficiency

v. Localizing signs of infections
vi. Skin infection or pneumonia, signs of HIV infection, fever (temperature ≥37.5°C or ≥99.5°F)
vii. Hypothermia (rectal temperature <35.5°C or <95.9°F), mouth ulcers, skin changes of kwashiorkor.

Management of Severe Malnutrition

Children with severe malnutrition undergo physiologic changes to preserve essential processes, which include reductions in the functional capacity of organs and slowing of cellular activities. These alterations and coexisting infections put severely malnourished children at particular risk of death from hypoglycemia, hypothermia, electrolyte imbalance, heart failure and untreated infection.

The general treatment involves *ten steps* in *two phases:*

- The initial *stabilization phase* focuses on restoring homeostasis and treating medical complications and usually takes 2–7 days of inpatient treatment.
- The *rehabilitation phase* focuses on rebuilding wasted tissues and may take several weeks.

The ten essential steps and the time frame are shown in Fig. 6.6 and Table 6.11.

Step 1: Treat/Prevent Hypoglycemia

All severely malnourished children are at risk of hypoglycemia (blood glucose level <54 mg/dl or 3 mmol/l), hence blood glucose should be measured immediately at admission. If blood glucose cannot be measured, one must assume hypoglycemia and treat.

Hypoglycemia may be asymptomatic or symptomatic. *Symptomatic hypoglycemia* manifesting as lethargy, unconsciousness, seizures, peripheral circulatory failure or hypothermia is more common in marasmus, where energy stores are depleted or when feeding is infrequent. For correction of *asymptomatic* hypoglycemia, 50 ml of 10% glucose or sucrose solution (1 rounded teaspoon of sugar in 3½ tablespoons of water) should be given orally or by nasogastric tube followed by the first feed. For correction of *symptomatic* hypoglycemia, 5 ml/kg of 10% dextrose should be given intravenously. This should be followed with 50 ml of 10% dextrose or sucrose solution by nasogastric tube. Blood glucose levels must be estimated every 30 min till the glucose level becomes normal and stabilizes. Once stable, the 2 hourly feeding regimens should be started.

Feeding should be started with starter F-75 (Formula 75 which is a WHO recommended starter diet for severe acute malnutrition containing 75 kcal/100 ml of feed (described later) as quickly as possible and then continued 2–3 hourly day and night (initially a quarter of the 2 hourly feed should be given every 30 min till the blood glucose stabilizes). Most episodes of symptomatic hypoglycemia can be prevented by frequent, regular feeds and the child should be fed regularly throughout the night. *Hypoglycemia, hypothermia and infection generally occur as a triad.*

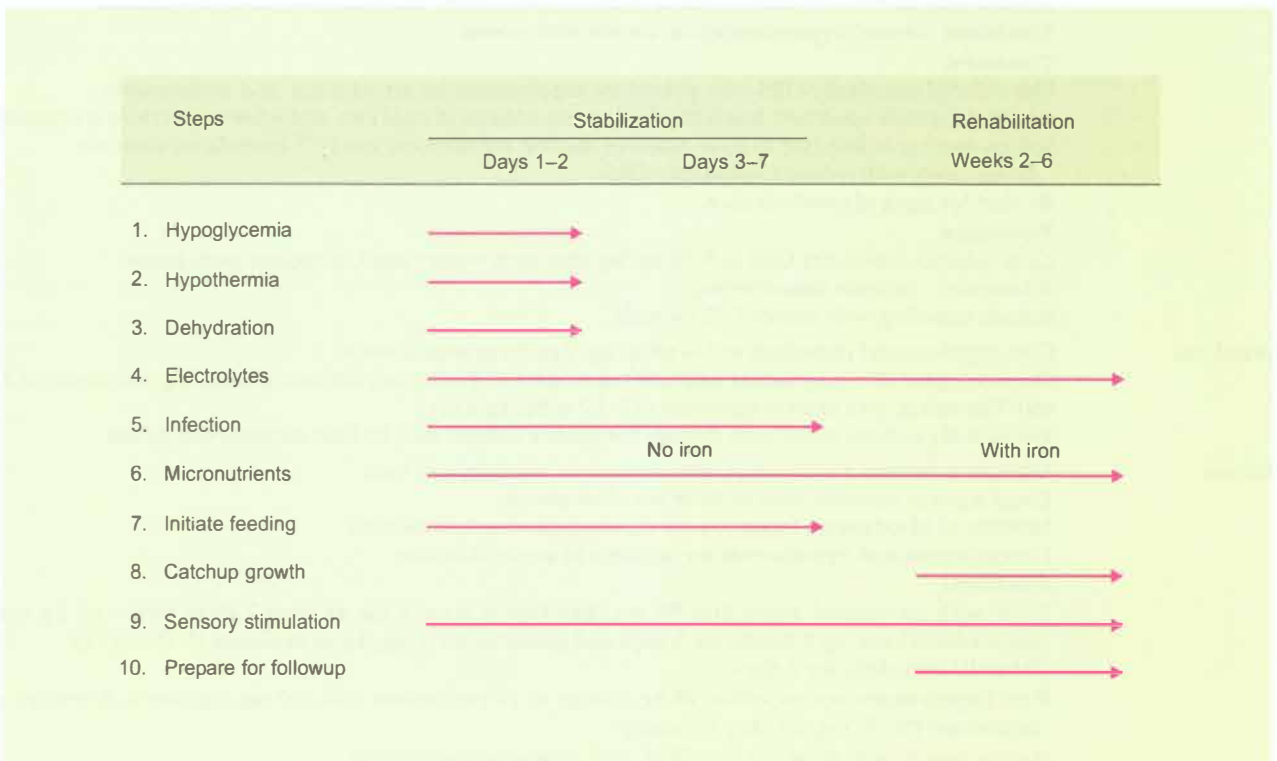


Fig. 6.6: The time frame for initiating and achieving 10 steps

Table 6.11: Summary of the management of severe malnutrition

Hypoglycemia	Blood glucose level <54 mg/dl or 3 mmol/l If blood glucose cannot be measured, assume hypoglycemia Hypoglycemia, hypothermia and infection generally occur as a triad **Treatment** Asymptomatic hypoglycemia Give 50 ml of 10% glucose or sucrose solution orally or by nasogastric tube followed by first feed Feed with starter F-75 every 2 hourly day and night Symptomatic hypoglycemia Give 10% dextrose IV 5 ml/kg Follow with 50 ml of 10% dextrose or sucrose solution by nasogastric tube Feed with starter F-75 every 2 hourly day and night Start appropriate antibiotics **Prevention** Feed 2 hourly starting immediately Prevent hypothermia
Hypothermia	Rectal temperature less than <35.5°C or 95.5°F or axillary temperature less than 35°C or 95°F Always measure blood glucose and screen for infections in the presence of hypothermia **Treatment** Clothe the child with warm clothes; ensure that the head is also covered with a scarf or cap Provide heat using overhead warmer, skin contact or heat convector Avoid rapid rewarming as this may lead to disequilibrium Feed the child immediately Give appropriate antibiotics **Prevention** Place the child's bed in a draught free area Always keep the child well covered; ensure that head is also covered well May place the child in contact with the mother's bare chest or abdomen (skin-to-skin) Feed the child 2 hourly starting immediately after admission
Dehydration	Difficult to estimate dehydration status accurately in the severely malnourished child Assume that all severely malnourished children with watery diarrhea have some dehydration Low blood volume (hypovolemia) can coexist with edema **Treatment** Use reduced osmolarity ORS with potassium supplements for rehydration and maintenance Amount depends upon how much the child wants, volume of stool loss, and whether the child is vomiting Initiate feeding within two to three hours of starting rehydration; use F-75 formula on alternate hours along with reduced osmolarity ORS Be alert for signs of overhydration **Prevention** Give reduced osmolarity ORS at 5–10 ml/kg after each watery stool, to replace stool losses If breastfed, continue breastfeeding Initiate refeeding with starter F-75 formula
Electrolytes	Give supplemental potassium at 3–4 mEq/kg/day for at least 2 weeks On day 1, give 50% magnesium sulphate (equivalent to 4 mEq/ml) IM once (0.3 ml/kg; maximum of 2 ml). Thereafter, give extra magnesium (0.8–1.2 mEq/kg daily) Excess body sodium exists even though the plasma sodium may be low; decrease salt in diet
Infection	Multiple infections are common; assume serious infection and treat Usual signs of infection such as fever are often absent Majority of bloodstream infections are due to gram-negative bacteria Hypoglycemia and hypothermia are markers of severe infection **Treatment** Treat with parenteral ampicillin 50 mg/kg/dose 6 hourly for at least 2 days followed by oral amoxicillin 15 mg/kg 8 hourly for 5 days and gentamicin 7.5 mg/kg or amikacin 15–20 mg/kg IM or IV once daily for 7 days If no improvement occurs within 48 hr, change to IV cefotaxime (100–150 mg/kg/day 6–8 hourly) or ceftriaxone (50–75 mg/kg/day 12 hourly) If other specific infections are identified, give appropriate antibiotics

Contd.

Table 6.11: Summary of the management of severe malnutrition *(Contd.)*

	Prevention Follow standard precautions like hand hygiene Give measles vaccine if the child is >6 mo and not immunized, or if the child is >9 mo and had been vaccinated before the age of 9 months
Micronutrients	Use up to twice the recommended daily allowance of various vitamins and minerals On day 1, give vitamin A orally (if age >1 yr give 2 lakh IU; age 6–12 mo give 1 lakh IU; age 0–5 mo give 50,000 IU) Folic acid 1 mg/day (give 5 mg on day 1) Zinc 2 mg/kg/day Copper 0.2–0.3 mg/kg/day Iron 3 mg/kg/day, once child starts gaining weight; after the stabilization phase
Initiate feeding	Start feeding as soon as possible as frequent small feeds If unable to take orally, initiate nasogastric feeds Total fluid recommended is 130 ml/kg/day; reduce to 100 ml/kg/day if there is severe edema Continue breastfeeding *ad libitum* Start with F-75 starter feeds every 2 hourly If persistent diarrhea, give a cereal based low lactose F-75 diet as starter diet If diarrhea continues on low lactose diets give, F-75 lactose free diets (rarely needed)
Catch-up growth	Once appetite returns in 2–3 days, encourage higher intakes Increase volume offered at each feed and decrease the frequency of feeds to 6 feeds per day Continue breastfeeding *ad libitum* Make a gradual transition from F-75 to F-100 diet Increase calories to 150–200 kcal/kg/day, and proteins to 4–6 g/kg/day Add complementary foods as soon as possible to prepare the child for home foods at discharge
Sensory stimulation	A cheerful, stimulating environment Age appropriate structured play therapy for at least 15–30 min/day Age appropriate physical activity as soon as the child is well enough Tender loving care
Prepare for followup	*Primary failure to respond* is indicated by: Failure to regain appetite by day 4 Failure to start losing edema by day 4 Presence of edema on day 10 Failure to gain at least 5 g/kg/day-by-day 10 *Secondary failure to respond* is indicated by: Failure to gain at least 5 g/kg/day for consecutive days during the rehabilitation phase

Step 2: Treat/Prevent Hypothermia

All severely malnourished children are at risk of hypothermia due to impairment of thermoregulatory control, lowered metabolic rate and decreased thermal insulation from body fat. Children with marasmus, concurrent infections, denuded skin and infants are at a greater risk. Hypothermia is diagnosed if the rectal temperature is less than 35.5°C or 95.9°F or axillary temperature is less than 35°C or 95°F. A low reading thermometer (range 29–42°C) should be used to measure the temperature of malnourished children. If the temperature does not register on a normal thermometer, hypothermia should be assumed and treated. It can occur in summers as well.

The child should be rewarmed providing heat using radiation (overhead warmer) or conduction (skin contact) or convection (heat convector). Rapid rewarming may lead to disequilibrium and should be avoided.

In case of severe hypothermia (rectal temperature <32°C) warm humidified oxygen should be given followed immediately by 5 ml/kg of 10% dextrose IV or 50 ml of 10% dextrose by nasogastric route (if IV access is difficult). If clinical condition allows the child to take orally, warm feeds should be given immediately or else the feeds should be administered through a nasogastric tube. If there is feed intolerance or another contraindication for nasogastric feeding, maintenance IV fluids (prewarmed) should be started.

In a hypothermic child, hypoglycemia must be looked for and managed. The child's temperature should be monitored every 2 hr till it rises to more than 36.5°C. Temperature monitoring must be ensured especially at night when the ambient temperature falls.

In most cases, hypothermia may be prevented by frequent feeding. Therefore, the child should be fed immediately and subsequently, every 2 hourly. All children should be nursed

in a warm environment, clothed with warm clothes and covered using a warm blanket. The head should also be covered well with a scarf or a cap. The child could also be put in contact with the mother's bare chest or abdomen (skin-to-skin) as in kangaroo mother care to provide warmth. Besides these measures, hypothermia can also be prevented by placing the child's bed in a draught free area away from doors and windows, minimizing exposure after bathing or during clinical examination and keeping the child dry always.

Step 3: Treat/Prevent Dehydration

Dehydration tends to be overdiagnosed and its severity overestimated in severely malnourished children. Loss of elasticity of skin may either be due to loss of the subcutaneous fat in marasmus or loss of extracellular fluid in dehydration. In dehydration, the oral mucosa feels dry to the palpating finger gently rolled on the inner side of the cheek. Presence of thirst, hypothermia, weak pulses and oliguria are other signs of dehydration in severely malnourished children. It is important to recognize that low blood volume (hypovolemia) can coexist with edema. Since estimation of dehydration may be difficult in severely malnourished children, it is safe to assume that all patients with watery diarrhea have some dehydration.

The Indian Academy of Pediatrics has recommended the use of one solution for all types of diarrhea in all clinical settings and there is evidence to suggest that the new reduced osmolarity ORS with potassium supplements, given additionally, is effective in severe malnutrition.

Dehydration should be corrected slowly over a period of 12 hr. *Some dehydration* can be corrected with ORS. Intravenous therapy should be given only for *severe dehydration and shock* or if the *enteral route cannot be used*. ORS is given orally or by nasogastric tube at 5 ml/kg every 30 min for first 2 hr and then at 5–10 ml/kg every hour for the next 4–10 hr. The exact amount actually depends on how much the child wants, volume of stool loss and whether child is vomiting. Ongoing stool losses should be replaced with approximately 5–10 ml/kg of the ORS after each watery stool. The frequent passage of small unformed stools should not be confused with profuse watery diarrhea as it does not require fluid replacement.

Breastfeeding should be continued during the rehydration phase. Refeeding must be initiated with starter F-75 within 2–3 hr of starting rehydration. The feeds must be given on alternate hr (e.g. 2, 4, 6 hr) with reduced osmolarity ORS (hr 1, 3, 5). Once rehydration is complete, feeding must be continued and ongoing losses replaced with ORS.

The progress of rehydration should be monitored every half hourly for first 2 hr and then hourly for the next 4–10 hr. Pulse rate, respiratory rate, oral mucosa, urine frequency or volume and frequency of stools and vomiting should be monitored. One must be alert for signs of overhydration (increase in respiratory rate by 5/minute and pulse rate by 15/minute, increasing edema and periorbital puffiness), which can be dangerous and may lead to heart failure. In case of signs of overhydration, ORS should be stopped immediately and child reassessed after one hour. On the other hand a decrease in the heart rate and respiratory rate (if increased initially) and increase in the urine output indicate that rehydration is proceeding. The return of tears, a moist oral mucosa, less sunken eyes and fontanelle and improved skin turgor are also indicators of rehydration. Once any four signs of hydration (child less thirsty, passing urine, tears, moist oral mucosa, eyes less sunken, faster skin pinch) are present, ORS for rehydration must be stopped and continued to replace the ongoing losses.

Severe dehydration with shock It is important to recognize severe dehydration in malnourished children. Severe dehydration with shock is treated with intravenous fluids. Ideally, Ringer lactate with 5% dextrose should be used as rehydrating fluid. If not available, half normal saline (N/2) with 5% dextrose or Ringer lactate alone can be used. After providing supplemental oxygen, the rehydrating fluid should be given at a slow infusion rate of 15 ml/kg over the first hour with continuous monitoring of pulse rate, volume, respiratory rate, capillary refill time and urine output.

If there is improvement (pulse slows, faster capillary refill) at the end of the first hour of IV fluid infusion, a diagnosis of severe dehydration with shock should be considered and the rehydrating fluid repeated at the same rate of 15 ml/kg over the next hour. This should be followed by reduced osmolarity ORS at 5–10 ml/kg/hr, either orally or by nasogastric tube. Patients should be monitored for features of overhydration and cardiac decompensation.

Septic shock If at the end of the first hour of IV rehydration, there is no improvement or worsening, septic shock must be considered and appropriate treatment started.

Step 4: Correct Electrolyte Imbalance

In severely malnourished children excess body sodium exists even though the plasma sodium may be low. Sodium intake should be restricted to prevent sodium overload and water retention during the initial phase of treatment. Excess sodium in the diet may precipitate congestive cardiac failure.

All severely malnourished children have deficiencies of potassium and magnesium, which may take two weeks or more to correct. Severely malnourished children may develop severe hypokalemia and clinically manifest with weakness of abdominal, skeletal and even respiratory muscles. This may mimic flaccid paralysis. Electrocardiography may show ST depression, T waves inversion and presence of U waves. If serum potassium is <2 mEq/l or <3.5 mEq/l with ECG changes, correction should be started at 0.3–0.5 mEq/kg/hr infusion of potassium chloride in intravenous fluids, preferably with continuous monitoring of the ECG.

Once severe hypokalemia is corrected, all severely malnourished children need supplemental potassium at

3–4 mEq/kg/day for at least 2 weeks. Potassium can be given as syrup potassium chloride; the common preparation available has 20 mEq of potassium/15 ml.

On day 1, 50% magnesium sulfate (equivalent to 4 mEq/ml) should be given at 0.3 ml/kg to a maximum of 2 ml intramuscularly. Thereafter, 0.8–1.2 mEq/kg magnesium should be given orally as a supplement mixed with feeds.

Step 5: Treat/Prevent Infection

Infection may not produce the classical signs of fever and tachycardia in severely malnourished children. Instead, severe infection may be associated with hypothermia. Localizing signs of infection are often absent. The most common sites for infection are the skin, the alimentary tract, the respiratory tract (including the ears, nose and throat) and the urinary tract. Majority of the infections and septicemia are caused by gram-negative organisms. Therefore, all severely malnourished children should be assumed to have a serious infection on their arrival in hospital. In addition, hypoglycemia and hypothermia are considered markers of severe infection in children.

The following investigations are done for identifying infections: (i) Hb, TLC, DLC, peripheral smear, (ii) urinalysis antituberculous and culture, (iii) blood culture, (iv) chest X-ray, (v) Mantoux test, (vi) gastric aspirate for AFB, (vii) peripheral smear for malaria (in endemic areas), and (viii) CSF examination (if meningitis is suspected).

All children with suspected infection should be treated with broad spectrum parenteral antibiotics; ampicillin and gentamicin or amikacin (Table 6.12). Antimalarial and antituberculous treatment should only be given when the particular conditions are diagnosed.

Response to treatment will be indicated by resolution of initial symptoms and signs of infection, if any. The child's activity, interaction with parents and appetite should improve. If there is no improvement or deterioration of the symptoms/signs of infection, the child should be screened for infection with resistant bacterial pathogens, tuberculosis, HIV and unusual pathogens.

Prevention of Hospital Acquired Infection

The health care personnel should follow standard precautions. The effectiveness of hand hygiene should be emphasized to all health care providers, attendants and patients. It is essential that adequate safety measures are taken to prevent the spread of hospital acquired infections, since these children are at higher risk of acquiring infections due to their compromised immune status.

Step 6: Correct Micronutrient Deficiencies

All severely malnourished children have vitamin and mineral deficiencies. Micronutrients should be used as an adjunct to treatment in safe and effective doses. Up to twice the recommended daily allowance of various vitamins and minerals should be used. Although anemia is common, iron should not be given initially due to danger of promoting free radical generation and bacterial proliferation. It should be added only after a week of therapy when the child has a good appetite and starts gaining weight.

Vitamin A deficiency is not an infrequent association and is an important cause of blindness caused by keratomalacia. Vitamin A should therefore be given to all severely malnourished children on day 1 at 50,000 IU, 100,000 IU and 200,000 IU for infants 0–5 month, 6–12 months and children >1 yr of age unless there is definite evidence that a dose has been given in the last month. In presence of xerophthalmia, the same dose should be repeated on the next day and 2 weeks later. Children >1 yr but weighing <8 kg should receive half the age related dose. In presence of clinical evidence of xerophthalmia the administration of vitamin A should be considered an emergency as the changes may progress to keratomalacia within hours.

Vitamin K should be administered in a single dose of 2.5 mg intramuscularly at the time of admission. Daily multivitamin supplements containing thiamine 0.5 mg/1000 kcal, riboflavin 0.6 mg/1000 kcal and nicotinic acid (niacin equivalents) 6.6 mg/1000 kcal should be given. It is better to give a formulation that is truly multivitamin (e.g. one that has vitamin A, C, D, E and B12). Folic acid 1 mg/day (5 mg on day 1), zinc 2 mg/kg/day and copper 0.2–0.3 mg/kg/day should be given daily. Iron 3 mg/kg/day should be added once child starts gaining weight, after the stabilization phase.

Table 6.12: Recommended antibiotics for infections in severely malnourished children

Type of infection	*Recommended antibiotics*
No obvious infections or complications	Oral cotrimoxazole (5 mg/kg 12 hourly of trimethoprim) or oral amoxicillin 10 mg/kg 8 hourly for 5 days
Infected child or complications	IV ampicillin 50 mg/kg/dose 6 hourly and IV gentamicin 5–7 mg/kg/day in 1–2 doses; add IV cloxacillin 100 mg/kg/day 6 hourly if staphylococcal infection is suspected; revise therapy based on the culture sensitivity report
For septic shock or no improvement or worsening	Add third generation cephalosporin, i.e. IV cefotaxime 100 mg/kg/day 8 hourly
Meningitis in initial 48 hr	IV cefotaxime 200 mg/kg/day IV 6 hourly with IV amikacin 15 mg/kg/day 1–2 doses
Dysentery	Ciprofloxacin 20 mg/kg/day in 2 divided doses; IV ceftriaxone 50 mg/kg/day 12 hourly if child is sick or has already received nalidixic acid

Emergency treatment of severe anemia If a severely malnourished child has severe anemia with a hemoglobin less than 4 g/dl or between 4 and 6 g/dl but with respiratory distress, a blood transfusion should be given with whole blood 10 ml/kg bodyweight slowly over 3 hr. Furosemide should be given at the start of the transfusion. If the severely anemic child has signs of cardiac failure, packed cells rather than whole blood should be transfused.

The hemoglobin concentration may fall during the first week of treatment. This is normal and no transfusion should be given. In mild to moderate anemia, iron should be given for two months to replete iron stores but this should not be started until after the initial stabilization phase has been completed.

Step 7: Initiate Re-feeding

Feeding should be started as soon as possible with a diet which has osmolarity less than 350 mOsm/l; lactose not more than 2–3 g/kg/day; appropriate renal solute load (urinary osmolarity <600 mOsm/l); initial percentage of calories from protein of 5%; adequate bioavailability of micronutrients and low viscosity. The preparation should be easy to prepare and socially acceptable and there should be facilities for adequate storage, cooking and refrigeration.

Start cautious feeding Feeding should be started as soon as possible as frequent small feeds. If child is unable to take orally with a cup and spoon or takes <80% of the target intake, nasogastric feeds should be initiated. Breastfeeding should be continued *ad libitum*. The suggested starter formulae are usually milk based, such as starter F-75 (with 75 kcal/100 ml and 0.9 g of protein/100 ml). Older children could be started on cereal based diets (Table 6.13).

One should begin with 80 kcal/kg/day and gradually increase to 100 kcal/kg/day. To fulfill this, one should start with 2 hourly feeds of 11 ml/kg/feed. Night feeds are essential. The volume of feeds are increased gradually while decreasing the frequency of administration. The calories are increased only after the child can accept the increased volume of feeds.

Step 8: Achieve Catchup Growth

Once appetite returns, higher intakes should be encouraged. Starter F-75 feeds should be gradually replaced with feeds which have a higher calorie density (100 kcal/100 ml) and have at least 2.5–3.0 g protein/100 ml. These feeds are called F-100 diets (Table 6.14). It is recommended that each successive feed is increased by 10 ml until some is left

Table 6.14: Catchup diets

Diet contents (per 100 ml)	*F-100 Catchup*	*F-100 Catchup (cereal based)*
Cow milk/toned dairy milk (ml)	95	75
(Approximate measure of one katori)	(3/4)	(1/2)
Sugar (g)	5	2.5
(Approximate measure of one level teaspoon)	(1)	(1/2)
Cereal: Puffed rice (g)	–	7
(Approximate measure of one level teaspoon)		(2)
Vegetable oil (g)	2	2
(Approximate measure of one level teaspoon)	(1/2)	(1/2)
Water to make (ml)	100	100
Energy (kcal)	101	100
Protein (g)	2.9	2.9
Lactose (g)	3.8	3

Table 6.13: Starter diets

Diet contents (per 100 ml)	*F-75 Starter*	*F-75 Starter (cereal based) Example: 1*	*F-75 Starter (cereal based) Example: 2*
Cow milk or equivalent (ml)	30	30	25
(Approximate measure of one katori)	(1/3)	(1/3)	(1/4)
Sugar (g)	9	6	3
(Approximate measure of one level teaspoon)	(1½)	(1)	(1/2)
Cereal: Powdered puffed rice* (g)	–	2.5	6
(Approximate measure of one level teaspoon)		(3/4)	(2)
Vegetable oil (g)	2	2.5	3
(Approximate measure of one level teaspoon)	(1/2)	(1/2)	(3/4)
Water: make up to (ml)	100	100	100
Energy (kcal)	75	75	75
Protein (g)	0.9	1.1	1.2
Lactose (g)	1.2	1.2	1.0

* Powdered puffed rice may be replaced by commercial precooked rice preparations (in same amounts)
Wherever feasible, actual weighing of the constituents should be carried out. Household measure should be used only as an alternative, as they may not be standardized
The above charts give the composition for 100 ml diet. Wherever, there is a facility for refrigeration, 1 liter diet could be prepared by multiplying the requirement of each constituent by 10

uneaten. The frequency of feeds gradually decreased to 6 feeds/day and the volume increased till the child is being offered 200 ml/kg/day and 4–6 g/kg/day of protein. Breastfeeding should be continued *ad libitum*.

Ready to use therapeutic food (RUTF) In the 1990s, the *RUTF* was developed, which has allowed much of the management of severe malnutrition to move out of hospitals, by shortening the duration of inpatient treatment from an average of 6 weeks to only 5–10 days. This energy dense, mineral and vitamin enriched ready to use therapeutic food with a similar nutrient profile but greater energy and nutrient density than F-100 has greatly improved cost effectiveness of treating severe malnutrition. F-100, although extremely effective during rehabilitation phase in inpatient centers, is very vulnerable to bacterial contamination and must be used within a couple of hours of being made. This restricts its use to inpatient facilities. RUTF is an oil based paste and as such can be stored at home unrefrigerated with little risk of microbial contamination for several months. The daily amount of RUTF to be consumed varies according to body weight as follows: 3–4.9 kg: 105–130 g; 5–6.9 kg: 200–260 g; 7–9.9 kg: 260–400 g and 10–14.9 kg: 400–460 g. This amount is to be given along with plenty of water in 2–3 hourly feeds. The child should continue to receive other foods and brestfeeding during medical nutrition therapy with RUTF.

Complementary foods should be added as soon as possible to prepare the child for home foods at discharge. They should have comparable energy and protein concentrations once the catchup diets are well tolerated. Khichri, dalia, banana, curd-rice and other culturally acceptable and locally available diets can also be offered liberally (*see* Table 6.2).

Special diets for diarrhea For children with persistent diarrhea, who do not tolerate low lactose diets, lactose free diet can be started. In these diets, carbohydrates (rice, sugar and glucose) can be given in varying proportions according to the patients' individual tolerance to achieve optimal balance between osmolarity and digestibility.

Monitoring progress during treatment If there is a good weight gain of >10 g/kg/day, the same treatment should be continued till recovery. If there is a moderate weight gain of 5–10 g/kg/day; food intake should be checked and the children should be screened for systemic infection. In case of poor weight gain of <5 g/kg/day possible causes like inadequate feeding, untreated infection, psychological problems and coexisting infections like tuberculosis and HIV should be looked for and managed appropriately.

Step 9: Provide Sensory Stimulation and Emotional Support

Delayed mental and behavioral development often occurs in severe malnutrition. In addition to the above management, one should encourage a cheerful, stimulating environment; structured play therapy for at least 15–30 min/day; physical activity as soon as the child is well enough and tender loving care.

Step 10: Prepare for Followup after Recovery

The child is said to have recovered when his weight for height is 90% of the NCHS median and he has no edema. The child is still likely to have a low weight for age because of stunting.

Criteria for discharge and failure of response Ideally 6–8 weeks of hospitalization is required for complete recovery. The child is said to have recovered when his weight for height is 90% of the NCHS median or has 15% weight gain, and he has no edema. The child may be discharged earlier if it is certain that the final stages of recovery will not be jeopardized by early discharge.

Severely malnourished children are ready for discharge when the child:

- Is alert and active, eating at least 120–130 kcal/kg/day with a consistent weight gain (of at least 5 g/kg/day for 3 consecutive days) on exclusive oral feeding
- Is receiving adequate micronutrients
- Is free from infection
- Has completed immunization appropriate for age
- The caretaker has been sensitized to home care.

The caregiver should be advised to bring child back for regular followup checks, ensure booster immunizations, make sure that vitamin A is given every six months, feed frequently with energy and nutrient dense foods and give structured play therapy.

Criteria for discharge before recovery is complete For some children, earlier discharge may be considered if effective alternative supervision is available. Domiciliary care should only be considered if the child:

- Is aged >12 months
- Has a good appetite with satisfactory weight gain
- Has completed antibiotic treatment
- Has taken 2 weeks of potassium/magnesium/mineral/vitamin supplement (or continuing supplementation at home is possible).

It is important to be sure that the mother/caretaker has the financial resource to feed the child, is specifically trained to give appropriate feeding (types, amount, frequency), lives within easy reach of the hospital, is trained to give structured play therapy and is motivated to follow advice given.

Care at home For children being rehabilitated at home, it is essential to give frequent meals with a high energy and protein content. One should aim at achieving at least 150 kcal/kg/day and adequate protein (at least 4 g/kg/day). This would require feeding the child at least 5 times per day with foods that contain approximately 100 kcal and 2–3 g protein per 100 g of food. A practical approach should be taken using simple modifications of usual staple home

foods. Vitamin, iron and electrolyte/mineral supplements can be continued at home. High energy snacks should be given between meals (e.g. milk, banana, bread, biscuits). The child should be assisted and encouraged to complete each meal.

Community-based Therapeutic Care

A growing number of countries and international relief agencies have adopted a new concept called the Community-based Therapeutic Care (CTC) for the management of severe acute malnutrition. The CTC concept combines facility or inpatient management of severe acute malnutrition with complications, and community-based management of severe acute malnutrition without complications or mild or moderate malnutrition. These facility-based and community-based components of management should be closely linked so that children who are too ill to be treated at the community level or who are not responding to treatment can be referred to the facility level and those receiving facility based treatment who have regained their appetites can be transferred for continued care in the community. For this community-based therapeutic care approach a suggested classification and treatment system for acute malnutrition is given in Table 6.15.

Phenomena Encountered during Nutritional Rehabilitation

Pseudotumor cerebri Overenthusiastic nutritional correction in malnourished infants may be accompanied by transient rise of intracranial tension. The phenomenon is benign and self limiting.

Nutritional recovery syndrome It refers to a sequence of events seen in children who are being treated with very high quantity of proteins during the course of rehabilitation. It presents as (i) abdominal distention, (ii) increasing hepatomegaly, (iii) ascites, (iv) prominent thoracoabdominal venous network, (v) hypertrichosis, (vi) parotid swelling, (vii) gynecomastia, (viii) eosinophilia, and (ix) splenomegaly. Its development may be related to endocrinal disturbances, possibly by an increase in the estrogen level and by a variety of trophic hormones produced by the recovering pituitary gland.

Encephalitis like syndromes Up to one-fifth of patients with kwashiorkor may become drowsy within 3–4 days after initiation of dietary therapy. Most often the condition is self limiting. Occasionally, it may be accompanied by progressive unconsciousness with fatal outcome. Even more rarely a transient phenomena marked by coarse tremors, parkinsonian rigidity, bradykinesia and myoclonus may appear several days after starting the dietary rehabilitation. These encephalitis states are considered to be the result of too much proteins in the diet.

Prevention of Malnutrition

Improvement of nutrition status of children is an essential component of health care.

Prevention at National Level

Nutrition supplementation. This can be done by improvement of food and feeding; by fortification of staple food; iodination of common salt and food supplementation.

Nutritional surveillance. Surveillance defines the character and magnitude of nutritional problems and selects appropriate strategies to counter these problems.

Nutritional planning. Nutritional planning involves a political commitment by the government, formulation of a nutrition policy and planning to improve production and supplies of food and ensure its distribution.

Prevention at Community Level

a. *Health and nutritional education.* Lack of awareness of the nutritional quality of common foods, irrational beliefs about certain foods and cultural taboos about feeding contribute to the development of malnutrition. People should be informed of the nutritional quality of various locally available and culturally accepted low cost foods.

Table 6.15: Suggested classification and treatment system for malnutrition

Suggested classification	*Suggested treatment*
Severe acute malnutrition with complications like anorexia, lower respiratory tract infection, high fever, severe dehydration, severe anemia or lethargy	Stabilization center (SC): inpatient care, also known as 'phase 1 treatment', useful for acutely malnourished children with medical complications and no appetites managed using standard WHO guidelines
Severe acute malnutrition without complications where the child is clinically well, alert and has a good appetite	Outpatient therapeutic program (OPT): home based treatment and rehabilitation with specially formulated ready to use therapeutic feed (RUTF) provided on a weekly or two weekly basis; medical treatment using simplified medical protocols and regular followup for children with severe acute malnutrition without complications
Moderate acute malnutrition without complications where weight for height is between 70 and 80%; without edema, or MUAC is 11–12.5 cm	Supplementary feeding program (SFP): take home ration for children with moderate acute malnutrition without complications

b. *Promotion of education and literacy in the community,* especially nonformal education and functional literacy among village women.
c. *Growth monitoring.* The growth should be monitored periodically on growth cards. Velocity of growth is more meaningful than the actual weight of a child.
d. *Integrated health package.* Primary health care package should be made available to all sectors of population including preventive immunization, oral hydration, periodic deworming and early diagnosis and treatment of common illnesses.
e. Vigorous promotion of *family planning programs* to limit family size.

Prevention at Family Level

a. Exclusive breastfeeding of infants for first 6 months of life should be vigorously promoted and encouraged.
b. Complementary foods should be introduced in the diet of infants at the age of 6 months.
c. Vaccination.
d. Iatrogenic restriction of feeding in fevers and diarrhea should be discouraged.
e. Adequate time should be allowed between two pregnancies so as to ensure proper infant feeding and attention to the child before the next conception.

Integrated Child Development Services (ICDS) Programme

The ICDS programme is an intersectoral program which seeks to directly reach out to children, below six years, especially from vulnerable groups and remote areas. The Scheme provides an integrated approach for converging basic services through community-based workers and helpers. The services are provided at a center called the 'Anganwadi'. A package of six services is provided under the ICDS Scheme:

a. *Supplementary nutrition.* The norms are given in Table 6.16
b. *Immunization.* Immunization of pregnant women and infants is done against the six vaccine preventable diseases.
c. Nonformal preschool education.
d. *Health check-up.* This includes health care of children less than six years of age, antenatal care of expectant mothers and postnatal care of nursing mothers. These services are provided by the ANM and Medical Officers under the RCH programme. The various health services include regular health check-ups, immunization, management of malnutrition, treatment of diarrhea, deworming and distribution of simple medicines.
e. *Referral services.* During health check-ups and growth monitoring, sick or malnourished children are referred to the Primary Health Centre or its subcenter.
f. Nutrition and health education.

Table 6.16: Norms for supplementary nutrition in ICDS

Beneficiaries	*Calories, kcal*	*Protein, g*
Children <3 yr	300	8–10
Children 3–6 yr	300	8–10
Severely malnourished children	Double of above	
Pregnant and lactating mothers	500	20–25

National Programme of Mid-day Meals in Schools

With a view to enhancing enrolment, retention and attendance and simultaneously improving nutritional levels among children, the National Programme of Nutritional Support to Primary Education (rechristened National Programme of Mid-day Meals in Schools in 2007) was launched as a centrally sponsored scheme on 15th August 1995, initially in 2408 blocks in the country. The National Programme of Mid-day Meals in Schools covers approximately 9.70 crore children studying at the primary stage of education in 9.50 lakh Government (including local bodies), Government aided schools and the centers run under Education Guarantee Scheme and Alternative and Innovative Education Scheme.

The program provides a mid-day meal of 450 kcal and 12 g of protein to children at the primary stage. For children at the upper primary stage, the nutritional value is fixed at 700 kcal and 20 g of protein. Adequate quantities of micronutrients like iron, folic acid and vitamin A are also recommended. The program has helped in protecting children from classroom hunger, increasing school enrolment and attendance, improved socialization among children belonging to all castes, addressing malnutrition and social empowerment through provision of employment to women.

National Nutrition Anemia Prophylaxis Programme

This program was launched in 1970 to prevent nutritional anemia in mothers and children. Under this program, the expected and nursing mothers as well as acceptors of family planning are given one tablet containing 100 mg elementary iron and 0.5 mg of folic acid. Children in the age group of 1–5 yr are given one tablet containing 20 mg elementary iron (60 mg of ferrous sulfate) and 0.1 mg of folic acid daily for a period of 100 days.

Suggested Reading

Dalwai S, Choudhury P, Bavdekar SB, Dalal R, et al. Indian Academy of Pediatrics. Consensus statement of the Indian Academy of Pediatrics on integrated management of severe acute malnutrition. Indian Pediatr 2013;50:399–404

WHO Child Growth Standards and the identification of severe acute malnutrition in infants and children. A joint statement by WHO and UNICEF. 2009. Accessed from http//who.int/nutrition/publications/severemalnutrition/9789241598163-eng.pdf

7 Micronutrients in Health and Disease

Ashima Gulati, Arvind Bagga

Vitamins are organic compounds, required in tiny amounts, that cannot be synthesized by an individual, and must be obtained from the diet. Vitamins perform diverse bio-chemical functions, including as hormones (e.g. vitamin D), antioxidants (e.g. vitamin E), mediators of cell signaling and regulators of tissue growth and differentiation (e.g. vitamin A). Several vitamins (e.g. B complex vitamins) function as precursors for enzyme cofactor biomolecules (coenzymes) that help act as catalysts and substrates in metabolism. Fat soluble vitamins (A, D, E, K) control protein synthesis at either transcriptional or post-transcriptional level. Breast milk is deficient in vitamins D and K and exclusively breastfed infants must be supplemented with these vitamins.

Certain minerals are required in trace or small amounts to support biochemical processes involved in cell structure and function. Important minerals include calcium, chloride, cobalt, copper, iodine, iron, magnesium, manganese, molybdenum, nickel, phosphorus, potassium, selenium, sodium, sulfur and zinc. Essential trace elements are required in amounts ranging from 50 µg to 18 mg per day, and act as catalytic or structural components of larger molecules. Marginal or severe imbalances in trace elements are considered risk factors for several diseases. In addition to deficiencies of iron and iodine, features of deficiency of copper, zinc and selenium are recognized.

Intakes of micronutrients recommended by the National Academy of Science 2006 are available at www.nap.edu. Intakes proposed by the Indian Council of Medical Research in 2010 are listed in Table 6.1 and are also available at icmr.nic.in/final RDA-2010.pdf.

FAT SOLUBLE VITAMINS

Vitamin A

Vitamin A (retinol) refers to compounds structurally related to retinol that have biological activity. Six isomers are known, including 5 *cis*-forms and *trans*-retinol. The active forms of vitamin A are the oxidation products of retinol, all-*trans*-retinal and all-*trans*-retinoic acid. Carotenoids are provitamin A substances found in vegetables. All-*trans* β-carotene is the most effective precursor and is widely distributed.

Absorption and metabolism Vitamin A is absorbed as an ester, as part of chylomicrons. Absorption is affected by impaired chylomicron formation and altered fat absorption. Retinol is absorbed as free alcohol by an active transport system containing a cellular retinol binding protein (RBP) II. The yellow β-carotene requires bile salts for absorption and is converted to vitamin A in the intestines. Once absorbed, vitamin A is stored in the liver as retinyl palmitate. The liver releases vitamin A to the circulation, bound to RBP and transthyretin.

Sources The richest sources of preformed vitamin A include oils extracted from shark and cod liver. Carrots, dark-green leafy vegetables, squash, oranges and tomatoes are also good sources. Many processed foods and infant formulas are fortified with preformed vitamin A.

Recommended daily allowance The recommended daily allowance of vitamin A is as follows: (i) infants 300–400 µg; (ii) children 400–600 µg; (iii) adolescents 750 µg. 1 µg retinol = 3.3 international units (IU) of vit A; = 12 µg β-carotene. Hence, 30 mg retinol = 100,000 IU vit A.

Physiological functions The main functions of vitamin A are: (i) maintenance of vision, especially night vision; (ii) maintenance of epithelial tissues and (iii) differentiation of various tissues, particularly during reproduction and gestation by regulating gene expression. The role of vitamin A in vision is related to the retinal form. Within the eye, 11-*cis*-retinal is bound to rhodopsin (rod cells) and iodopsin (cones). As light enters the eye, 11-*cis*-retinal is isomerized to the all-*trans* form. The all-*trans*-retinal dissociates from the opsin in a series of steps called bleaching. This isomerization induces a nervous signal

along the optic nerve to the visual center of the brain. Subsequently, the all-*trans*-retinal is recycled and converted to 11-*cis*-retinal form *via* a series of enzymatic reactions. Some of the all-*trans*-retinal is converted to all-*trans*-retinol and transported with an interphotoreceptor RBP to pigment epithelial cells. Further esterification into all-*trans*-retinyl esters allows this form to be stored within the pigment epithelial cells to be reused when needed. Deficiency in vitamin A inhibits the reformation of rhodopsin and leads to night blindness.

Vitamin A Deficiency

In developing countries, a large number of preschool children become blind owing to vitamin A deficiency, and many die because of increased vulnerability to infections especially measles. Defective dark adaptation is a characteristic early clinical feature, resulting in night blindness. The syndrome of vitamin A deficiency in infants consists of Bitot spots, xerophthalmia, keratomalacia, corneal opacities (Fig. 7.1), hyperkeratosis, growth failure and death. The deficiency disease in humans was called *xerophthalmia* (dry eyes) because of the prominence of the eye signs (Table 7.1). Other findings include infertility, metaplastic bones and keratinization of epithelial tissue particularly in the skin, genitourinary system and the lung. Urinary calculi are common and fetal abnormalities are seen in pregnancy. Diets consisting of polished rice with little or no vegetables or fruits increase the risk of xerophthalmia.

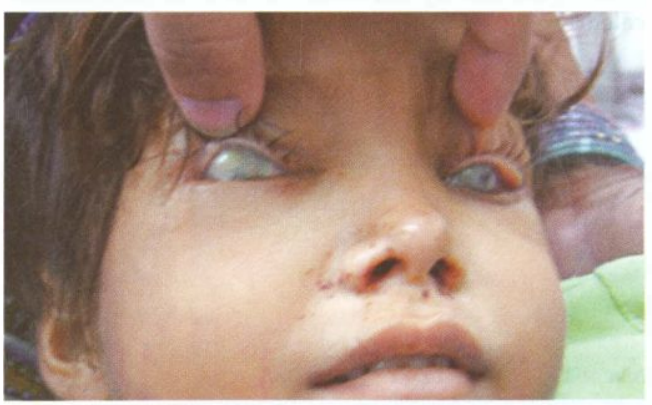


Fig. 7.1: Bilateral keratomalacia in a child with protein energy malnutrition (PEM) severe vitamin A deficiency precipitated by an episode of pneumonia. Note the bilateral corneal opacification and corneal perforation in the left eye

Table 7.1: WHO classification of xerophthalmia

Primary signs	*Secondary signs*
X1A Conjunctival xerosis	XN Night blindness
X1B Bitot's spots	XF Fundal changes
X2 Corneal xerosis	XS Corneal scarring
X3A Corneal ulceration (<1/3 of cornea)	
X3B Corneal ulceration (>1/3 of cornea)	

Laboratory tests show mild leukopenia and serum retinol level of 15 µg/dl or less (normal 20 to 80 µg/dl). Clouding of the cornea in a child with vitamin A deficiency is an emergency and requires parenteral administration of 50,000 IU to 100,000 IU (15 to 30 mg retinol).

Treatment of vitamin A deficiency Specific treatment consists of oral vitamin A at a dose of 50,000 IU, 100,000 IU and 200,000 IU in children aged <6 months, 6–12 months and >1 yr, respectively. The same dose is repeated next day and 4 weeks later. Alternatively, parenteral water-soluble preparation are administered in children with persistent vomiting or severe malabsorption (parenteral dose is half the oral dose for children above 6–12 months and 75% in <6 months old). Local treatment with antibiotic drops and ointment and padding of the eye enhances healing.

Prevention Under the National Vitamin A Prophylaxis program, sponsored by the Ministry of Health and Family Welfare, children between 1 and 5 yr were previously given oral doses of 200,000 IU vitamin A every six months. Evaluation studies since then revealed inadequate coverage in most states. Currently, vitamin A is given only to children less than three years old since they are at greatest risk and the administration of the first two doses is linked with routine immunization to improve the coverage. Hence, a dose of 100,000 IU is given with measles vaccine at 9 months and 200,000 IU with the DPT booster at 15–18 months. In endemic areas 3 more doses are administered at 24, 30 and 36 months. Dietary improvement is necessary to prevent vitamin A deficiency. Children with measles and severe malnutrition should receive vitamin A at 100,000 IU if <1-yr-old and 200,000 IU if older.

Carotenemia

β-carotene is an important precursor of vitamin A in vegetable-based diets; 6 µg β-carotene has the biological potency of 1 µg retinol. Excessive dietary intake of carotene containing foods, most commonly carrots and carrot containing products, does not produce symptoms other than yellow skin pigmentation. Carotene is normally present in keratin and subcutaneous fat. At high plasma levels, yellow pigmentation (carotenemia) shows in superficial skin (face, palms and soles), but not in sclerae. The color returns to normal within 2–6 weeks of discontinuing intake of carrots. Carotenemia might be mistaken for jaundice.

Hypervitaminosis A and Teratogenicity

Toxicity has been observed in those ingesting more than 50,000 IU/day of vitamin A for several months in form of fish liver oil, therapeutic vitamin preparations or, in adolescents, as retinol or retinoic acid for acne. Acute manifestations include pseudotremor cerebri (vomiting, irritability, bulging fontanel, diplopia, headache). Patients

with chronic hypervitaminosis may have dermatitis, alopecia, hepatosplenomegaly and/or hyperostosis. When taken by pregnant women in early gestation at daily levels of more than 7500 µg, fetal anomalies and poor reproductive outcomes are reported. The WHO recommends that vitamin A intake during pregnancy should not exceed 3000 µg daily or 7500 µg every week.

Vitamin D

Vitamin D is the generic term for secosteroids, which have an important role in maintaining calcium and phosphorus homeostasis. Secosteroids have three intact rings and one open ring with conjugated double bonds. Various vitamin D metabolites differ in the side chains attached to the fourth ring. Vitamin D is a group of precursors of a hormone, 1,25-dihydroxycholecalciferol, synthesized and secreted by the kidneys under the control of parathormone and tissue phosphate levels (Fig. 7.2). Dietary vitamin D is essential if the cutaneous synthesis of vitamin D3 is insufficient. When deficient, disease manifestations include rickets, with defective mineralization of growing bone, and osteomalacia with impaired mineralization of non-growing bones.

Absorption, metabolism and mechanism of action

Vitamin D refers to two prohormones, vitamin D2 (ergocalciferol; derived from plants) and D3 (cholecalciferol, available from animal sources) and their derivatives. Vitamin D is absorbed in the duodenum by an active transport system. In the enterocyte, vitamin D is incorporated into chylomicrons and transported to the liver, where its hydroxylation take place to form 25-hydroxyvitamin D2 [25OHD2] and 25-hydroxyvitamin D3 [25OHD3], known as ercalcidiol and calcidiol respectively. This hydroxylation is substrate dependent and without any negative feedback control. Calcidiol is released into the bloodstream and has a biological half-life of approximately 3 weeks. Subsequent hydroxylation by 1α-hydroxylase in the proximal renal tubule leads to formation of 1,25-dihydroxyvitamin D2 [$1,25(OH)_2D2$] or ercalcitriol and 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D3$] or calcitriol (Fig. 7.2). While circulating $1,25(OH)_2D$ almost exclusively results from renal production, extrarenal conversion also takes place in the skin, colon, macrophages, vascular smooth muscle cells, bone and parathyroid glands. Renal conversion is regulated by parathormone, calcitonin, calcium and phosphate; and inhibited by calcitriol and the phosphaturic hormone, fibroblast growth factor 23 (FGF-23). A negative relationship exists between serum 25OHD and parathormone levels (Fig. 7.2). Vitamin D supplementation suppresses serum parathormone and increases bone mineral density.

Active vitamin D affects calcium homeostasis through its action on the intestine, kidney and bones. In the intestine, the hormone induces calcium transport proteins and an intracellular calcium-binding protein (calbindin) which aid in transport of calcium across the enterocyte. In the kidney, the hormone enhances calcium resorption in the tubule by a similar mechanism. It also inhibits the activity of 1α-hydroxylase and stimulates renal 24-hydroxylase activity that inactivates both the substrate and calcitriol.

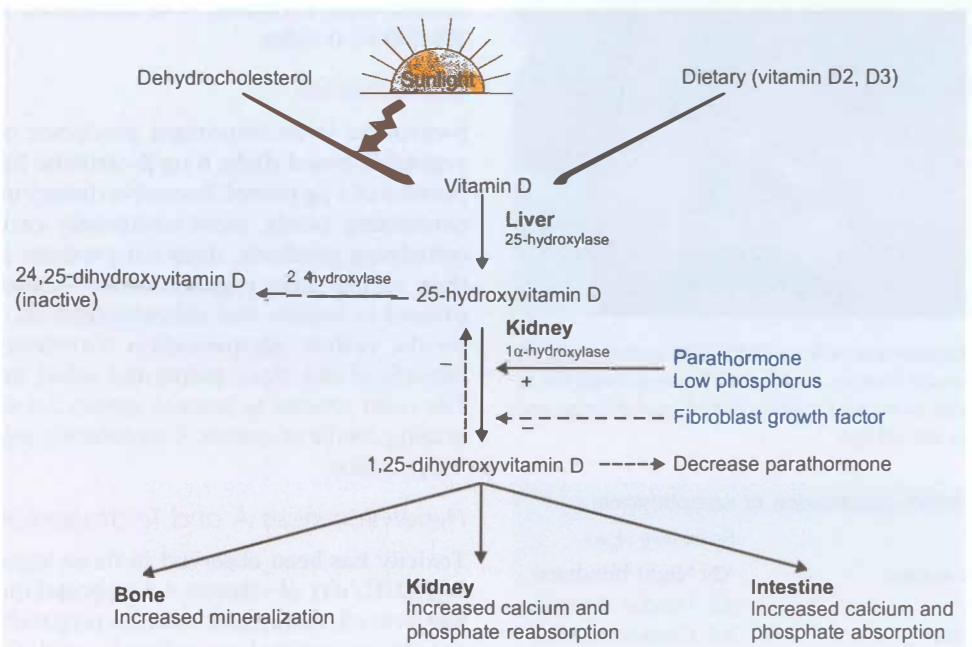


Fig. 7.2. Vitamin D metabolism. Serum levels of fibroblast growth factor (FGF) 23 are elevated in response to increased serum phosphate and also inhibit the production of parathormone

Sources The major source of vitamin D is its synthesis in the skin following exposure to ultraviolet B (UVB) solar irradiation (wavelength 290–315 nm). The dermal concentration of melanin regulates the amount of UV rays that reach the epidermal layers (stratum basale and spinosum) containting the highest concentrations of the substrate, 7-dehydrocholesterol. The time required for adequate sun exposure depends on skin pigmentation, timing of the day, season and clothing. The exposure of the skin to UV-B is measured as the minimum erythema dose (amount of UV-B exposure that will cause minimal erythema). Exposure of 40% of the body to one-fourth of the minimum erythema dose results in generation of <1000 IU vitamin D per day. Excessive exposure to sunlight does not increase vitamin D production as previtamin D3 is degraded into inert products such as lumisterol-3 and tachysterol-3, and vitamin D3 photoisomerizes to suprasterol and inert products.

Dietary vitamin D usually accounts for 5–10% of the total vitamin D. Significant dietary sources are fish and fish oils, egg yolk, supplemented cereals and margarine. The amount in vegetable sources is negligible, and dietary intakes are low in the absence of food fortification. Human milk contains only 30–40 IU/L. Exposure to sunlight and vitamin D supplementation to the nursing mother can increase the vitamin D content in breast milk.

Vitamin D requirements Since vitamin D3 is produced endogenously in the skin through the action of sunlight on 7-dehydrocholesterol, there is no nutritional requirement for vitamin D when sufficient sunlight is available. However, when shielded from sunlight, breastfed infants will develop rickets unless supplemented with vitamin D. The recommended daily allowance in infants is 5 µg (200 IU) per day and children 10 µg (400 IU) per day. Human milk is deficient in vitamin D and contains only 30–40 IU per liter, mostly from 25(OH) D3. Breastfed infants must therefore receive an additional source of vitamin D.

Hypervitaminosis D

An epidemic of 'idiopathic hypercalcemia' in infants, with anorexia, vomiting, hypertension, renal insufficiency and failure to thrive in England in the 1950s was traced to an intake of vitamin D between 2,000 and 3,000 IU/day. In adults, dosages of 10,000 IU/day of vitamin D for several months have resulted in marked disturbances in calcium metabolism with hypercalcemia, hyperphosphatemia, hypertension, anorexia, nausea, vomiting, weakness, polyuria, polydipsia, azotemia, nephrolithiasis, ectopic calcification and renal failure.

Vitamin D Deficiency and Rickets

A lack of adequate mineralization of growing bones results in rickets and that of trabecular bone in osteomalacia. Osteoporosis is due to proportionate loss of bone volume and mineral, which in children is often caused by excessive administration of corticosteroids.

Etiology In most developed countries nutritional rickets (vitamin D deficiency rickets) was virtually eradicated by fortification of milk or direct administration of vitamin D. In India and many other developing countries, however, nutritional rickets is still widely prevalent. Recent reports suggest that nutritional rickets is reappearing in the developed countries, particularly among dark-skinned infants who are exclusively breastfed for prolonged periods without vitamin supplements.

Rickets results from deficiency of either calcium or phosphorus, since both are needed for bone mineralization. The former results from insufficient amount of vitamin D, resulting in secondary hyperparathyroidism; blood parathormone levels are raised. Besides poor dietary intake and insufficient exposure to sunlight, vitamin D deficiency may result from various malabsorption syndromes and chronic liver disease. Anticonvulsant drugs induce hepatic cytochrome P450 oxidase that leads to conversion of 25(OH)D3 into its inactive metabolites. Rickets may also occur secondary to severe dietary deficiency of calcium; such patients show normal serum concentrations of 25(OH)D3 but elevated levels of $1,25(OH)_2D3$. Calcium supplements alone lead to healing of rickets in such cases.

Clinical features These include skeletal deformities, including bow legs (genu varum) in toddlers, knock-knees (genu valgum) in older children, craniotabes (soft skull), spinal and pelvic deformities, growth disturbances, costochondral swelling (rickety rosary), Harrison groove, double malleoli due to metaphyseal hyperplasia, increased tendency for fractures, especially greenstick fractures, bone pain or tenderness, muscle weakness and dental problems (Fig. 7.3). Nutritional rickets usually presents in infancy or preschool age, usually as widened wrists or bowing of legs. Presentation in early infancy and findings of seizures or tetany suggest a defect in vitamin D metabolism.

Evaluation Radiologic changes are characteristically seen at the metaphysis. The first change is loss of normal zone of provisional calcification adjacent to the metaphysis. This begins as an indistinctness of the metaphyseal margin, progressing to a frayed appearance with widened growth plate due to lack of calcification of metaphyseal bone (Fig. 7.4). Weight bearing and stress on uncalcified bone gives rise to splaying and cupping of metaphysis. Eventually, a generalized reduction in bone density is seen.

Laboratory diagnosis of vitamin D deficiency is based on low circulating levels of 25(OH)D3. Values below 10 µg/ml are indicative of deficiency (Table 7.2). An increased plasma level of $1, 25(OH)_2D3$ indicates deficient intake of calcium or phosphorus. Blood levels of alkaline phosphate are elevated; calcium and phosphate levels may be normal or low.

Management Vitamin D is administered orally either in a single dose of 600,000 IU or over 10 days (60,000 IU

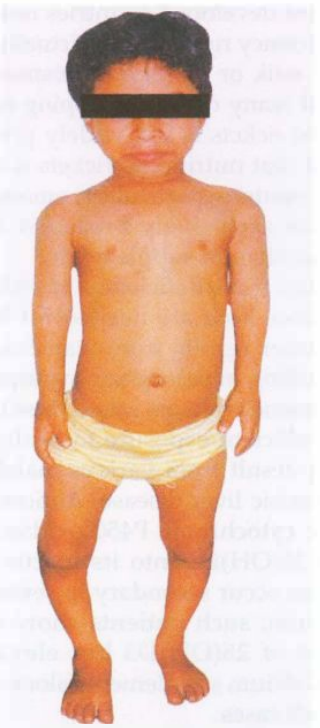


Fig. 7.3: A 5-yr-old child with rickets with wide wrists and bow legs

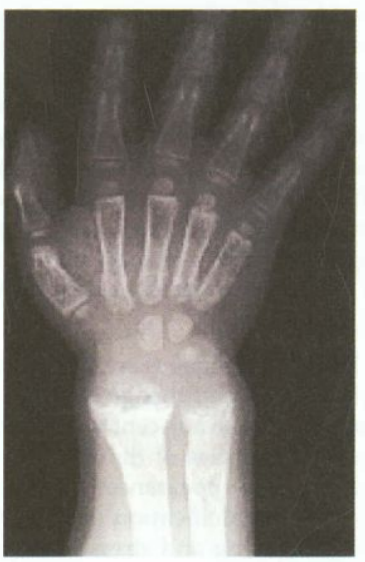


Fig. 7.4: Radiograph of wrist in 4-yr-old boy with rickets. Note widening, cupping and fraying at the metaphyseal ends of forearm bones

Table 7.2: Vitamin D levels in serum

	25-hydroxyvitamin D level (ng/ml)
Deficient	Less than 10
Insufficient	10–20
Optimal	20–60
High	60–90
Toxic	Greater than 90

daily for 10 days) followed by a maintenance dose of 400–800 IU/day and oral calcium supplements (30–75 mg/kg/day) for 2 months. Following adequate therapy, most patients with vitamin D deficiency rickets show radiological evidence of healing (Fig. 7.5) within 4 weeks. Reduction in blood levels of alkaline phosphatase and resolution of clinical signs occur slowly. If radiologic healing cannot be demonstrated, despite 1–2 large doses of vitamin D, patients should be evaluated for refractory rickets (Fig. 7.6).

Familial Hypophosphatemic Rickets

This is the most commonly inherited form of refractory rickets, being inherited as X-linked dominant with variable penetrance. Sporadic instances are frequent and an autosomal recessive inheritance has also been reported.

Pathogenesis The gene for X-linked hypophosphatemic rickets is termed the *PHEX* gene (phosphate regulating gene with homology to endopeptidases on the X chromosome). The underlying defect involves impaired proximal tubular reabsorption of phosphate. Despite hypophosphatemia the blood levels of $1,25(OH)_2D3$ are low, which

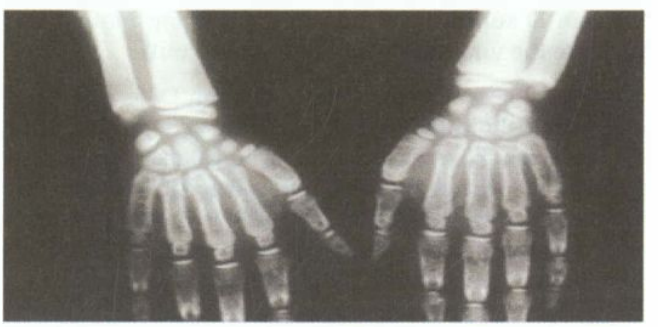


Fig. 7.5: Healing of the growth plate after vitamin D therapy

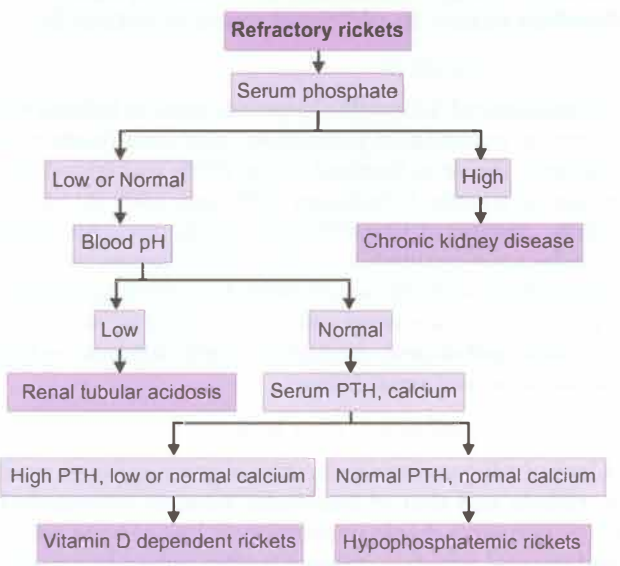


Fig. 7.6: Biochemical evaluation of a child with refractory rickets

implies a deranged response of renal 1α-hydroxylase to a low phosphate signal.

Clinical features Limb deformities such as coxa vara, genu valgum, genu varum and short stature may occur. Abnormalities of maxillofacial region and premature fusion of cranial sutures may lead to deformities of skull. Dental abnormalities are commonly seen including pulp deformities with intraglobular dentine, and frequent dental abscesses. Symptoms of hypocalcemia (tetany and muscle weakness) are absent. The mother of affected patient(s) may have bowing of legs and short stature or fasting hypophosphatemia.

Evaluation Changes of active rickets in spine and pelvis are rarely seen even in advanced stages. The level of serum calcium is normal or slightly low (9–9.5 mg/dl), that of phosphate decreased (1.5–3 mg/dl). Serum alkaline phosphatase level is raised. PTH levels are normal. Blood levels of $1,25(OH)_2D3$ are inappropriately low for the level of serum phosphate. Urinary phosphate excretion is increased with decreased tubular reabsorption of phosphate.

Management Oral phosphate and vitamin D supplements are administered. Phosphates are provided in a dosage of 30–50 mg/kg (total 1–3 g elemental phosphorus) divided into 5 to 6 equal parts and can be given in the form of Joulie solution or as neutral phosphate effervescent tablets. Joulie solution contains 30.4 mg of phosphate/ml. Diarrhea is a frequent problem with higher doses.

Vitamin D supplementation is necessary for healing of rickets. Treatment is started with alpha-calcidiol at a dose of 25–50 ng/kg/day (maximum 2 μg/day) until there is biochemical and radiological evidence of healing of rickets. Periodic monitoring of serum and urine levels of calcium and phosphate is essential. A level of serum phosphate greater than 3.0 to 3.2 mg/dl is desirable.

Vitamin D Dependent Rickets (VDDR)

These rare autosomal recessively inherited rickets are seen in infants between 3 and 6 months of age, who have been receiving the usual amounts of vitamin D. Two forms are seen.

VDDR type I This condition is characterized by a deficiency of the enzyme, 25-hydroxyvitamin D 1α-hydroxylase. Reduced blood levels of calcium, normal to low phosphate and elevated alkaline phosphatase are characteristic. Blood levels of 25(OH)D3 are normal but those of 1, $25(OH)_2D3$ are markedly decreased despite hypocalcemia.

The clinical features are similar to vitamin D deficiency rickets and include hypotonia, growth failure, motor retardation (poor head control, delayed standing and walking), convulsions due to hypocalcemia, anemia and occasionally respiratory difficulty. Physical examination shows thickening of wrists and ankles, frontal bossing, widely open anterior fontanelle, rickety rosary, bony deformities and positive Trousseau and Chvostek signs. Dentition is delayed and development of tooth enamel impaired.

The treatment of VDDR type I is with physiological doses of alpha-calcidiol or calcitriol (1–2 μg daily). Most subjects require concomitant treatment with calcium with or without phosphate supplements. With appropriate therapy the serum calcium levels rise and radiological healing occurs within 6 to 8 weeks.

VDDR type II The features are similar to VDDR type I. There is end organ resistance to $1,25(OH)_2D3$. This leads to virtual abolition of actions of $1,25(OH)_2D3$, despite its markedly raised levels in circulation (secondary to hypocalcemia and low 24-hydroxylase activity).

Early onset of rickets, a high prevalence of alopecia and ectodermal defects (oligodontia, milia and epidermal cysts) are characteristic. Hypocalcemia, secondary hyperparathyroidism, elevated circulating levels of $1, 25(OH)_2D3$ and an absence or decreased response to vitamin D analogs are seen. The response to treatment in patients with VDDR type II is not satisfactory. An occasional patient may get clinical and biochemical improvement and radiological healing following longterm administration of large amounts of intravenous or oral calcium.

Other Causes of Rickets

Renal tubular acidosis Proximal or distal renal tubular acidosis (RTA) are important causes of refractory rickets in children. The conditions are characterized by hyperchloremic metabolic acidosis with normal blood levels of urea and creatinine. Patients with proximal RTA may show low blood levels of phosphate, aminoaciduria and low molecular weight proteinuria. The use of bicarbonate and phosphate supplementation (in proximal RTA) results in healing of rickets.

Chronic kidney disease Refractory rickets may occasionally be the presenting manifestation of chronic kidney disease (GFR below 30–35 ml/min/1.73 m^2), particularly in patients with tubulointerstitial disease. The features of mineral bone disease depend on patient age and duration of disease. Elevated blood levels of creatinine, phosphate and parathormone are characteristic. Therapy consists of restricting phosphate intake and providing supplements of calcium and active vitamin D analogs.

Oncogenous rickets Benign mesenchymal tumors may secrete fibroblast growth factor that results in phosphaturia, hypophosphatemia, rickets and muscle weakness. The tumor may be small and difficult to detect but its removal reverses the biochemical abnormalities and heals the rickets.

Metaphyseal dysplasia Several types of disorders are described. Short stature with bowing of legs and waddling gait are prominent. There are no biochemical abnormalities except for occasional hypercalcemia in Jansen metaphyseal chondrodysplasia. Radiological changes resemble rickets. There is no treatment for these disorders.

Fluorosis Endemic fluorosis might present with bony deformities and radiological features of rickets in school going children. Pain in limbs and spine, mottling of teeth and family history of a similar illness are important features. Osteosclerosis and calcification of ligaments may be found in older children and adults; levels of alkaline phosphatase and parathormone are raised. Levels of fluoride are increased in the water consumed, urine and blood.

Vitamin E

Vitamin E (tocopherol) functions as a membrane bound antioxidant. Only 20–40% of ingested tocopherol and/or its esters are absorbed. The absorption is enhanced by simultaneous digestion and absorption of dietary lipids. Medium chain triglycerides, and bile and pancreatic juices enhance absorption of tocopherol, which is incorporated into chylomicrons and delivered to the liver. From the liver it is secreted with VLDL and LDL and delivered to peripheral tissues. Red blood cells, which contain about 20% of vitamin E in plasma, also participate in transport.

Nutritional requirements Vitamin E requirement of normal infants is approximately 0.4 µg/kg body weight/day. For premature infants, 15 to 20 mg/day is required. The RDA for infants increases from 3 to 6 mg tocopherol from birth to 2 yr of age. One mg of tocopherol provides 1.5 IU activity of vitamin E.

Sources The common sources of vitamin E are vegetable oils (corn, cottonseed, safflower) and margarine. Other sources include leafy vegetables and nuts; breast milk and colostrum are rich sources.

Vitamin E Deficiency

Infants particularly if prematures are born in a state of relative tocopherol deficiency. This is attributed to limited placental transfer of vitamin E, relative dietary deficiency, intestinal malabsorption and rapid growth. The risk of vitamin E deficiency is increased in infants fed on formulae high in polyunsaturated fats and low tocopherol content. As the digestive system matures, tocopherol absorption improves and its blood levels rise. A common presentation of the deficiency is in preterm babies in hemolytic anemia. The levels of hemoglobin range between 7 and 9 g/dl. Reticulocytosis and hyperbilirubinemia are accompanied by low levels of vitamin E. Administration of iron exacerbates hemolysis, unless vitamin E is also administered. Parenteral therapy with vitamin E improves anemia and corrects hemolysis.

A common cause of vitamin E deficiency in older children and adolescents is fat malabsorption. Abetalipoproteinemia, caused by the genetic absence of apolipoprotein B, causes fat malabsorption and steatorrhea, with progressive neuropathy and retinopathy in the first two decades of life. Plasma levels are undetectable and high dose vitamin E improves neurological symptoms. Other manifestations include the neurologic syndrome of spinocerebellar ataxia with loss of deep tendon reflexes, truncal and limb ataxia, loss of vibration and position sense, ophthalmoplegia, muscle weakness, ptosis and dysarthria. A pigmented retinopathy may also occur.

Isolated form of vitamin E deficiency without fat malabsorption has been reported. Most malabsorption syndromes respond to large doses of oral vitamin E (100–200 mg/kg/day) with amelioration of deficiency and prevention of neurological sequelae.

Hypervitaminosis E

Relatively large amounts of vitamin E, in range of 400 to 800 mg tocopherol, have been taken daily by adults for months to years without causing any apparent harm. Occasionally, muscle weakness, fatigue, nausea and diarrhea are reported in persons ingesting 800–3200 mg/day. Vitamin E intoxication, at dosages exceeding 1,000 mg/day, results in antagonism to vitamin K action and enhanced effect of oral coumarin anticoagulants, with hemorrhage.

Vitamin K

Vitamin K is a generic term for derivatives of 2-methyl-1, 4-naphthoquinone with procoagulant activity. This is an essential vitamin, since the 1,4-naphthoquinone moiety is not synthesized in animal cells. The natural forms are substituted in position 3 with an alkyl side chain. Vitamin K1 (phylloquinone) has a phytol side chain in position 3 and is the homolog of vitamin K in plants. Vitamin K2 (menaquinone), with an isopropyl side chain, is synthesized by bacteria in the gut.

Absorption and metabolism The absorption of phylloquinone and menaquinone require bile and pancreatic juice. Dietary vitamin K is absorbed in the small bowel, incorporated into chylomicrons and delivered to the circulation *via* the lymph. The liver is the primary site of action of vitamin K. The total body pool of vitamin K is small, 80% being in the liver.

Physiological function The main role of vitamin K is as a cofactor in post-translational carboxylation of glutamic acid to form glutamate in the liver. Vitamin K carboxylates glutamic acids of translation products of vitamin K-dependent proteins, to produce γ-carboxyglutamates. Factors II (prothrombin), VII, IX and X are procoagulant proenzymes whereas proteins C and S are anticoagulant proenzymes. The function of these proteins is to facilitate the chelation of calcium ions to glutamate and platelet phosphatide, which is essential for the coagulation cascade to operate.

Nutritional requirements Vitamin K requirements are met by combination of dietary intake and microbiological biosynthesis in the intestines. The vitamin K dependent coagulation factors are <30% of normal at birth in full-term infants and even lower in premature newborns. Vitamin K requirement for the normalization of prothrombin and other factor in newborns is 3 to 5 µg/day. Since breast milk contains only 2 µg/L phylloquinone, breastfed infants should receive additional vitamin K to prevent hemorrhagic disease of the newborn. The requirement increases from 5 µg/day at birth to 10 µg/day at 2 yr and 10 to 30 µg/day in older children.

Sources Green leafy vegetables are rich in phylloquinone, animal foods are intermediate and cereals low in the vitamin. Bacterial gut flora is capable of synthesizing the vitamin, sufficient to meet daily needs.

Vitamin K Deficiency

Most natural foods have high vitamin K content, relative to its requirement. Thus, primary deficiency is very rare. Deficiency can however result from elimination of intestinal bacterial flora, exclusive parenteral alimentation with no added vitamin K, fat malabsorption, biliary obstruction, cystic fibrosis and short bowel syndrome.

Hemorrhagic disease of the newborn is a syndrome of systemic bleeding and ecchymoses appearing in the first week of life, predominating in breastfed infants. Because of routine administration of prophylactic vitamin K at birth, most cases of hemorrhagic disease of the newborn are of late onset (after 2 weeks of life) and are associated with a variety of conditions such as antibiotic therapy, cholestasis, maternal use of antagonist drugs (primidone, warfarin, diphenylhydantoin), low dietary intake and fat malabsorption. Confirmation of the diagnosis depends on a rapid therapeutic response to administration of vitamin K intramuscularly. Healthy newborns should receive vitamin K at a dose of 0.5–1.0 mg IM to prevent hemorrhagic disease. Parenterally fed infants and children should receive 1 mg vitamin K once weekly.

WATER SOLUBLE VITAMINS

Thiamine (Vitamin B1)

Requirements The recommended daily allowance is 0.4 mg/1000 kcal of carbohydrate intake.

Dietary sources These include unrefined or fortified cereal grains, enriched bakery products, organ meats (liver, kidney) and legumes. Thiamine is sensitive to heat, sulfites, pasteurization and sterilization; freezing results in little loss. Thiamine content of human milk is relatively low (16 µg/ml) compared to cow milk (40–50 µg/ml).

The vitamin is absorbed chiefly from the jejunum through a sodium dependent mechanism; ethanol inhibits absorption. Although thiamine deficiency during pregnancy is described, the fetus appears protected by active placental transport; vitamin levels in cord blood are higher than in maternal blood.

Biologic action Thiamine pyrophosphate is involved in several enzymatic steps of carbohydrate metabolism. It is a cofactor for oxidative decarboxylation of pyruvate to form acetyl-CoA, a step catalyzed by the pyruvate dehydrogenase complex. This pathway is not directly involved in carbohydrate metabolism, but is the major source of five carbon compounds for nucleic acid synthesis and NADPH for fatty acid synthesis. The transketolase reaction is affected rapidly in thiamine deficiency, and its rate in erythrocytes is used as an index of thiamine status.

Deficiency Thiamine deficiency or beriberi affects people who consume diets based on polished rice, when the intake is below 1 mg/day. The classic signs of beriberi appear after prolonged periods of low thiamine intake. Three forms of beriberi are described: dry, wet and acute. The dry and wet (edematous) forms are different manifestations of a polyneuritis. The dry form has no edema and typically includes severe muscle wasting and cardiomegaly. Wet beriberi is characterized by peripheral edema, ocular paralysis, ataxia and mental impairment. The pathogenesis of edema in wet beriberi is unclear. Infantile beriberi may be more subtle than that found in adults. It occurs in breastfed infants of thiamine-deficient mothers (who may not have signs of beriberi), or with very low thiamine intake. The clinical picture is dominated by cardiomegaly, cyanosis, dyspnea and aphonia. The disease may result in death after a few weeks, in the infantile form.

Diagnosis Thiamine deficiency may be suspected in all cases of malnutrition. The diagnosis is confirmed by measurement of 24 hr urinary thiamine excretion, which in children is 40–100 µg/day; values below 15 µg/day are deficient. Diagnosis of deficiency can also be based on the response of red cell transketolase to the addition of thiamine *in vitro*. Erythrocytes from deficient persons have a greater response to thiamine pyrophosphate addition than do those of normal controls. An increase in transketolase activity of less than 15% is normal, 15–25% is mild deficiency and over 25% are severely deficient.

Treatment Treatment with thiamine leads to resolution of neurologic and cardiac symptoms within 24–48 hr. Treatment of patients with mild beriberi with thiamine (5 mg/day) is satisfactory. Severely ill children should receive 10 mg intravenously twice daily. In management of fulminant heart disease, higher doses with vigorous treatment of congestive heart failure are necessary.

Riboflavin (Vitamin B2)

Riboflavin is a flavoprotein, widely distributed in plants. Meat, poultry fish and dairy products and broccoli, spinach and asparagus are good sources. Riboflavin is resistant to oxidation and to heat and is not destroyed by pasteurization. Human milk contains 40–70 µg/100 kcal

of riboflavin and cow milk 250 µg/100 kcal. Maternal riboflavin supplementation may be used to increase its concentration in breast milk. Riboflavin is efficiently absorbed from the small intestine by site-specific, saturable, specialized transport. Biliary obstruction, high dietary fiber and antacids decrease its bioavailability.

Riboflavin is a constituent of two coenzymes involved in oxidation-reduction reactions: flavin adenine dinucleotide and flavin mononucleotide. A number of redox enzymes, including glutathione reductase and xanthine oxidase, require flavin coenzymes. The enzymes catalyzing the synthesis of niacin from tryptophan and the conversion of pyridoxal phosphate to an active coenzyme are flavin-dependent and link riboflavin with these two vitamins. Riboflavin deficiency affects fatty acid synthesis and decrease in plasma levels of linoleic and linolenic acids. By impairing conversion of phosphorylated vitamin B6 to its coenzyme, it affects reactions involved in amino acid metabolism requiring this vitamin.

Riboflavin requirements The recommended daily intake is 0.4 mg/1000 kcal for infants and 0.8–1.2 mg/1000 kcal for children.

Deficiency Riboflavin deficiency occurs from inadequate intake or malabsorption. It takes 1–2 months to develop and is associated with other deficiencies. Features of ariboflavinosis are photophobia, glossitis, angular stomatitis, seborrheic dermatitis, corneal vascularization and cataracts. Nonspecific symptoms include anorexia, weight loss, weakness, dizziness and confusion.

Diagnosis of deficiency Diagnosis should be considered with a history of dietary deficiency and clinical manifestations. A reliable indicator of riboflavin status is the daily losses of the vitamin; urinary excretion of less than 10% of intake over 24 hr is indicative of deficiency. Activity of glutathione reductase in erythrocytes gives a functional index of flavin coenzyme activity; cofactor-induced increase of 20% above the basal level indicates deficiency.

Treatment Children are treated with 1 mg riboflavin three times daily for several weeks; infants respond to 0.5 mg twice daily. Therapeutic doses of vitamin help in improving corneal lesions rapidly.

Niacin (Vitamin B3)

Nicotinic acid and nicotinamide, biologically equivalent vitamins, are both referred to as niacin. Biosynthesis of this vitamin occurs in all organisms; the conversion ratio of tryptophan to nicotinic acid is 60:1, making it possible for large amounts of tryptophan to meet niacin needs.

Sources Niacin is distributed in plants and in animal foods, only in pyridine nucleotide form. Milk, cereals, leafy vegetable, fish, coffee and tea are good sources. The vitamin is resistant to heating. Human milk contains 30 mg/100 kcal of niacin compared with 0.12 mg/100 kcal in cow milk.

Absorption and metabolism Niacin is absorbed in the proximal small bowel and incorporated into nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP). Excess niacin is methylated in the liver, forming N^1-methylnicotinamide. This compound and its oxidation product, 2-pyridone, are the two major niacin metabolites found in urine.

Niacin requirements Requirements are expressed in terms of *niacin equivalents* (NE) One NE equals 1 mg of niacin or 60 mg of tryptophan. RDA for niacin is related to dietary energy intake; the recommended intake is 6.4 to 8 NE/1000 kcal, human milk provides about 8 NE/1000 kcal. High doses of nicotinic acid (but not nicotinamide) reduce serum cholesterol and triglyceride levels in humans. A number of side effects, including skin flares, hyperuricemia, hyperglycemia and abnormal tests of liver function have been described.

Niacin deficiency Niacin deficiency leads to pellagra, the pathognomonic skin change. It was originally thought to be caused by a factor deficient in maize, subsequently identified as nicotinic acid. Clinical features of deficiency are chronic, relapsing and popularly characterized by three Ds: dermatitis, diarrhea and dementia. The cutaneous lesions consist of a pigmented rash aggravated by sunlight. More acute cases may progress to vesiculation, ulceration and secondary infection. Classically, the erythema progresses to roughening and keratosis with scaling; a characteristic red tongue is seen. While neurologic features may appear without skin manifestations, they usually follow the skin lesions. Neurologic symptoms include apathy, headache and loss of memory. In most chronic forms, posterolateral cord degeneration and peripheral nerve lesions are seen. Only in the most severe and chronic cases, the neurologic lesions persist after adequate treatment with niacin.

Diagnosis of niacin deficiency The diagnosis is suspected on history of inadequate diet, INH treatment or chronic alcohol ingestion when typical manifestations are present. Determination of urinary excretion of N^1-methylnicotinamide is most helpful; normal 24 hr excretion is between 4 and 6 mg, values below 3 mg indicate deficiency. In pellagra these values are usually between 0.5 to 0.8 mg/day.

Treatment of pellagra The daily dose for treatment is about 10 times the recommended dietary intake. Oral treatment with nicotinamide is preferred to nicotinic acid to avoid unpleasant side effects. Parenteral therapy is considered when gastrointestinal absorption is deficient. Prevention of pellagra is achieved by an adequate protein diet containing tryptophan and niacin rich foods.

Pyridoxine (Vitamin B6)

Pyridoxine aids in food assimilation and protein and essential fatty acid metabolism. It activates many enzyme

systems and is involved in the production of antibodies against bacterial diseases. It is linked to cardiovascular health by decreasing the formation of homocysteine. It is also required for absorption of vitamin B12 and for production of monoamine neurotransmitters serotonin, dopamine, noradrenaline and adrenaline. Lack of pyridoxine may cause anemia, neuropathy, seizures, skin problems and mouth sores. Pyridoxine is given 10–50 mg/day to patients on INH (isoniazid) to prevent peripheral neuropathy and other neurologic effects.

Vitamin B6 is absorbed mainly in the jejunum. Although colonic bacteria synthesize B6, it is not absorbed to significant extent. Small quantities of the vitamin are stored in the body. Rich sources of vitamin B6 include yeast, sunflower seeds, wheat germ, soya beans and walnuts.

Cobalamin (Vitamin B12)

Cyanocobalamin is the most common commercially available form of vitamin B12, but the active forms in tissues are methylcobalamin and 5′-deoxyadenosyl cobalamin. Methylcobalamin is a coenzyme in the reaction that transfers a methyl group to homocysteine to form methionine. The methyl group donor for this reaction is methylfolate, which is then regenerated to its active form, tetra-hydrofolate. Vitamin B12 deficiency blocks this reaction, trapping folate into the inactive methyl form, thus favoring the development of folate deficiency. The other coenzyme, 5′-deoxyadenosyl cobalamin, helps in formation of succinyl-CoA, an essential step in catabolism of valine, isoleucine and other amino acids through the Kreb cycle.

Sources Vitamin B12 is only produced by micro-organisms. Animals contain cobalamin either ingested with micro-organisms or produced by bacteria in the upper segments of the intestine. Highest concentrations are in organs such as liver, kidney, heart and muscle meat; clams and oysters are excellent sources.

Absorption and metabolism A specific receptor-mediated process in the ileum involves a glycoprotein, *intrinsic factor*. Absence of this gastric protein results in pernicious anemia, an inability to absorb ingested vitamin B12. Passive diffusion accounts for a fraction of total absorption, but has implications for management of pernicious anemia with megadoses of vitamin. Cobalamin undergoes enterohepatic recirculation; this process accounts for a long half-life of the vitamin. Vitamin B12 is transported in plasma bound to transcobalamin II. The average total body pool in an adult is enough to sustain daily vitamin B12 needs for several years.

Requirements The recommended intake of vitamin B12 for infants is 0.3 µg/day. Older children should receive 0.5–1.5 µg/day and adolescents 2.0 µg/day. These needs are met by any mixed diet.

Deficiency Most deficiencies are caused by impaired absorption, due to the deficiency of the intrinsic factor, or intestinal or liver disease and they are more common in adults and elderly persons. True dietary vitamin B12 deficiency occurs in persons who follow strict diets containing no animal or fish products. Vitamin B12 status is assessed by measurement of serum cobalamin levels, with values below 1.1 pmol/l indicative of negative vitamin B12 balance. Plasma levels of methylmalonic acid and homocysteine are increased because of block in vitamin B12-dependent steps of metabolism. Methylmalonic aciduria may also occur but is a less consistent finding. Since development of clinical vitamin B12 deficiency takes a long time, it is rare in infants. Exclusively breastfed infants of strict vegetarian mothers, however, may be at risk of deficiency, manifested by methylmalonic aciduria and megaloblastic anemia. Other features of deficiency are neutrophil hypersegmentation, megaloblastic anemia and thrombocytopenia.

A specific feature of B12 deficiency is a diffuse and progressive demyelination, which begins in peripheral nerves and progresses to involve the posterior and lateral columns of the spinal cord and central nervous system. These lesions are possibly due to a generalized methyl group deficiency in the nervous system and perhaps also to toxic accumulation of homocysteine.

Diagnosis of deficiency The anemia is macrocytic and nucleated RBC showing megaloblastic morphology may be seen in blood. Levels of red cell folate are low; serum LDH levels are elevated.

Treatment Deficiency is treated with parenteral administrations of vitamin B12 (1 mg). Reticulocytosis is seen within 2–4 days. Patents with neurologic involvement require day therapy for 2 weeks.

Folic Acid (Pteroylglutamic Acid)

Folic acid is the parent compound of a group of naturally occurring, structurally related compounds known as the folates. Folic acid is essential for normal growth and maintenance of cells, since it acts as a coenzyme for normal DNA and RNA synthesis. Folate is vital for multiplication of cells within the fetus. A deficiency therefore affects normal cell division and protein synthesis, impairing growth. Folic acid, with vitamin B12 converts homocysteine to methionine, thereby reducing blood levels of homocysteine and lowering risks of heart disease. It also maintains integrity of the central nervous system and intestinal tract function and is involved in production of neurotransmitters such as serotonin. Leafy vegetables such as spinach, turnip greens, lettuces, dried beans and peas, fortified cereal products, sunflower seeds and certain fruits and vegetables are rich sources.

Requirements The recommended daily allowance of folic acid varies from 25 mg in infancy to 200 mg by adolescence (Table 7.1). Deficiency is corrected using folic acid at a dose of 0.5–1 mg/day orally for 3–4 weeks.

Deficiency of folate limits cell division and protein synthesis and affects normal growth and repair of tissues. The tissues that have the fastest rate of cell replacement are affected first. Erythropoiesis is hindered, resulting in megaloblastic anemia; other symptoms are impaired brain and nerve functions, especially memory problems. Maternal deficiency of folate, during pregnancy, is implicated in neural tube defects. Periconceptional folate supplements, begun 1 month before conception and continued for 3 months after, is recommended to reduce the risk.

Biotin

Biotin is a coenzyme for carboxylation reactions. Four such reactions require biotin as a cofactor: (a) acetyl-CoA carboxylase synthesizes malonyl-CoA, the initial step in fatty acid synthesis; (b) pyruvate carboxylase forms oxaloacetate, a key intermediate of the Krebs cycle; (c) propionyl-CoA carboxylase forms methylmalonyl-CoA, permitting the entry to the Krebs cycle of carbons derived from branched chain amino acids, fatty acids and cholesterol; (d) methylcrotonyl-CoA carboxylase participates in the catabolism of leucine.

Biotin deficiency has been observed in individuals who consume large number of raw eggs (rich in avidin) for several months. The avidin is not hydrolyzed by gastrointestinal enzymes; it binds biotin and prevents its absorption. Cooking of eggs destroys avidin. Clinical features of biotin deficiency include anorexia, vomiting, dry scaly dermatitis, glossitis and hypercholesterolemia. Longterm parenteral alimentation without biotin can also lead to deficiency in pediatric and adult patient. Multiple carboxylase deficiency is a genetic metabolite disorder affecting the activity of carboxylase synthetase, which catalyzes the transfer of biotin to the apocarboxylase moiety. This condition responds to large doses of biotin. Another genetic defect affects the activity of biotinidase, an enzyme involved in the recycling of biotin.

Dietary sources of biotin include liver, egg yolk, milk, yeast extracts and meat. Requirements are difficult to determine, since biotin is produced by gastrointestinal flora. Recommendations are 0.15 mg biotin in the multivitamin supplements for infants and children. For treatment of biotin deficiency, oral administration of 2–5 mg daily for 2 to 3 weeks is recommended for mild cases. A parenteral biotin dose of 200 µg daily for 2 to 5 days can be used in more severe cases.

Pantothenic Acid

Pantothenic acid (vitamin B5) is present in virtually all naturally occurring foods and is also synthesized by microorganisms from pantoic acid and β-alanine. Pantothenate is absorbed in the proximal small intestine; in the liver it becomes an integral part of coenzyme A, which is essential for acyl transfer reactions of fatty acid, steroids and cholesterol synthesis, as well as for the metabolism of pyruvate and α-ketoglutarate. Isolated pantothenate deficiency is rare and includes burning feet, insomnia and gastrointestinal symptoms. In cases of extreme malnutrition, such a deficiency coexists with other vitamin deficiencies. The suggested daily intake is 2–3 mg for infants and 3–5 mg for children.

Vitamin C

Vitamin C (ascorbic acid), structurally related to glucose, has a striking capacity for reversible oxidation-reduction. Humans and other primates do not synthesize vitamin C.

Sources Dietary sources include vegetables (cauliflower, broccoli, cabbage) and fruits (berries, citrus). Much of vitamin C may be lost in cooking, but is stable in canned and frozen foods. Vitamin C in human and cow milk ranges from 5 to 15 mg/100 kcal and 0.2–2.0 mg/100 kcal respectively. Daily requirements are 30–40 mg for infants and 40–70 mg for children.

Absorption and metabolism Ascorbic acid is absorbed by an active, sodium-dependent process in the upper small intestine. The vitamin circulates in plasma in its free, anionic form, reaching high concentrations in adrenal and pituitary glands and in leukocytes. Vitamin C appears unchanged in the urine when renal threshold is exceeded.

Biologic action Vitamin C functions as a strong reducing agent or in electron transport within biological systems. Ascorbic acid is essential for normal function of leukocytes, fibroblasts, osteoblasts and microsomes and participates in metabolism of carnitine, serotonin and folate. Ascorbic acid affects the immune response, detoxification, collagen synthesis and wound healing.

Deficiency Prolonged vitamin C deficiency results in scurvy. It usually occurs in those who are deprived of citrus fruits, fresh vegetables or vitamins for some cultural or geographic reasons. In infancy, features of scurvy are anorexia, diarrhea, pallor, irritability and increased susceptibility to infections. Subperiosteal hemorrhages and long bone tenderness (pseudoparalysis of lower extremities) can occur; radiologic abnormalities are frequent. In older children, hemorrhagic signs predominate, with bleeding from gums, conjunctiva and intestinal tract.

Diagnosis of scurvy The diagnosis is made by presence of characteristic physical findings and history of inadequate dietary intake of vitamin C. X-rays of long bones show a ground glass appearance with thinning of cortex and sharply outlined epiphyseal ends. The finding of a zone of rarefaction under the white line of metaphysis, as a linear break in the bone running proximal and parallel to the white line, is diagnostic in infantile scurvy. The lateral part of the rarefaction appears as a triangular defect. There may be spurs at the level of the white line. Other characteristic

findings include the white line of Frenkel, an irregular thickened line at the metaphyses representing calcified cartilage at the zone of calcification and white rings surrounding the epiphyseal centers of ossification. Vitamin C therapy often results in dramatic improvement within 24–48 hr.

Therapy for scurvy Therapy with 100–200 mg of vitamin C orally or parenterally results in prompt and rapid improvement in symptoms. Daily intake of 100 ml of orange juice or tomato pulp has the same effect.

MINERALS AND TRACE ELEMENTS

Calcium

Calcium is the most abundant mineral in the body and is located primarily (98%) in bone. Calcium is essential for the coagulation cascade, nerve conduction and muscle stimulation. Intestinal absorption of calcium varies inversely with intake and is regulated by 1,25(OH)D3, which controls the synthesis of calcium-binding protein at the brush border. In the presence of vitamin D, calcium absorption can adapt to a wide range of dietary calcium intakes, varying from 10 to 80% of available calcium. Calcium absorption also depends on the interaction of calcium with other dietary constituents, including fiber, phytate, oxalate, fat and lactose.

The main sources of calcium for infants are milk and dairy products, with smaller amounts derived from grains and fruits once solid foods are introduced. Children consuming strict vegetarian diets may develop calcium deficiency, either alone or in combination with vitamin D deficiency. Strict vegetarian diets may provide as little as 250 mg of calcium per day and include generous amounts of substances that inhibit calcium absorption, such as fiber and phytates. Secondary calcium deficiency may develop in association with steatorrhea, chronic malabsorption syndromes, or intestinal or renal abnormalities of calcium metabolism.

Children aged 1 to 10 yr require an intake of 500 to 800 mg per day. During the pubertal growth spurt calcium requirements are as high as 1000 to 1200 mg per day. Pregnant and lactating women require 400 mg per day. Calcium deficiency may cause tetany characterized by muscle cramps, numbness and tingling in limbs. Rickets and osteoporosis may occur with chronic deficiency.

Magnesium

Magnesium is essential for bioenergetic reactions controlling fuel oxidation, membrane transport and signal transmission contributing to the action of more than 300 enzymes. Over 80% of the total body magnesium is in bone and skeletal muscle. Rich sources of magnesium include legumes, nuts, bananas and whole grains. Magnesium is absorbed efficiently by the intestine and regulation of its balance depends on renal tubular reabsorption. Deficiency is usually secondary to intestinal malabsorption, excessive gastrointestinal losses through fistulae or continuous suction or renal disease affecting tubular reabsorption. Clinical manifestations of magnesium deficiency include irritability, tetany and hypo or hyper-reflexia. Magnesium requirements in the first 6 months range between 40 and 50 mg/day; 60 mg/day for 6–12 months and approximately 200 mg/day for older children.

Trace Element Deficiencies

Eleven 'major' elements constitute 99% of human body weight. These essential-for-life elements are hydrogen, carbon, nitrogen, oxygen, sodium, potassium, chlorine, calcium, phosphorus, sulfur and magnesium. In addition, the body is composed of numerous "trace" elements. The term trace elements comprise an increasing number of compounds with proven or putative essentiality for human nutrition. Each of these contributes less than 0.01% of total body weight. Their major functions are related to enzyme systems where they act either as cofactor for metal-ion-activated enzymes or as specific constituents of metalloenzymes. This section provides an overview of all trace elements of established importance in human nutrition.

Zinc

Functions Zinc is a component of over 100 metalloenzymes and participates in many biological processes. As a component of zinc finger proteins, zinc regulates gene transcription and participates in nucleic acid metabolism, protein synthesis and thereby, cellular growth. Thymidine kinase, DNA polymerase and RNA polymerase are reported to be zinc dependent enzymes.

Absorption and metabolism Zinc is absorbed throughout the small intestine by a process of facilitated diffusion. Most absorbed zinc is taken up temporarily by the liver, which plays a central role in zinc metabolism. Absorbed zinc is transported in the portal system attached to albumin or transferrin. In the systemic circulation, the major fraction of plasma zinc is loosely bound to albumin. Almost 90% of total body zinc is localized in bone and skeletal muscle. Zinc status is regulated both at the absorptive step and by intestinal re-excretion. The major excretory route for endogenous zinc is via the feces.

Deficiency Zinc deficiency is usually seen as a part of malnutrition or malabsorption syndromes, caused by low dietary intake or intestinal disease. Severe zinc deficiency syndromes have occurred in patients on prolonged intravenous feeding without adequate trace element supplements. Poor physical growth is an important feature of zinc depletion in preschool and school-age children and its supplementation results in accelerate growth in adolescents with intestinal malabsorption and sickle cell disease. Delayed sexual maturation and hypogonadism is also a prominent feature of zinc deficiency in adolescents. Other features include anemia, anorexia, diarrhea,

hair loss, dermatitis, impaired immune function, poor wound healing and skeletal abnormalities.

Acrodermatitis enteropathica is an autosomal recessive syndrome of severe zinc deficiency, caused by defective intestinal absorption due to defect in intestinal zinc transporter protein. Presentation is in early infancy, with vesicobullous, dry, scaly or eczematous skin lesions chiefly involving the perioral, perineal and acral areas. Alopecia and eye changes, such as conjunctivitis, blepharitis and photophobia, may be present. Chronic diarrhea, growth retardation, stomatitis, irritability and delayed wound healing are other findings. Catchup growth and resolution of symptoms is noted following oral zinc therapy.

The diagnosis of zinc deficiency is often derived from the combination of dietary history of chronic low zinc intake or excessive intestinal losses, presence of clinical features compatible with deficiency and low levels of zinc in plasma or hair.

Requirement and treatment of deficiency The normal requirements for children range between 3.5 and 5.0 mg per day. Acquired zinc deficiency states can be treated with 0.5 to 1.0 mg elemental zinc/kg/day for several weeks or months. One mg of elemental zinc is available from 4.5 mg zinc sulfate or 3 mg zinc acetate. Intravenous requirements for patients maintained on prolonged intravenous feeding approximate 50 µg of elemental zinc/kg body weight/day. These requirements can be considerably higher in the presence of excessive zinc losses. Zinc therapy should be monitored with plasma zinc and copper concentrations as excessive zinc therapy can lead to a copper deficiency syndrome.

Copper

Copper is a component of several metalloenzymes required for oxidative metabolism. Ceruloplasmin, a glycoprotein that contains eight copper atoms per molecule, accounts for 95% of the ion in blood.

Absorption and metabolism Approximately 40% of ingested copper is absorbed in stomach and small intestine, from where it is transported to the liver bound to albumin and utilized by hepatocytes for synthesis of ceruloplasmin that is subsequently released into the systemic circulation. Approximately one-third of fecal copper is contributed by bile acids, the rest is unabsorbed copper and from epithelial desquamation; urinary excretion is minimal.

Sources The richest sources are meats, liver, seafood, nuts and seeds. Additional copper may enter the food chain through pesticides and contamination of water by pipes and cooking utensils.

Deficiency Primary dietary deficiency is infrequent. Secondary deficiency may develop in malabsorption syndromes, liver disease, peritoneal dialysis and other conditions causing excessive copper losses. Features of deficiency are microcytic, hypochromic anemia unresponsive to iron therapy, neutropenia and osteoporosis. Copper deficiency decreases the lifespan of the erythrocyte and impairs mobilization of stored iron from liver and bone marrow. Skeletal lesions include periosteal elevation, changes in metaphyses of long bones, and rarely submetaphyseal fractures, flaring of the anterior ribs and spontaneous fractures of the ribs. Infants show pallor, depigmentation of skin and hair, prominent dilated superficial veins, lesions resembling seborrheic dermatitis, anorexia, diarrhea and failure to thrive.

Copper transport is disrupted in two human diseases: Wilson disease and Menkes disease. Both have defects in copper transporting membrane proteins. Central nervous system manifestations include hypotonia, psychomotor retardation and apneic episodes. In the Menkes steely-hair syndrome there is severe neurological degeneration leading to a fatal outcome by early childhood. Laboratory findings include hypocupremia, low plasma ceruloplasmin, neutropenia and anemia.

Selenium

Selenium is a constituent of glutathione peroxidase, an antioxidant in red blood cells and other tissues. Glutathione peroxidase scavenges free hydroperoxides generated during fatty acid oxidation, thus protecting the cell from damage due to free radical formation. Severe deficiency is the major cause of Keshan disease, which presents as a cardiomyopathy in young children. Skeletal myopathies have also been reported. Mild deficiency is associated with macrocytosis and loss of hair pigment.

Chromium

Glucose intolerance, which complicates malnutrition in young children, has been attributed in part to chromium deficiency. Chromium acts in glucose homeostasis by potentiating insulin action, possibly by facilitating binding to its receptor. Symptoms of chromium deficiency are usually in the setting of total parenteral alimentation and include glucose intolerance, peripheral neuropathy and evidence of disturbed nitrogen and lipid metabolism.

Iodine

The term iodine deficiency disorders (IDD) refers to the effects of iodine deficiency in a population that can be prevented by ensuring an adequate intake of iodine. Iodine deficiency disorders (IDD) jeopardize children's mental health and often their very survival. Serious iodine deficiency during pregnancy can result in stillbirth, spontaneous abortion and congenital abnormalities such as cretinism, an irreversible form of mental retardation that affects people living in iodine-deficient areas. However, of far greater significance is the less visible mental impairment that reduces intellectual capacity at home, in school and at work. The effects of iodine deficiency on growth and development are summarized in Table 7.3.

Table 7.3: Spectrum of iodine deficiency disorders IDD

Fetus	Abortions, stillbirths
	Congenital anomalies
	Endemic cretinism
	Increased perinatal mortality
Neonate	Neonatal goiter
	Endemic mental retardation
	Neonatal hypothyroidism
Child, adolescent	Goiter
	Impaired mental function
	Subclinical hypothyroidism
	Retarded physical development

Recommended daily intake of Iodine The recommended daily allowance of iodine is as follows: 90 mg for preschool children (0 to 59 months); 120 mg for school children (6 to 12 yr); 150 mg for adults (above 12 yr); and 200–250 mg for pregnant and lactating women.

Iodine Deficiency in the Fetus

The consequence of iodine deficiency during pregnancy is impaired synthesis of thyroid hormones by the mother and the fetus. Since the physiologic role of thyroid hormones is to ensure the coordination of different developmental events through specific effects on the rate of cell differentiation and gene expression, an insufficient supply of thyroid hormones to the developing brain results in mental retardation.

Iodine Deficiency in the Neonate

The brain of the human infant at birth has only reached about one-third of its full size and continues to grow rapidly until the end of the second year. The thyroid hormone, dependent on an adequate supply of iodine, is essential for normal brain development. The continuing presence of iodine deficiency is a threat to early brain development.

Neonatal chemical hypothyroidism is defined by serum levels of T4 lesser than 3 mg/dl and TSH greater than 100 mU/ml. In severely iodine deficient environments in Northern India, where more than 50% of the population has urinary iodine levels below 25 mg/g creatinine, the incidence of neonatal hypothyroidism is 75–115 per thousand births. In Delhi, where only mild iodine deficiency is present with low prevalence of goiter, the incidence drops to 6 per thousand.

Neonatal hypothyroidism persists into infancy and childhood if the deficiency is not corrected and results in retardation of physical and mental development. These observations indicate a much greater risk of mental defect in severely iodine-deficient populations than is indicated by the presence of cretinism.

Iodine Deficiency in Children

Moderate iodine deficiency is associated with abnormalities in psychoneuromotor and intellectual development of children who are clinically euthyroid, but who do not exhibit other features of endemic cretinism. Some patients may show goiter (Fig. 7.7) (*see* Chapter 17). Studies in moderately iodine-deficient areas indicate that fine motor skills and visual problem solving improved in school children after iodine repletion.

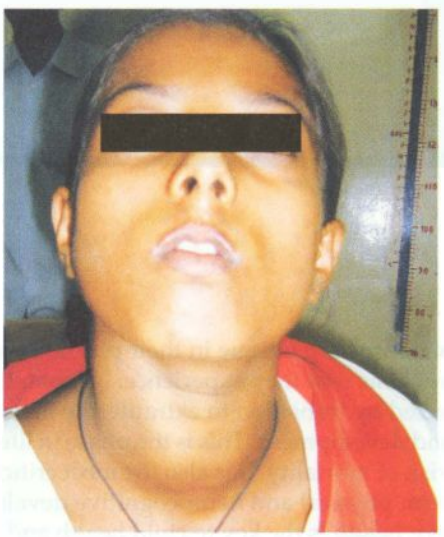


Fig. 7.7: A 14-yr-old girl with goiter

Therapy

Iodization of salt is the most practical option. Other options for correction of IDD are administration of iodized oil capsules every 6–10 months, direct administration of iodine solutions, such as Lugol iodine at regular intervals and iodization of water supplies by direct addition of iodine solution. The **National Goiter Control Program** (1962) for control of iodine deficiency disorders was started by establishment of salt iodination plants to ensure an adequate supply of iodized salt in the country. Based on an assumption of a mean intake of salt of 5 g/day, the recommended level of iodination is one part of iodine in 25,000 to 50,000 parts of salt.

Iron

Iron deficiency remains a major nutritional problem among infants and young children. The National Family Health Survey (NFHS) II, conducted in 1998–99, documented that 74% children between the ages of 6–35 months were anemic. The NFHS III (2005–06) shows similar data. Iron deficiency anemia is associated with impaired performance in mental and physical functions, including physical coordination and capacity, cognitive abilities, and social and emotional development. The precise effects vary with the age groups studied. The health consequences of iron deficiency in young children are serious and often irreversible. A description of clinical features, diagnosis, treatment and prevention of iron deficiency anemia is given in Chapter 12.

8 Newborn Infants

Ramesh Agarwal, Vinod K Paul, Ashok K Deorari

Newborn infants are unique in their physiology and the health problems that they experience. Neonatal period is characterized by transition to extrauterine life and rapid growth and development. This is the phase in life with the greatest risk of mortality. It is also the most critical period for longterm physical and neurocognitive development.

Newborn health is the key to child health and survival. More than under half of under 5 child deaths occur in the neonatal period (*see* Chapter 1). Preterm birth complications account for 35% of all neonatal deaths and constitute the most important cause of neonatal mortality (Fig. 8.1). Bacterial infections (sepsis, pneumonia and diarrhoea) contribute to 33% of neonatal deaths. Other causes of neonatal mortality are birth asphyxia (20%) and congenital malformations (9%). Almost three-fourths of all neonatal deaths occur among the low birth weight newborns. Of all the neonatal deaths, about 40% occur within first 24 hr, half within 72 hr and three fourths within one week of birth. Predominant causes of death in the first week of life include birth asphyxia and preterm birth complications. Health of the mother and care during pregnancy and at childbirth has profound influence on neonatal outcome. As noted in Chapter 1, decline in neonatal mortality is critical to achieve national health goals. The stagnant early neonatal mortality is a cause for concern.

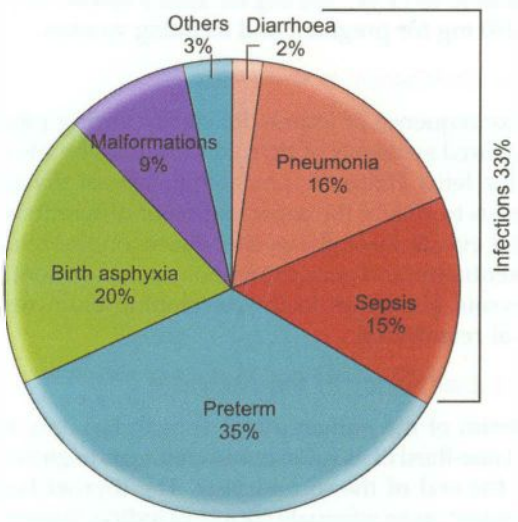


Fig. 8.1: Causes of neonatal deaths (2010)

Definitions

Neonatal period. From birth to under four weeks (<28 days) of age. An infant is called a neonate during this phase. First week of life (<7 days or <168 hr) is known as early neonatal period. Late neonatal period extends from 7th to <28th day.

Postneonatal period. Period of infancy from 28 days to <365 days of life.

Weeks of gestation refer to completed weeks of gestation, e.g. 36 weeks gestation, refer to range of gestation from 36 weeks 0 day to 36 weeks and 6 days.

Perinatal period. Perinatal period extends from 22nd week of gestation (≥154 days or weighing ≥500 g at birth) to less than 7 days of life.

Live birth. A product of conception, irrespective of weight or gestational age, that, after separation from the mother, shows any evidence of life such as breathing, heart-beat, pulsation of umbilical cord or definite movement of voluntary muscles.

Fetal death. A fetal death is a product of conception that, after separation from the mother, does not show any evidence of life.

Still-birth. Fetal death at a gestational age of 22 weeks or more or weighing more than 500 g at birth.

Term neonate. A neonate born between 37 and <42 weeks (259–293 days) of gestation.

Preterm neonate. A neonate born before 37 weeks (<259 days) of gestation irrespective of the birth weight.

Post-term neonate. A neonate born at a gestation age of 42 weeks or more (294 days or more).

Low birthweight (LBW) neonate. A neonate weighing less than 2500 g at birth irrespective of the gestational age.

Very low birthweight (VLBW) neonate. A neonate weighing less than 1500 g at birth irrespective of the gestational age.

Extremely low birthweight (ELBW) neonate. A neonate weighing less than 1000 g at birth irrespective of the gestational age.

Neonatal mortality rate (NMR). Deaths of infants under the first 28 days of life per 1000 live births per year.

Perinatal mortality ratio (PNMR). Number of perinatal deaths (stillbirths plus neonatal deaths before 7 days of life) per 1000 live births. It is designated as a ratio since the numerator is not part of the denominator. (For rate, like in NMR, numerator is part of denominator.)

Online Learning Resource Material

The Newborn Division of Department of Pediatrics, AIIMS, has produced excellent resource material for learning of health professionals. The material is in form of modules, posters, videos and webinars on common newborn issues and is available at: www.newbornwhocc.org.

The online material complements the information provided in this Chapter. The readers are encouraged to visit the website and use the resource to enhance their learning.

RESUSCITATION OF A NEWBORN

Of the 25 million infants born every year in India, 3–5% experience asphyxia at birth. Asphyxia is characterized by progressive hypoxia, hypercapnia, hypoperfusion and acidosis. It may lead to multiorgan dysfunction that may cause death. Hypoxic ischemic encephalopathy (HIE) resulting from asphyxia may lead to longterm neuromotor sequelae.

There is broad consensus on the evidence based resuscitation of newborn babies at birth. The American Heart Association (AHA) and the American Academy of Pediatrics (AAP) have recently updated the resuscitation guidelines that are being propagated worldwide through the Neonatal Resuscitation Program (NRP). A summary of the recommendations of AHA-AAP (2010) is provided here.

Pathophysiology of Asphyxia

When an infant is deprived of oxygen, an initial brief period of rapid breathing occurs. If the asphyxia continues, the respiratory movements cease and the infant enters into a period of apnea known as *primary apnea*. During primary apnea, the heart rate begins to fall, neuromuscular tone gradually diminishes but the blood pressure remains normal. In most instances, tactile stimulation during this period will reinitiate respiration.

If the asphyxia continues, the infant develops deep gasping respiration, the heart rate continues to decrease, the blood pressure begins to fall and the infant becomes flacid. The breathing becomes weaker until the infant gasps and enters into a period of *secondary apnea*. The infant is now unresponsive to stimulation and does not spontaneously resume respiratory efforts unless resuscitation in the form of positive pressure ventilation is initiated.

It is important to note that as a result of fetal hypoxia, the infant may go through the phases of primary and secondary apnea even *in utero*. Hence, apnea at birth may be either primary or secondary apnea. These two are clinically indistinguishable; in both instances, the infant is not breathing and the heart rate may be below 100 beats per minute. Hence, when faced with an apneic infant at birth, one should assume that one is dealing with secondary apnea and be ready to undertake full resuscitation efficiently without wasting too much of time in providing tectile stimulation.

Lung Inflation

During intrauterine life, the lungs do not take part in gas exchange, which is taken care of by the placenta. The lung alveoli in the fetus are filled with fluid secreted by type II alveolar cells. The process of fluid removal starts with onset of labor. The fluid gets reabsorbed from the alveoli into the perivascular space and then into blood and lymphatic channels. The process of labor may facilitate removal of lung fluid, whereas removal is slowed when labor is absent (as in elective cesarean section).

Removal of lung fluid from the alveoli is facilitated by respiration soon after birth. The first few breaths after birth are effective in expanding the alveoli and replacing the lung fluid with air. Problems in clearing lung fluid may occur in infants whose lungs have not inflated well with the first few breaths, such as those who are apneic at birth or have a weak initial respiratory effort as with prematurity or sedation.

Pulmonary Circulation

Oxygenation depends not only on air reaching the alveoli, but also on pulmonary circulation. During intrauterine life, there is little blood flow in the lungs due to pulmonary vasoconstriction. After birth, pulmonary vasodilatation takes place resulting in fall in pulmonary vascular resistance and increased blood flow in the pulmonary circuit.

An asphyxiated infant has hypoxemia (low-oxygen content of the blood) and acidosis (low pH). In the presence of hypoxemia and acidosis, the pulmonary arterioles remain constricted and ductus arteriosus remains open (persistence of fetal circulation). As long as there is poor pulmonary blood flow, proper oxygenation of the tissues of the body is impossible because there is inadequate uptake of oxygen, even when the infant is being properly ventilated.

In mildly asphyxiated babies whose oxygen and pH are only slightly lowered, it may be possible to increase pulmonary blood flow by quickly restoring ventilation. However, pulmonary perfusion in severely asphyxiated infants may not improve with ventilation alone. The combination of oxygenation and correction of metabolic acidosis would be necessary to open the pulmonary arterioles that would improve pulmonary blood flow.

Cardiac Function and Systemic Circulation

In asphyxia, there is redistribution of blood flow to preserve blood supply to vital organs. There is vasoconstriction in the bowel, kidney, muscles and skin, thus preserving blood flow to the heart and brain (diving-in reflex).

As asphyxia is prolonged, myocardial function and cardiac output too deteriorate and blood flow to all organs is further reduced. This sets in the stage for progressive organ damage. At this point, it may be necessary to provide cardiac stimulants (epinephrine) and volume expanders (normal saline) to support the heart and circulation.

Preparing for Resuscitation

With careful consideration of antepartum and intrapartum risk factors, asphyxia can be anticipated in up to only half of the newborns who will eventually require some form of resuscitation. In others, the need for resuscitation can come as a complete surprise. Therefore, each delivery should be viewed as an emergency and basic readiness must be ensured to manage asphyxia. Preparation for delivery should include:

i. A radiant heat source ready for use
ii. All resuscitation equipments immediately available and in working order (Table 8.1)
iii. At least one person skilled in neonatal resuscitation

Table 8.1: Neonatal resuscitation supplies and equipment

Suction equipment
Mechanical suction
Suction catheters 10, 12 or 14 F
Meconium aspirator
Bag and mask equipment
Neonatal resuscitation bags (self-inflating)
Face-masks (for both term and preterm babies)
Oxygen with flow meter and tubing
Intubation equipment
Laryngoscope with straight blades no. 0 (preterm) and no. 1 (term)
Extra bulbs and batteries (for laryngoscope)
Endotracheal tubes (internal diameter of 2.5, 3.0, 3.5 and 4.0 mm)
Medications
Epinephrine
Normal saline or Ringer lactate
Naloxone hydrochloride
Miscellaneous
Linen, shoulder roll, gauze
Radiant warmer
Stethoscope
Syringes 1, 2, 5, 10, 20, 50 ml
Feeding tube 6 F
Umbilical catheters 3.5, 5 F
Three way stopcocks
Gloves

Evaluation

Evaluation is based primarily on the following three signs: respiration, heart rate (HR) and color. Though all three signs are evaluated simultaneously, *low heart rate* is the most important sign for proceeding to the next step.

Role of Apgar Scores in Resuscitation

The Apgar score is an objective method of evaluating the newborn's condition (Table 8.2). It is generally performed at 1 minute and again at 5 minutes after birth. However, resuscitation must be initiated before the 1-minute score is assigned. *Therefore, the Apgar score is not used to guide the resuscitation.*

While the Apgar score is not useful for decision making at the beginning of resuscitation, the change of score at sequential time points following birth can reflect how well the baby is responding to resuscitative efforts. Hence, Apgar scores should be obtained every 5 minutes for up to 20 minutes, if the 5-minute Apgar score is less than 7.

TABC of Resuscitation

The components of the neonatal resuscitation procedure related to the TABC of resuscitation are shown here:

T-Temperature: Provide warmth, dry the baby and remove the wet linen.

A-Airway: Position the infant, clear the airway (wipe baby's mouth and nose or suction mouth, nose and in

Table 8.2: Apgar score

Sign	*0*	*1*	*2*
Heart rate	Absent	Slow (<100 beats/min)	Normal (>100 beats/min)
Respiration	Absent	Weak cry	Good strong cry
Muscle tone	Limp	Some flexion	Active movements
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue or pale	Body pink, extremities blue	Completely pink

some instances, the trachea in non-vigorous baby born through meconium stained liqor). If necessary, insert an endotracheal (ET) tube to ensure an open airway.

B-Breathing: Tactile stimulation to initiate respirations, positive-pressure breaths using either bag and mask or bag and ET tube when necessary.

C-Circulation: Stimulate and maintain the circulation of blood with chest compressions and medications as indicated.

Resuscitation Algorithm

Figure 8.2 presents the algorithm of neonatal resuscitation. At the time of birth, one should ask three questions about the newborn:

i. Term gestation?
ii. Breathing or crying?
iii. Good muscle tone? (flexed posture and active movement of baby denotes good tone)

If answers to all the three questions are 'Yes', the baby does not require any active resuscitation and "Routine care" should be provided. Routine care consists of four steps:

i. *Warmth:* Provided by putting the baby directly on the mother's chest in skin-to-skin contact.
ii. *Clearing of airway if required:* Done by wiping the baby's mouth and nose using a clean cloth. No need to suction routinely.
iii. Dry the baby
iv. *Ongoing evaluation* for vital parameters. Helping mother in breastfeeding will facilitate easy transition to extrauterine environment.

If answer to *any* of the three questions is "No", the baby requires resuscitation. After cutting the cord, the baby should be subjected to a set of interventions known as *Initial steps*.

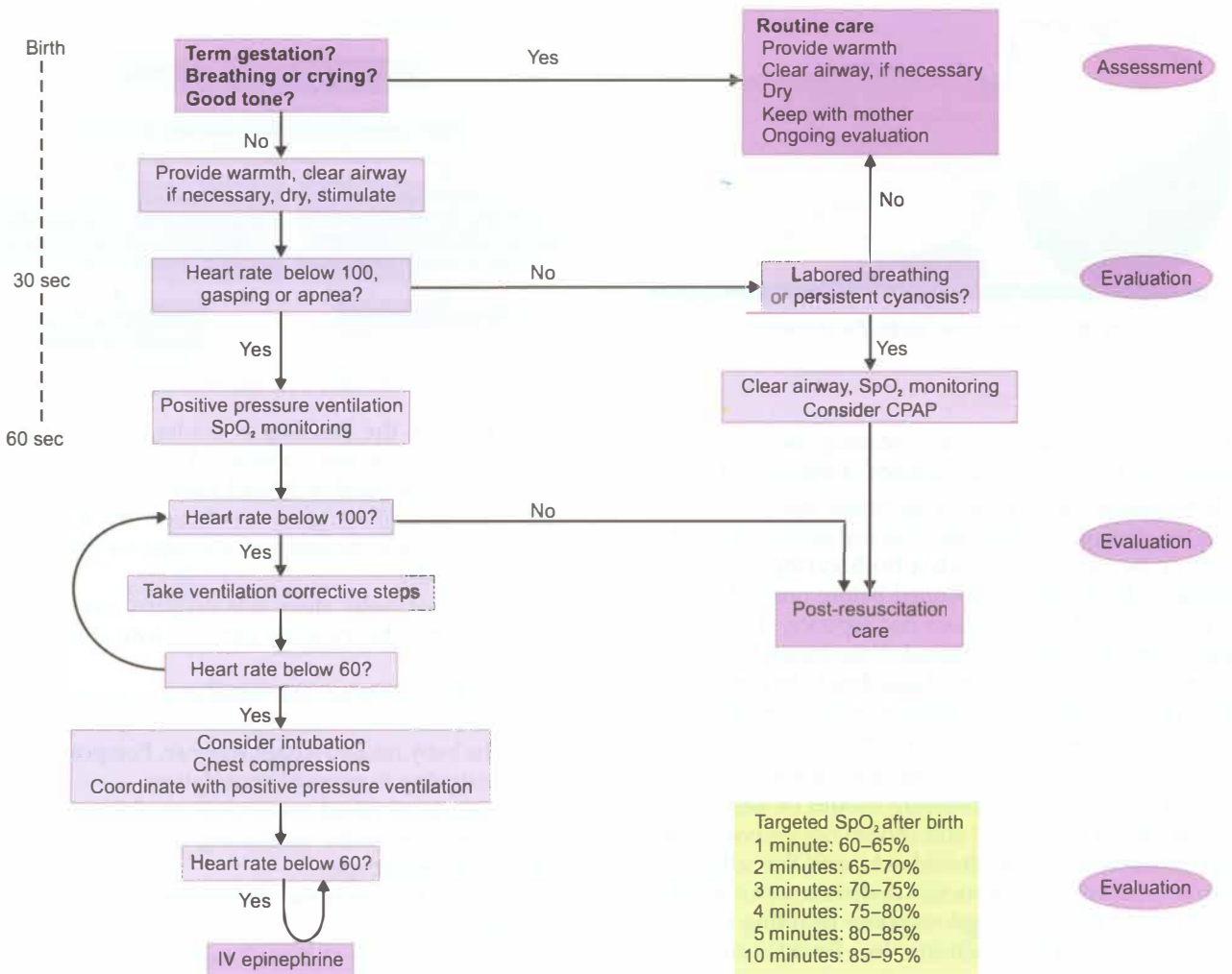


Fig. 8.2: The algorithm of neonatal resuscitation. CPAP continuous positive airway pressure; PPV positive ventilation; SpO_2 saturation of oxygen. (Adapted with permission from American Academy of Pediatrics 2010)

Initial Steps

Warmth

The baby should be placed under the heat source, preferably a radiant warmer. The baby should not be covered with blankets or towels to ensure full visualization and to permit the radiant heat to reach the baby.

Positioning

The baby should be placed on her back or side with the neck slightly extended. This brings the posterior pharynx, larynx and trachea in line and facilitates breathing. Care should be taken to prevent hyperextension or flexion of the neck, since either may interfere with respiration.

To help maintain the correct position, place a rolled blanket or towel under the shoulders, elevating them ¾ or 1 inch off the mattress. This *shoulder roll* is particularly helpful if the infant has a large occiput resulting from molding, edema, or prematurity (Fig. 8.3).

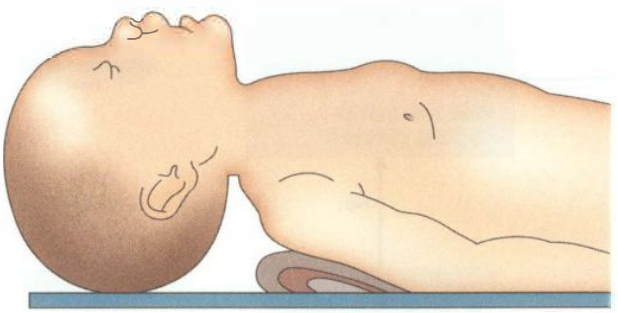


Fig. 8.3: Rolled towel under the shoulders

Clear Airway if Necessary

The appropriate method for clearing the airway will depend on the presence or absence of meconium.

If no meconium is present, secretion may be removed from the airway by wiping the nose and mouth with a clean cloth or by suctioning with a bulb syringe or suction catheter. The mouth is suctioned before nose ('M' before 'N') to ensure the infant does not aspirate, if she should gasp when the nose is suctioned. If the infant has copious secretion from the mouth, the head should be turned to the side. This will allow secretions to collect in the side of mouth, where they can be easily removed.

For suctioning, the size of suction catheter should be 12 or 14 Fr. The suction pressure should be kept around 80 mm Hg (100 cm water) and should not exceed 100 mm Hg (130 cm water). One should not insert the catheter too deep in mouth or nose for suction as stimulation of posterior pharynx can produce vagal response resulting in brady-cardia or apnea. The maximum time limit for suctioning is 15 seconds.

Clearing of the airways in babies born through meconium stained liquor is discussed later.

Dry, Stimulate and Reposition

After suctioning, the baby should be dried adequately using pre-warmed linen to prevent heat loss. The wet linen should be removed away from the baby. The act of suctioning and drying itself provides enough stimulation to initiate breathing. If the newborn continues to have poor respiratory efforts, additional tactile stimulation in form of flicking the soles or rubbing the back gently may be provided *briefly* to stimulate the breathing. However, one should not waste too much of time in providing tactile stimulation.

Management of Infant Born Through Meconium-Stained Liquor (MSL)

When baby passes meconium *in utero*, meconium may be aspirated into infant's mouth and potentially into the trachea and lungs. Steps must be taken after delivery to reduce serious consequences of aspiration of meconium (Fig. 8.4). *(Note: Intrapartum suctioning of the mouth and nose after delivery of the head and before delivering the shoulders is no longer recommended).*

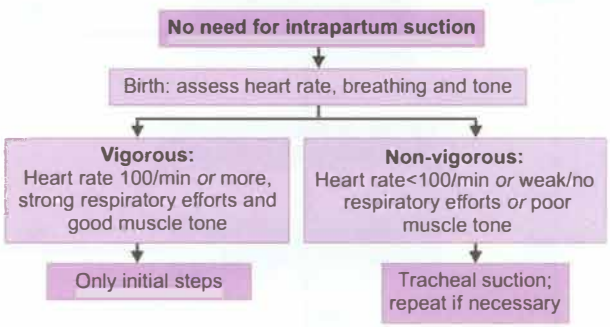


Fig 8.4: Management of a baby born through meconium stained liquor

After delivery, the first step is to identify whether the infant is *vigorous* or *non-vigorous*. A newborn infant is classified as vigorous if he has all the three signs namely *strong respiratory efforts, good muscle tone and a heart rate greater than 100/min*. Absence of any sign would imply a *non-vigorous* baby.

The vigorous baby does not require any tracheal suctioning and the routine care or initial steps are provided.

For *non-vigorous babies*, the initial steps are modified as below:

- Place the baby under radiant warmer. Postpone drying and suctioning to prevent stimulation.
- Remove the residual meconium in the mouth and posterior pharynx by suctioning under direct vision using a laryngoscope.
- Intubate and suction out meconium from the lower airway.

Tracheal suctioning is best done by applying suction directly to the endotracheal tube (ET). Continuous suction is applied to the ET tube as it is withdrawn. Tracheal suctioning can be repeated if the previous suctioning has

revealed meconium and baby has not developed significant bradycardia.

Evaluation

After providing initial steps, the baby should be evaluated by assessing respiration, HR and color (or oxygen saturation by pulse oximetry).

Respiration is evaluated by observing the infant's chest movements. HR can be assessed by auscultating the heart or by palpating the umbilical cord pulsation for 6 seconds. The number of beats or pulsation is multiplied by 10 to obtain the HR per minute (e.g. a count of 12 in 6 seconds is a HR of 120 per minute). Color is evaluated by looking at tongue, mucous membranes and trunk. A blue hue to the lips, tongue and central trunk indicates central cyanosis. Presence of cyanosis in extremities (acrocyanosis) does not have any significance.

- If the baby has good breathing, HR 100/min or more and no cyanosis, then she does not require any additional intervention and the baby should be monitored frequently.
- If the baby has labored breathing or persistent central cyanosis, administration of CPAP in preterm babies and supplemental oxygen in term babies is recommended. Baby should have its oxygen saturation monitored and supplemental oxygen is titrated to achieve the targeted saturations (Fig. 8.2).
- If the baby is apneic, has gasping breathing or heart rate is below 100 min, positive pressure ventilation (PPV) is needed.

Supplemental Oxygen

Central cyanosis requires supplemental oxygen, which can be provided by an oxygen mask or oxygen tube held in cupped hand over baby's face or by flow inflating bag and mask. The flow of oxygen should be at least 5 l/minute. Supplemental oxygen cannot be provided by self inflating bags.

Positive Pressure Ventilation (PPV)

PPV is usually given by using a self-inflating bag and face mask (bag and mask ventilation or BMV). The self-inflating bag is easy to use as it reinflates completely without any external compressed source of gas. The disadvantage of such bag is that it cannot be used to administer free-flow of oxygen.

The resuscitation bag (Fig. 8.5) should have a capacity of 240 to 750 ml. If the bag is attached to an oxygen source (at 5–6 liter/min) and a reservoir, it delivers 90–100% oxygen. In absence of reservoir, it delivers 40% to 50% oxygen.

Oxygen should be treated as a drug. Both too little or too much of oxygen is bad for the baby. Even a brief exposure to high concentration of oxygen can have detrimental effect on the baby. Studies have shown that

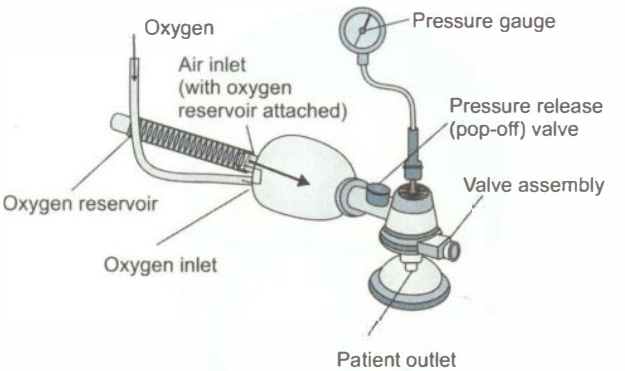


Fig. 8.5: Self-inflating bag
(Adapted with premission from AAP 2005)

term babies resuscitated with room air compared to 100% oxygen have better survival and longterm outcomes. The evidence in favor or against the use of oxygen in preterm babies is yet lacking.

It is therefore recommended that *term babies* should be initiated on room air resuscitation. Ideally, oxygen saturation should be monitored by pulse oximetry and oxygen delivery should be titrated to maintain the oxygen saturation in the targeted range (Fig 8.2). In absence of pulse oximetry, room air should be substituted by 100% oxygen if the baby fails to improve (improvement in HR and breathing) by 90 seconds.

PPV in *preterm babies* is recommended using intermediate concentration of oxygen (30% to 60%). The oxygen concentration should be titrated by continuously monitoring of oxygen saturation by pulse oximetry. BMV is indicated if:

i. The infant is apneic or gasping
ii. HR is less than 100 beats per minute
iii. Persistent central cyanosis despite administration of 100% free flow oxygen

In suspected or confirmed diaphragmatic hernia, bag and mask ventilation is contraindicated. Similarly, in non-vigorous babies born through MSL, bag and mask ventilation is carried out *only after* tracheal suctioning.

Procedure

The infant's neck should be slightly extended to ensure an open airway. The care provider should be positioned at head end or at the side of baby so as to have an unobstructed view of infant's chest and abdomen. Select an appropriate sized face mask that covers the mouth and nose, but not eyes of the infant (Fig. 8.6). The face mask should be held firmly on face to obtain a good seal. The bag should be compressed using fingers and not by hands.

PPV is the single most effective step in babies who fail to breathe at birth. Ensuring adequacy of ventilation is the most important priority in such babies.

If the baby is not responding to PPV by prompt increase in HR, ventilation corrective steps are taken: observe for

Fig. 8.6: Properly fitting mask
(Adapted with permission from AAP 2005)

an appropriate rise of the chest and auscultate for breath sounds. If chest does not rise and there are no audible breath sounds, the steps outlines in Table 8.3 should be undertaken.

Table 8.3: Ventilation corrective steps (MRSOPA)

Action	*Condition*
Inadequate seal	Re apply *m*ask
Blocked airway	*R*eposition the infant's head
Blocked airway	Clear *s*ecretions by suction
Blocked airway	Ventilate with mouth slightly *o*pen
Inadequate pressure	Increase *p*ressure slightly
Consider *a*lternate airway	Blocked *a*irway(endotracheal tube)

When normal rise of the chest is observed, one should begin ventilating. Ventilation should be carried out at a rate of 40 to 60 breaths per minute, following a 'squeeze, two, three' sequence (Fig. 8.7).

Usual pressure required for the first breath is 30–40 cm of water. For subsequent breaths, pressure of 15–20 cm of water is adequate. After the infant has received 30 seconds of PPV, evaluate the HR and take a followup action as in Fig. 8.2.

Improvement in the infant's condition is judged by increasing HR, spontaneous respiration and improving color. If the infant fails to improve, check adequacy of ventilation in form of visible chest rise. If chest rise is inadequate, one should take necessary action as described earlier.

PPV may cause abdominal distension as the gas escapes into the stomach via esophagus. Distended stomach presses on the diaphragm and compromises the ventilation. Therefore, if ventilation is continued for more than two minutes, an orogastric tube (feeding tube size 6–8 Fr) should be inserted and left open to decompress the abdomen.

Chest Compressions

The heart circulates blood throughout the body delivering oxygen to vital organs. When an infant becomes hypoxic, the HR slows and myocardial contractility decreases. As a result there is diminished flow of blood and oxygen to the vital organs.

Chest compressions (CC) consist of rhythmic compression of the sternum that compress the heart against the spine, increase intrathoracic pressure and circulate blood to the vital organs of the body. CC help in mechanically pumping the blood to vital organs of the body. CC must always be accompanied by BMV so that only oxygenated blood is being circulated during CC.

> Chest compressions are indicated if HR is below 60/min even after 30 seconds of PPV. Once the HR is 60/min or more, chest compressions should be discontinued.

Procedure

There are two techniques for chest compressions: (i) thumb technique (Fig. 8.8), and (ii) two-finger technique (Fig. 8.9). With the thumb technique, the two thumbs are used to depress the sternum, with the hands encircling the torso and the fingers supporting the back. In two-finger technique, the tips of the middle finger and either index or ring finger of one hand is used to depress the sternum. The other hand is used to support the infant's back, unless the infant is on a firm surface.

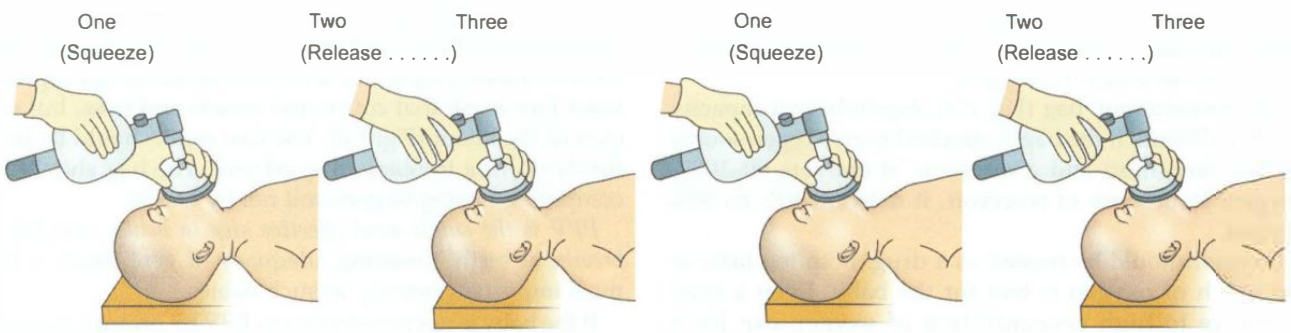


Fig. 8.7: Correct rhythm of providing positive pressure ventilation. (Adapted with permission from American Academy of Pediatrics 2005)

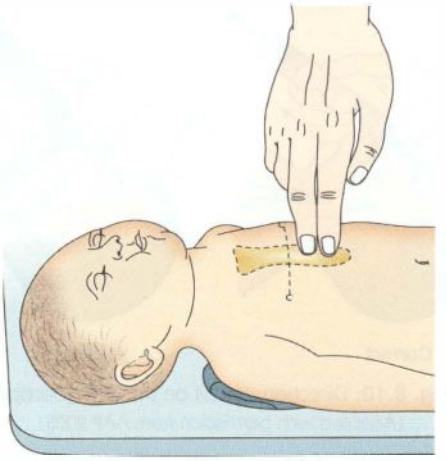


Fig. 8.8: Chest compression with two finger technique
(Adapted with permission from AAP 2005)

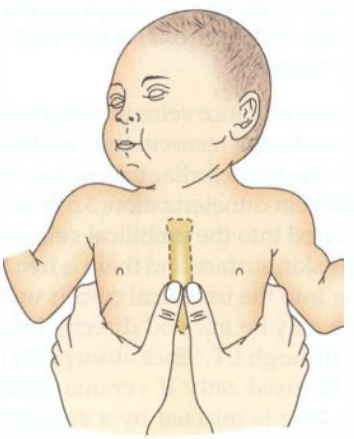


Fig. 8.9: Chest compression with thumb technique
(Adapted with permission from AAP 2005)

When chest compression is performed on a neonate, pressure is applied to the lower third of sternum. Care must be taken to avoid applying pressure to xiphoid. To locate the area, one should slide the fingers on the lower edge of thoracic cage and locate xiphisternum. The lower third of the sternum is just above it.

Rate

It is important to ventilate between chest compressions. A positive breath should follow every third chest compression. In one minute, 90 chest compressions and 30 breaths are administered (a total of 120 events). To obtain the proper ratio of 90 compressions and 30 ventilations in 1 minute (3:1), chest should be compressed three times in 1½ seconds, leaving out approximately ½ second for ventilation.

Thumbs or the tips of fingers (depending on the method used) should remain in contact with the chest during compression and release. Do not lift your thumbs or fingers off the chest between compressions.

To determine efficiency of chest compressions, the carotid or femoral pulsation should be checked periodically.

Possible complications of chest compressions include broken ribs, laceration of liver and pneumothorax.

Evaluation

After a period of 30 seconds of chest compressions, the heart rate is checked:

HR below 60. Chest compressions should continue along with bag and mask ventilation. In addition, medications (epinephrine) have to be administered.

HR 60 or above. Chest compressions should be discontinued. BMV should be continued until the heart rate is above 100 beats per minute and the infant is breathing spontaneously.

Endotracheal Intubation

Endotracheal (ET) intubation is required only in a small proportion of asphyxiated neonates. Intubation is a relatively difficult skill to learn and it requires frequent practice to maintain the skill.

Indications

The indications of ET intubation are: (i) when tracheal suction is required (in non-vigorous babies born through MSL), (ii) when prolonged BMV is required, (iii) when BMV is ineffective, and (iv) when diaphragmatic hernia is suspected. The other conditions where ET intubation may be considered are: before starting chest compressions and for administering epinephrine.

Endotracheal Tube (ET)

ET should be of uniform diameter throughout the length of the tube (and not tapered near the tip) and have vocal cord guide at the tip and centimeter markings. ET tube size depends on the weight or gestation of the baby (Table 8.5).

Table 8.4: Followup action for heart rate response

Heart rate	*Action*
Above 100	If spontaneous respiration is present, discontinue ventilation gradually: provide tactile stimulation by gently rubbing the body, and monitor heart rate, respiration and color
60 to 100	Continue ventilation; take ventilation corrective steps
Below 60	Continue to ventilate; start chest compressions

Table 8.5: Appropriate endotracheal tube size

Inner diameter of tube (mm)	*Weight (g)*	*Gestational age (weeks)*
2.5	<1000	<28
3.0	1000–2000	28–34
3.5	2000–3000	34–38
4.0	>3000	>38

Most ET currently manufactured for neonates have a black line near the tip of the tube which is called a vocal cord guide. Such tubes are meant to be inserted so that the vocal cord guide is placed at the level of the vocal cords. This helps position the tip of ET above the bifurcation of trachea.

For intubation, a neonatal laryngoscope, with straight blades of sizes '0' (for preterm babies) and '1' (term babies) is required. Before intubating, the appropriate blade is attached to the handle of laryngoscope and the light is turned on.

Procedure

The infant's head should be in midline and the neck kept slightly extended. The laryngoscope is held in the left hand between the thumb and the first three fingers, with the blade pointing away from oneself. Standing at the head end of the infant, the blade is introduced in the mouth and advanced to just beyond the base of the tongue so that its tip rests in the vallecula. The blade is lifted as shown in Fig. 8.10 and landmarks looked for; the epiglottis and glottis should come into view. The glottic opening is surrounded by vocal cords on the sides. Once the glottis and vocal cords are visualized, the ET is introduced from the right side of the mouth and its tip inserted into the glottis until the vocal cord guide is at the level of the glottis, thus positioning it half way between the vocal cords and carina.

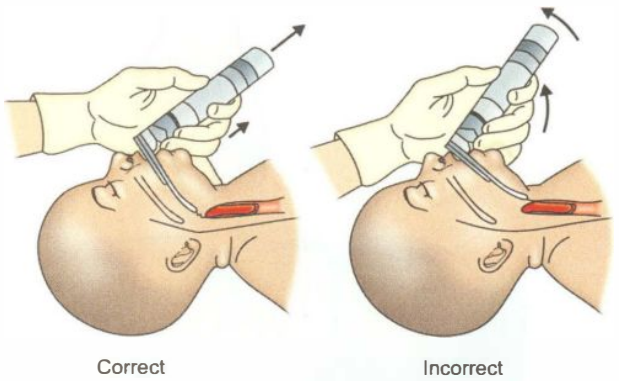


Fig. 8.10: Direction of pull on the laryngoscope
(Adapted with permission from AAP 2005)

8 Medications

The majority of infants requiring resuscitation will have a response to prompt and effective ventilation with 100% oxygen. Only a few require medications.

Medications used in resuscitation include epinephrine and volume expanders (Table 8.6). Sodium bicarbonate and naloxone are indicated only for special circumstances (Table 8.6). There is no role of atropine, dexamethasone, calcium, mannitol and dextrose for newborn resuscitation in the delivery room.

Route of administration: Since veins in scalp or extremities are difficult to access during resuscitation, umbilical vein is the preferred route. No intracardiac injection is recommended.

For umbilical vein catheterization, 3.5 Fr or 5 Fr umbilical catheter, is inserted into the umbilical vein such that its tip is just inside the skin surface and there is free flow of blood. Direct injection into the umbilical cord is undesirable.

Epinephrine may be injected directly into the tracheobronchial tree through ET. Since absorption is erratic, this method is to be used only if venous access cannot be obtained. The drug is injected by a syringe or a feeding tube (5 Fr) into the endotracheal tube, flushed with 0.5 ml of normal saline and dispersed into the lungs by PPV.

Indications

Use of adrenaline is indicated if HR remains below 60 despite adequate ventilation and chest compressions for 30 seconds.

Table 8.6: Medications: indication, dosage and effects

Medication (concentration)	*Indication*	*Effects*	*Concentration administered*	*Dose of the prepared solution*	*Route*
Epinephrine (1:1000)	HR <60/min after 30 sec of effective PPV and chest compressions	Inotropic; chronotropic; peripheral vasoconstrictor	1:10000	0.1–0.3 ml/kg	IV; through umbilical vein (endotracheal route if no IV access)
Normal saline, Ringer lactate	Acute bleeding with hypovolemia	Increased intravascular volume improves perfusion		10 ml/kg	Umbilical vein
Naloxone (0.4 mg/ml)	Respiratory depression with maternal history of narcotic use within 4 hr of birth	Narcotic antagonist	0.4 mg/ml	0.25 ml/kg (0.1 mg/kg)	IV preferred; delayed onset of action with intramuscular use; administer only after restoring ventilation

Sodium bicarbonate is administered only if prolonged asphyxia is associated with metabolic acidosis despite use of epinephrine and volume expanders. IV intravenous; PPV positive pressure ventilation

Suggested Reading

Kattwinkel J. Textbook of Neonatal Resuscitation. *In:* Kattwinkel J (ed). 6th ed. American Academy of Pediatrics and American Heart Association, 2010

ROUTINE CARE

Care at Birth

Personnel and equipment to be available at delivery. One health provider (physician or nurse) trained in neonatal resuscitation must be physically available at time of birth of all infant irrespective of its risk status (high or low). It is not good enough to have someone on call.

If high risk delivery is anticipated because of presence of risk factors identified before birth, more advanced resuscitation may be required. In such cases, 2 persons should be present solely to manage the baby. The goal should be to provide a 'resuscitation team', with specified leader and an identified role of each member. For multiple births, there should be separate teams.

The resuscitation corner must be physically located in the delivery room itself. The health professional designated to care for the baby at birth should check for the 'Resuscitation Preparedness' at the birthing place well in time before the baby is delivered. Details on neonatal resuscitation have been provided in the previous section.

Standard precautions and asepsis at birth. The personnel attending the delivery must exercise all the universal/standard precautions in all cases. All fluid from the baby/mother should be treated as potentially infectious. Gloves, masks and gowns should be worn when resuscitating the newborn. The protective eye wear or face shields should be worn during procedures that are likely to generate droplets of blood or other body fluids.

Observe 'five cleans' to prevent sepsis at birth:

i. *Clean hands:* Hand-hygiene and wear sterile gloves
ii. *Clean surface:* Use clean and sterile towel to dry and cover the baby
iii. *Clean blade:* The umbilical cord to be cut with a clean and sterile blade/scissor
iv. *Clean tie:* The cord should be clamped with a clean and sterile clamp or tie
v. *Nothing to be applied on the cord.* Keep it dry.

Prevention and management of hypothermia. Immediately after birth the newborn is at high risk of hypothermia. This early hypothermia may have a detrimental effect on the health of the infant. Special care should be taken to prevent and manage hypothermia. The temperature of delivery room should be 25°C and it should be free from draft of air. The baby should be received in a pre-warmed sterile linen sheet at birth. The infant should be dried thoroughly including the head and face, and any wet linen should not be allowed to remain in contact with the infant. The infant may be placed on the mother's abdomen immediately after the birth for early skin-to-skin (STS) contact. This will not only maintain the newborn's temperature, but also promote early breastfeeding and decreases the pain and bleeding in the mother. The baby should be observed during the transition period and made to wear the caps and socks.

Delayed clamping of umbilical cord. Umbilical cord clamping must be delayed for 1 to 2 minutes in order to allow transfer of additional amount of blood from placenta to the infant. This delayed cord clamping in term babies is associated with improved hematologic status, iron status and clinical anemia at 2 to 6 months. In preterm infants, delayed cord clamping is associated with reduced IVH and other morbidities.

Cleaning of baby. The baby should be dried and cleaned at birth with a clean and sterile cloth. The cleaning should be gentle and should only wipe out the blood and the meconium and not be vigorous enough to remove the vernix caseosa (white greasy material on the skin). The vernix, protects skin of the infant and helps maintain temperature. This gets absorbed on its own after sometime.

Clamping of the cord. The umbilical cord should be clamped at 2–3 cm away from the abdomen using a commercially available clamp, a clean and autoclaved thread or a sterile rubber band (Fig 8.11). The stump should be away from the genitals to avoid contamination. The cord should be inspected every 15–30 minutes during initial few hours after birth for early detection of any oozing.

Placement of identity band: Each infant must have an identity band containing name of the mother, hospital registration number, gender and birth weight.

Care of Baby In the Initial Few Hours After Birth

Recording of weight. The baby should be weighed after stabilization and when the temperature is documented to be normal. A sterile pre-heated sheet (or a single use paper towel) should be placed on weighing machine with 10 g

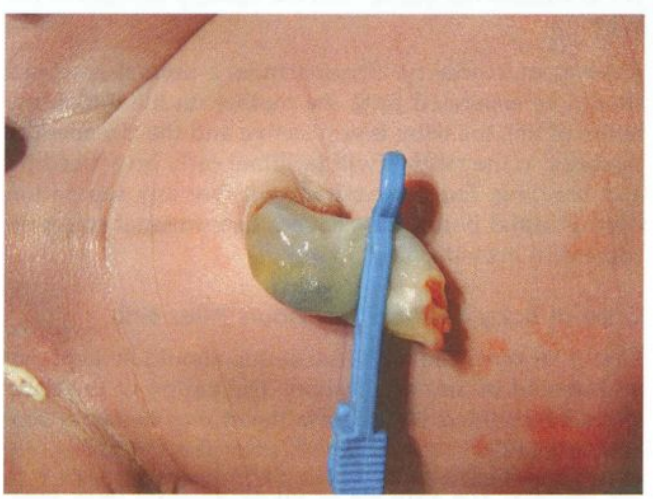


Fig. 8.11: Correct application of the umbilical clamp

sensitivity. Electronic weighing scales are ideal. Zeroing of the machine should be performed. The baby is then gently placed on the weighing machine and the weight is recorded.

First examination. The baby should be thoroughly examined at birth from head to toe and the findings should be recorded in neonatal record sheet. Examine midline structures for malformations (e.g. cleft lip, neck masses, chest abnormality, omphalocele, meningocele, cloacal abnormality). Special attention should be given to identify and document the patent anal opening. There is no need for routine passage of catheter in the stomach, nostrils and the rectum for detection of esophageal atresia, choanal atresia and anorectal malformation, respectively. The baby should be examined for presence of birth injuries. The axillary temperature of the baby should be recorded before the baby is shifted out from the birthing place.

Initiation of breastfeeding. The breastfeeding should be initiated at the earliest, but certainly within one hour of birth. The health provider should assist the mother to put the baby on breast irrespective of the mode of delivery. Breastfeeding counseling alone without proactive support is unlikely to result in high rates of successful breastfeeding. Extra support is provided to primipara mothers and small babies.

Vitamin K. It should be administered to all the babies (0.5 mg for babies less than 1000 g and 1 mg for babies more than 1000 g). It is preferable to administer the K1 preparation, however, if not available, vitamin K3 may be administered. Vitamin K3 can cause hemolysis in G6PD deficient babies.

Communication with the family. Before leaving the birthing place, the health professional should communicate with the mother and the family members. The following facts should be clearly told to the family: (i) gender of the baby, (ii) birth weight and (iii) well-being of the baby. One should ensure that the family members and the mother get to witness the gender and the identity number of the baby.

Rooming in. Under no circumstances a normal newborn should be separated from the mother. In the initial few hours of life, the baby is very active and the closeness of the baby to the mother will facilitate early breastfeeding and bonding. Studies have shown that any separation during initial hours may have a deterimental effect on successful breastfeeding.

Care of Baby Beyond Few Hours After Birth

Care of the cord. The umbilical stump should be kept dry and devoid of any application. The nappy of the baby should be folded well below the stump to avoid any contamination.

Oil massage. The benefits of oil application have been described for low birth weight babies in both developed and developing countries. Oil massage is a low cost traditional practice that is well ingrained into the Indian culture, with no reported adverse outcome. The same may be allowed in a gentle way and with clean hands. Care should be taken not to use oils with additives or the irritant oils (such as mustard oil) for this purpose. Coconut oil makes a good choice.

Exclusive breastfeeding. A proactive and a systematic approach should be followed to initiate, support and maintain breastfeeding. The various advantages of the breastfeeding should be discussed with the mother to motivate her. Availability of dedicated lactation nurse or counseler significantly improves the chances of successful breastfeeding.

Position of sleep. Evidence has linked prone position to the occurrence of sudden infant death syndrome (SIDS). All healthy term newborns should be put to sleep on their back (supine position).

Traditional practices that should be discouraged. The application of kajal or surma in the eyes, putting oil in the ear or applying cow-dung on cord must be strongly discouraged.

Timing of discharge in a normal newborn. A normal baby should stay in the health facility for at least 24 hr. Smaller babies or those with feeding problems or sickness should remain in hospital as required.

The following criteria should be met in all the babies prior to discharge:

- The routine formal examination of the newborn has been performed and documented
- The newborn is breastfeeding properly. The adequacy of feeds can be determined by:
  - Passage of urine 6 to 8 times every 24 hr
  - Baby sleeping well for 2–3 hr after feeds
- The newborn has received the immunization as per schedule
- The mother is confident and trained to take care of the neonate
- The newborn is not having significant jaundice or any other illness requiring closer observation by a health provider
- The mother has been counseled regarding routine newborn care and her queries are answered
- Followup advice should be communicated to the mother. Babies, particularly born to primigravida mothers should be called for followup visit at 48 hr of discharge if discharged before 48 hr
- Parents have been explained the following 'danger signs' when they need to bring the baby to the hospital:
  i. Difficulty in feeding
  ii. Convulsion
  iii. Lethargy (movement only when stimulated)
  iv. Fast breathing (RR >60/min)

v. Severe chest indrawing
vi. Temperature of more than 37.5°C or below 35.5°C

- A date for followup has been assigned. A normal newborn with adequacy of breastfeeding and no significant jaundice by 72 hr of age can be seen at 6 weeks of age. In presence of any high risk factor (e.g. low birth weight, prematurity significant jaundice, or feeding not established), the baby should be seen within 2–3 days of discharge.

Common Parental Concerns

- *Weight loss in first week:* Normally babies lose 8–10% of birth weight in the first week of life which is regained by 7–10 days age. Subsequently there should be a gain of 20 to 40 g per day.
- *Crying during micturition:* The sensation of a full bladder is uncomfortable to many babies who cry *before* passing urine and they quieten as soon as micturition starts. Crying *during* passage of urine as opposed to *before* the act of micturition should alert clinician to the possibility of urinary tract infection.
- *Bathing:* During the first week, till cord falls off, only sponging is recommended which can be given after the first 24 hr of life. Later, bathing every 2–3 days is quite sufficient. A draught-free warm room, warm water and quick completion of bath ensure that the baby does not get cold during bathing. The head constitutes a large surface area of the baby; therefore, it should be washed last and dried first. Bathing time can be used to inspect baby's cord, eyes and skin for any discharge, rash or redness.
- *Cosmetics:* Babies have a sensitive skin and use of cosmetics should be minimized. A low alkalinity, mild, non-perfumed/non-medicated soap should be used. Any oil except mustard oil can be used. Sprinkling talcum powder on babies can result in its inhalation and should be avoided. Avoid products containing boric acid (present in most prickly heat preparations).
- *Regurgitation:* Babies commonly regurgitate small amount of curdled milk soon after feeding. This behavior is normal as long as the baby gains weight and passes urine 6–8 times a day.
- *Frequent stools:* During the first few days of life, the stool color in breastfed neonates changes from black-green to yellow by the end of first week. In between, the stools appear loose ('transitional stools'). The stool frequency may increase at this time. It is attributed to the enhanced gastrocolic reflex which results in the passage of small stools just after feeding. If the baby remains well hydrated, has no signs of sepsis, feeds well, passes urine 6–8 times per day and gains weight, there is no cause for concern.
- *Breast engorgement:* Under the effect of transplacentally transmitted hormones, the breasts in boys and girls may get hypertrophied and secrete milk like fluid. It resolves spontaneously in a few days. Engorged breasts should not be sqeezed or massaged as it could lead to soreness and infection.
- *Rashes and skin peeling:* Papular lesions on erythematous base can be seen in many babies; dispersed over the trunk and face, on day two or three of life. These lesions, called *erythema toxicum*, are eosinophil-laden sterile lesions. They resolve spontaneously and require no treatment (Fig. 8.12). Pyoderma, on the other hand, are pus-filled lesions occurring in response to local infection of the skin, commonly occurring in creases where dirt accumulates such as thigh fold, back of neck, etc. If boils are <10 in number and there are no signs of sepsis, local cleaning with antiseptic solution and application of 1.0% gentian violet is sufficient. Further investigation and treatment for sepsis is indicated if there are >10 lesions, signs of sepsis or non-resolution after topical treatment.

  Skin peeling is another normal skin finding noted especially in post-term and IUGR babies. Oil massaging can decrease the flaking and no other intervention is required.

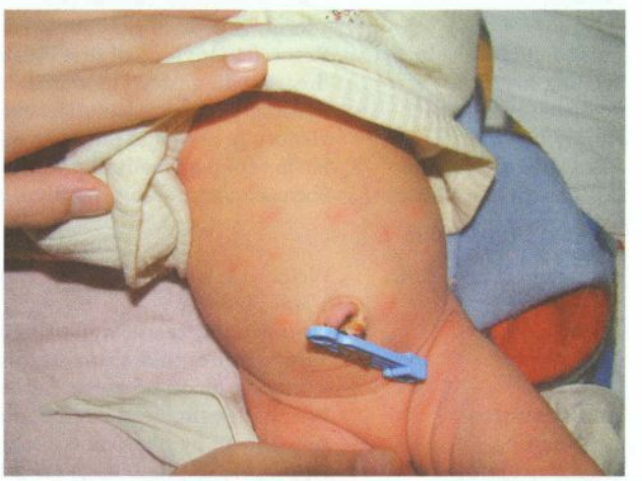


Fig. 8.12: Erythema toxicum

- *Diaper rash:* There is redness, inflammation and excoriation of skin in diaper area due to maceration by stools and urine. The problem is more frequent with plastic nappies. The treatment consists of keeping the area dry, avoiding rubbing of the skin for cleaning and application of a soothing cream. Use of cotton diaper is less often associated with this rash.

EVALUATION OF NEWBORN

Most neonates are born healthy, normal and free from disease. Some (approximately 10%) need observation in nursery.

Newborn examination yields different information at different times. Hence, newborns should be examined in detail at following time points: (i) soon after birth, (ii) at

24 hr of birth, (iii) before discharge from hospital, and again (iv) at followup visit.

Immediately after birth, the Apgar scores are assigned at 1 and 5 minutes (Table 8.2). If the score is less than 7, it is assigned every 5 minutes until 20 minutes or till two successive score are 7 or greater. These scores rapidly assess the cardiopulmonary status. Apgar scores may be falsely low in infants born very preterm and those with maternal drug intake, sepsis, congenital heart disease and central nervous system malformations. Low Apgar scores are poor predictor of long term neurodevelopmental outcome.

If systemic examination reveals an abnormal finding, laboratory evaluation may be warranted. Table 8.7 provides a schema for the comprehensive history and examination of the newborn.

Table 8.7: Newborn history and examination: Format for case presentation

History	
General	Mother's name and age, parity, last menstrual period, expected date of delivery
Past obstetric history	Past pregnancies: when, gestation, fetal or neonatal problems, current status of children
Antenatal	Number of antenatal visits, tests (hemoglobin; urine albumin, sugar; ultrasound; blood group, VDRL, HIV), tetanus toxoid immunization, supplements (iron, folic acid, calcium, iodine)
Obstetric or medical complications	Obstetric complications (toxemia, urinary tract infections, twins/triplets, placenta previa, accidental hemorrhage); fetal problems (IUGR, hydrops, Rh isoimmunization); medical problems (diabetes, hypertension); investigations, medications, course
Labor	Presentation, lie, onset of labor (spontaneous/induced), rupture of membranes (spontaneous/artificial), liquor (clear/meconium stained); duration of first and second stage of labor; fetal heart rate (tachycardia, bradycardia, irregular)
Delivery	Place of delivery, vaginal (spontaneous/forceps/vacuum), cesarean (indication, elective/emergency); local/general anesthesia; other drugs; duration of third stage; postpartum hemorrhage
Immediate care at birth	Resuscitation; time of first breath and cry; Apgar score; cord care; passage of urine/stool
Feeding history	Breastfeeding (when initiated, frequency, adequacy); other feeds
Postnatal problems	Feeding problems, jaundice, eye discharge, fever; current problems
Family history	History of perinatal illness in other siblings
Past medical problems	History of past medical problems, if any
Personal/social history	Socioeconomic status, family support
General examination	
Immediately after birth	Weight, gestation, congenital anomalies, sex assigning, Apgar scores, examination of umbilical vessel, and placenta
Appearance	Overall appearance: well or sick looking; alert/unconscious
Vital signs	Temperature, cold stress; respiratory rate, retractions, grunt/stridor; heart rate, palpable femoral arteries; blood pressure, capillary refill time; cry; apneic spells
Anthropometry	Weight, length, head circumference, chest circumference
Gestation	Assessment by physical criteria; more detailed assessment by expanded New Ballard examination
Classification by intrauterine growth	Appropriate/small/large for gestational age; symmetric or asymmetric small for gestational age; signs of IUGR
Congenital anomalies	Head to toe examination for malformations or abnormalities
Birth trauma	Signs of trauma; cephalohematoma
Common signs	Cyanosis, jaundice, pallor, bleed, pustules, edema, depressed fontanel
Special signs	Caput; eye discharge; umbilical stump: discharge or redness; jitteriness; eye discharge; oral thrush; development peculiarities (toxic erythema, Epstein pearls, breast engorgement, vaginal bleeding, capillary hemangioma, mongolian spot)
Feeding	Observe feeding on breast (check positioning and attachment)
Reflexes	Moro, grasp, rooting
Systemic examination	
Chest	Shape; respiratory rate; retractions; air entry; adventitious sounds
Cardiovascular system	Apical impulse, heart sounds, murmur
Abdomen	Distension, wall edema, tenderness, palpable liver/spleen/kidneys, any other lump, ascites, hernial sites, gonads, genitalia
Musculoskeletal system	Deformities; tests for developmental dysplasia of hip; club foot
Central nervous system	State of consciousness; vision, pupils, eye movements; facial sensation; hearing; sucking and swallowing; muscle tone and posture; power; tendon reflexes

IUGR intrauterine growth retardation

General Observation

The least disturbing examination should be done first; this gives an opportunity to assess the state of alertness, posture, spontaneous activity, color, any obvious respiratory distress or malformation. The newborns should be examined when they are in light sleep or awake but quiet (happens after 1–1.5 hr of feeding).

A newborn with hypotonia has an extended posture as in a baby with hypoxic encephalopathy. A clear note of the color of the baby, including cyanosis, pallor, jaundice and plethora should be made. One should also look at the spontaneous movements shown by the baby.

Vital Signs

In a sick baby, assessment of vital parameters takes priority over all other examination. Temperature is measured in the apex of the baby's axilla by holding the thermometer for at least 3 minutes. The finding of hypothermia (temperature of less than 36.5°C) in neonate has very important connotations. Neonates have a normal respiratory rate of 40–60 breaths/minute. The heart rate is faster in preterm babies compared to term babies. The normal range is 110–160 beats per minute. Bradycardia (rate <100/min) may be associated with heart disease while tachycardia (rate >160/min) may be due to sepsis, anemia, fever or congestive cardiac failure. Capillary refill time is assessed by applying firm pressure on the sternum area for 5 seconds than releasing and observing the time taken to refill. The refill time is prolonged (more than 3 sec) because of poor peripheral circulation as in the shock or hypothermia.

Assessment of Size and Growth

Depending on the weight, the neonates are termed as low birth weight (LBW, less than 2500 g), very low birth weight (VLBW, less than 1500 g) or extremely low birth weight (ELBW, less than 1000 g). The aberrant growth pattern is assessed by plotting the weight against the gestational age on a standard intrauterine growth curve (which is different from postnatal growth curves for assessing growth after birth), as shown in Fig. 8.13. A neonate whose weight falls between the 10th and <90th percentile is considered as appropriate for gestational age (AGA); if the weight falls below 10th percentile, the neonate is classified as small for gestational age (SGA); the neonate is classified as large for gestational age (LGA), if the weight falls at 90th percentile or above for gestational age.

Anthropometry

The weight is measured in grams (g). Length is measured using an infantometer. The newborn baby at birth is about 50 cm long. Head circumference is measured by placing a soft non-stretchable tape around the head just above the eyebrows and finding the largest circumference over the occiput. This is 33–37 cm at birth in term babies. A large

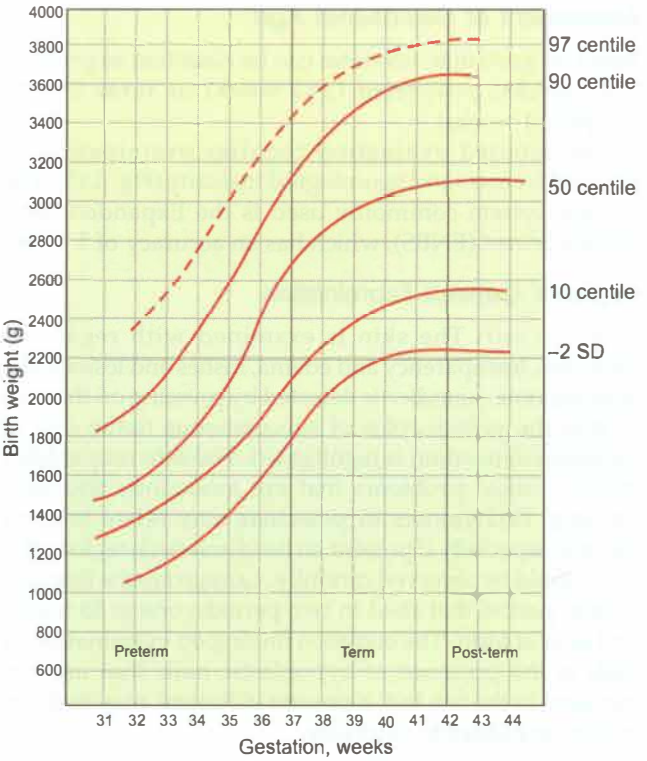


Fig. 8.13: Intrauterine growth curves. SD standard deviation

head may be due to macrocephaly (Fig. 8.14), the causes include hydrocephalus and cerebral parenchymal diseases. Chest circumference is about 3 cm lesser than head circumference and if the difference is more than 3 cm it is an indication of intrauterine growth retardation (IUGR). The Ponderal index (PI) is calculated by multiplying the weight in grams by hundred and then dividing by cube of length in cm. This parameter is usually less than 2 in asymmetric IUGR baby and 2 or more in a baby who has either normal growth or has symmetrical IUGR.

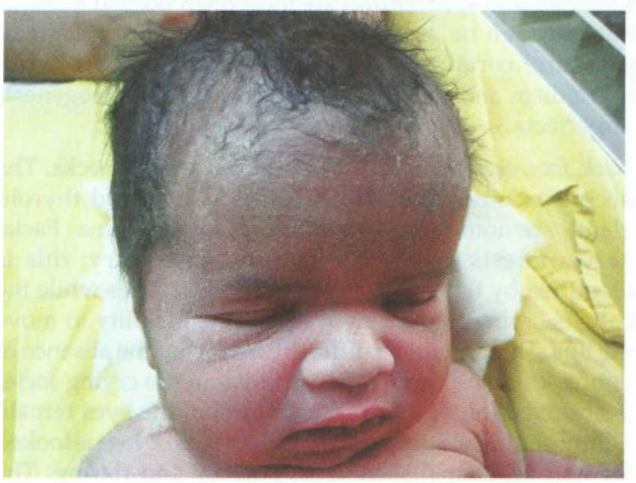


Fig. 8.14: A newborn infant with large head (macrocephaly). Note bossings of both frontal eminences

Assessment of Gestational Age

Based on gestation, neonates can be classified as preterm (<37 week), post-term (≥42 week) or term (37–41 completed weeks).

The detailed evaluation requires examination of physical features and neurological maturity (Fig. 8.15). The scoring system commonly used is the Expanded New Ballard Scores (ENBS), which has an accuracy of 1 week.

Regional General Examination

Skin and hair. The skin is examined with regard to thickness, transparency and edema, rashes and lesions like hemangioma. Jaundice is detected by pressing on the skin so that the yellow color of subcutaneous tissue due to billirubin deposition is highlighted. The skin may exhibit minor clinical problems that are innocuous and self-limiting. Ecchymoses or petechiae may relate to birth trauma, especially if present on head and neck region. The hair should be observed carefully. Lanugo are the fine hair of fetal period that shed in two periods; one at 28 weeks and later at term. The common finding on examination of nails is the presence of hypoplastic nails that may be transient in the toe, but, if present in fingers, may indicate *in utero* exposure to valproate.

Head and fontanel. The size and shape of the head along with sutures and fontanels should be examined carefully. Upon palpation, *molding* gives the impression of a cliff with rise on one side and a sharp fall on the other side, whereas a *synostosis* (fusion of bones) feels like a mountain range with rise on both sides of elevation. Some neonates have delayed ossification and resorption of bones making the skull feel soft like a ping pong ball. This condition, termed *craniotabes*, is benign in neonates and it resolves spontaneously. The most common findings after birth are *caput succedaneum* and *cephalohematoma* (Fig. 8.16). These should be differentiated as shown in Table 8.8. A full and tense fontanel is abnormal in a quiet neonate. Large fontanels and split sutures are most often normal variants but they can be associated with increased intracranial pressure, certain chromosomal abnormalities, hypothyroidism and impaired bone growth like osteogenesis imperfecta.

Neck, face, eyes and ears. Newborns have short necks. The neck is examined for masses such as enlarged thyroid gland, sternomastoid tumor and cystic hygroma. Facial nerve paresis may occur due to birth injury; this is identified by the presence of asymmetric facies while the baby is crying with open eyes and the inability to move the lips. This should be differentiated from the absence of depressor anguli oris in which asymmetric crying facies is observed; however, in this condition, the eyes remain tightly shut while crying (Fig. 8.17A and B). Nose is looked for its size, shape, secretions, patency and flaring. The flaring of the nostrils indicates an increase in respiratory efforts regardless of the cause.

The alveolar ridge may have natal teeth or retention cysts (also called Epstein pearls) that disappear in few weeks. It is very important to examine the palate for cleft. Subconjunctival hemorrhages are common after vaginal delivery and resolve spontaneously. The cornea should be clear. Pupils should be equal in size, reactive to light and symmetrical.

Gross hearing is often assessed by looking for blink on response to noise. More formal hearing screening for all newborns is now recommended. Accessory auricles and preauricular tags are common finding that may be associated with renal anomalies.

Umbilicus, anus and spine: Inspect the number of vessels in the umbilical cord. A single umbilical artery may be found in 0.7% of live births; this may be associated with renal and gastrointestinal tract anomalies.

One should palpate the base of the umbilical cord for a hernia and estimate the diameter of the fascial opening (Fig. 8.18). The spine should be palpated with a finger to exclude spina bifida, masses and any scoliosis. The anal opening should be examined for its patency and position.

Genitalia (male and female): The genital area is examined by the hips abducted in the supine position. The urethra and clitoris are examined for patency and cliteromegally respectively.

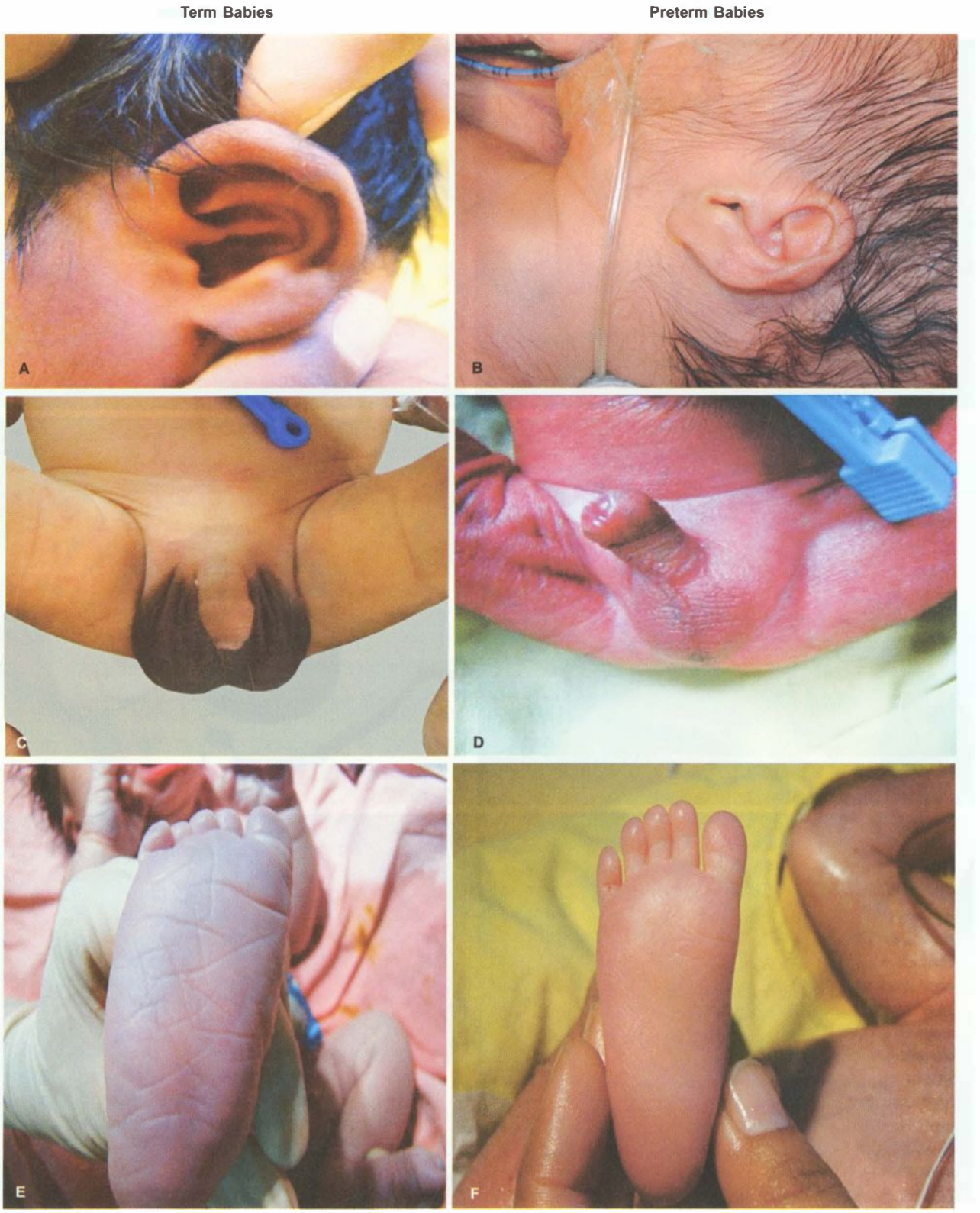
Extremities: One should make sure that the arms and limbs are fully movable with no evidence of dislocation or asymmetry of movements. The fingers are counted and any abnormality noted like nail hypoplasia, syndactyly, polydactyly, oligodactyly or unequal limbs. A calcaneo-valgus deformity is usually self-correcting within the next few months but equinovarus is much more sinister and should be brought to the notice of an orthopedic specialist (Fig. 8.19).

Systemic Examination

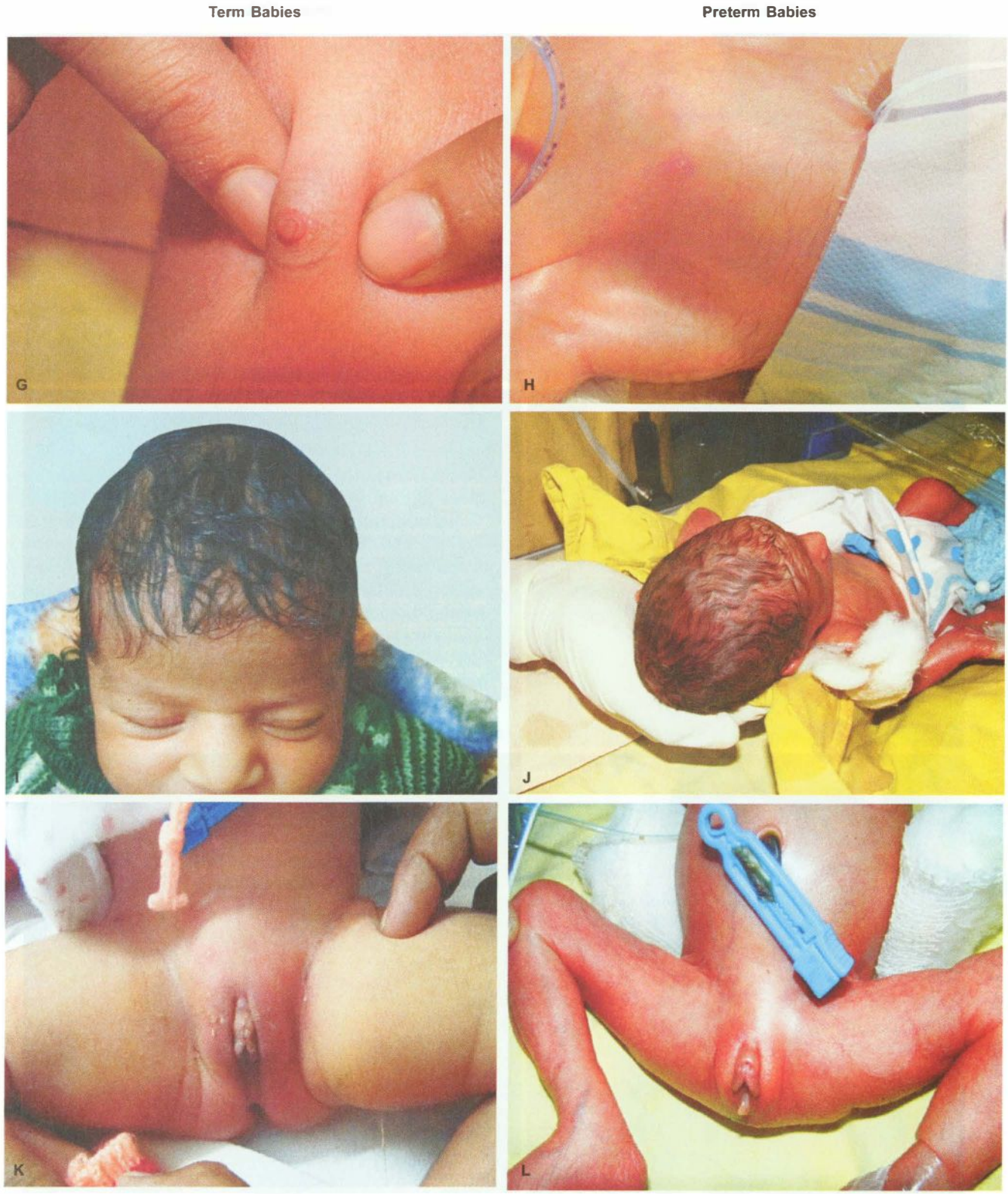
Chest The anteroposterior diameter of the neonate's chest is roughly same as the transverse diameter. Respiratory distress is indicated by nasal flaring, grunting, tachypnea and intercostal and subcostal retractions. Such distress may indicate pneumonia, respiratory distress syndrome (RDS), delayed reabsorption of lung fluid or any other cardiorespiratory cause. Stridor may be inspiratory, indicating large airway obstruction, or there may be expiratory prolongation, indicating a small airway obstruction.

Cardiovascular system An infant with heart disease manifests with tachypnea, cyanosis or both. The position of apical impulse may give idea regarding presence of conditions like congenital diaphragmatic hernia (CDH) and pneumothorax.

Abdomen Inspection of abdomen may reveal unusual flatness or scaphoid shape of abdomen that may be



Figs 8.15A to F: Salient difference in physical characteristics of preterm and term neonates: (A) Well-curved pinna, cartilage reaching up to periphery; (B) flat and soft pinna, cartilage not reaching up to periphery; (C) well pigmented and pendulous scrotal sacs, with fully descended testes; (D) light pigmentation and not yet descended testes; (E) deep transverse creases on the soles; (F) faint marks on the sole, no deep creases



Figs 8.15G to L: Salient difference in physical characteristics of preterm and term neonates: (G) Well formed breast bud (>5 mm); (H) Poorly developed breast bud; (I) silky hair, where individual strands can be made out; (J) fuzzy hair; (K) labia majora covering clitoris and labia minora; (L) prominent labia minora and clitoris

Table 8.8: Differences between caput succedaneum and cephalohematoma

Characteristic	*Caput succedaneum*	*Cephalohematoma*
Incidence	Common	Less common
Location	Subcutaneous plane	Over parietal bones, between skull and periosteum
Time of presentation	Maximum size and firmness at birth	Increasing size for 12–24 hr and then stable
Time course	Softens progressively from birth and resolves within 2–3 days	Takes 3–6 weeks to resolve
Characteristic findings	Diffuse; crosses suture line	Does not cross suture line; has distinct margins
Association	None	Linear skull fracture (5–25%); hyperbilirubinemia

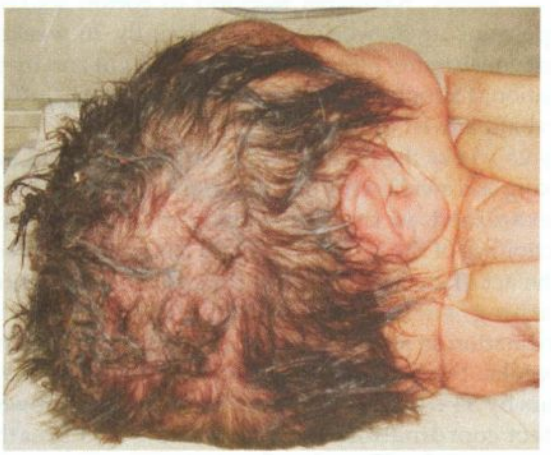


Fig. 8.16: Cephalohematoma. Note the overlying bruising

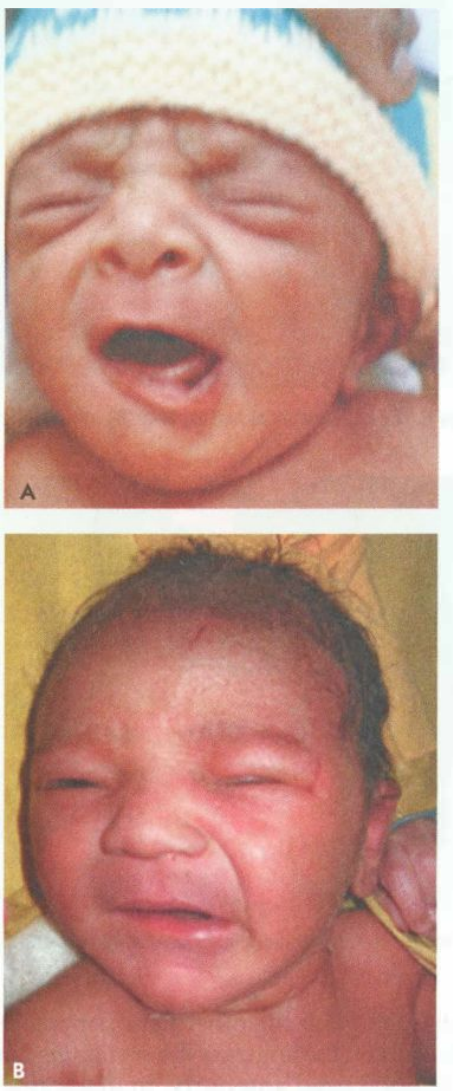
associated with CDH. Visible gastric or bowel patterns may indicate ileus or other obstruction. Normally 1–2 cm of liver, tip of the spleen and the lower pole of the left kidney may be palpated. Tenderness of abdomen is an important sign in necrotizing enterocolitis (NEC).

Musculoskeletal system The common alterations are deformations caused by adverse mechanical factors in utero. Most positional deformities are mild and resolve in time. The hips are to be examined to detect hip problems before permanent damage occurs by one year of age.

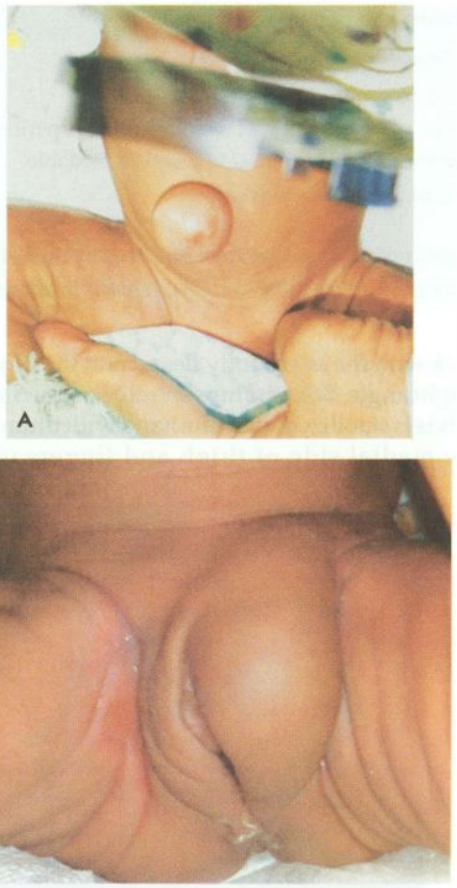
Developmental dysplasia of hips (DDH) occurs in 1 of 800 live births, more commonly in girls, those with a family history and delivered by breech. There are two major tests to detect developmental dysplasia of hip (DDH).

i. *Barlow maneuver:* Barlow test is done to dislocate the unstable hip joint. Both the hips should be tested separately. Pelvis is stabilized with one hand with thumb being on the medial side of thigh and fingers on greater trochanter. With the other hand, opposite hip is flexed and adducted, and posterior pressure is applied with thumb so as to dislocate hip. If the hip is dislocatable, a distinct outward movement of the hip is felt. Once pressure is released, hip moves again in the acetabulum.

ii. *Ortolani's sign.* This maneuver helps to judge if the hip has already been dislocated. The baby is placed on its back with the knees fully flexed and the hips flexed to a right angle. Both the hips should be tested separately. Pelvis is stabilized with one hand with thumb being on the medial side of thigh and fingers on greater



Figs 8.17A and B: (A) Absent depressor anguli oris muscle. Note asymmetry of face on crying, presence of nasolabial folds and closed eyes. (B) newborn with right sided lower motor nerve facial palsy secondary to forceps application. Note absence of nasolabial fold



Figs 8.18: (A) Umbilical hernia; and (B) Inguinal hernia

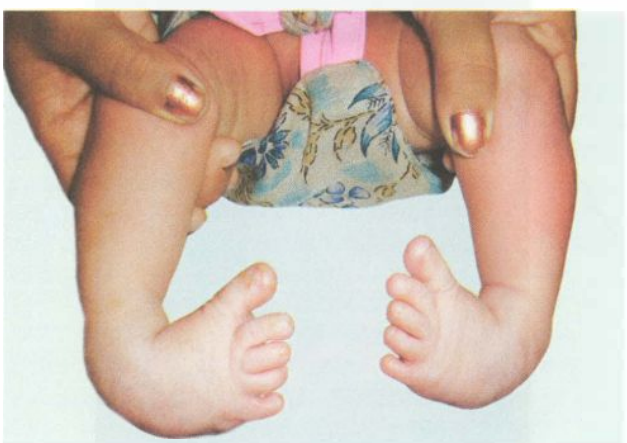


Fig. 8.19: Congenital talipes equinovarus deformity

trochanter. With the other hand, opposite thigh is abducted and the fingers of the examining hands push the femoral head anteriorly. In dislocated hip, the femoral head suddenly slips into the acetabulum with a distinctly palpable "clunk". If pressure is now applied with the thumbs outwards and backwards of the inner side of the thigh, the femoral head again slips over the posterior lip of the acetabulum. If the femoral head slips into the acetabulum again when the pressure is released, it is merely unstable, rather than dislocated. This test is important because the treatment in early neonatal life is simple and efficient and consists simply in maintaining the hips in full abduction and at least 90° flexion with malleable metal splints.

Neurological examination This consists of the assessment of the level of alertness and examination of cranial nerves, motor and sensory system and neonatal reflexes.

Cranial nerves. Neonates respond to cotton soaked in peppermint by 32 weeks of gestation. By 26 weeks the infant consistently blinks in response to light and by term gestation, fixation and following (tested using fluffy red yarn ball) is well established.

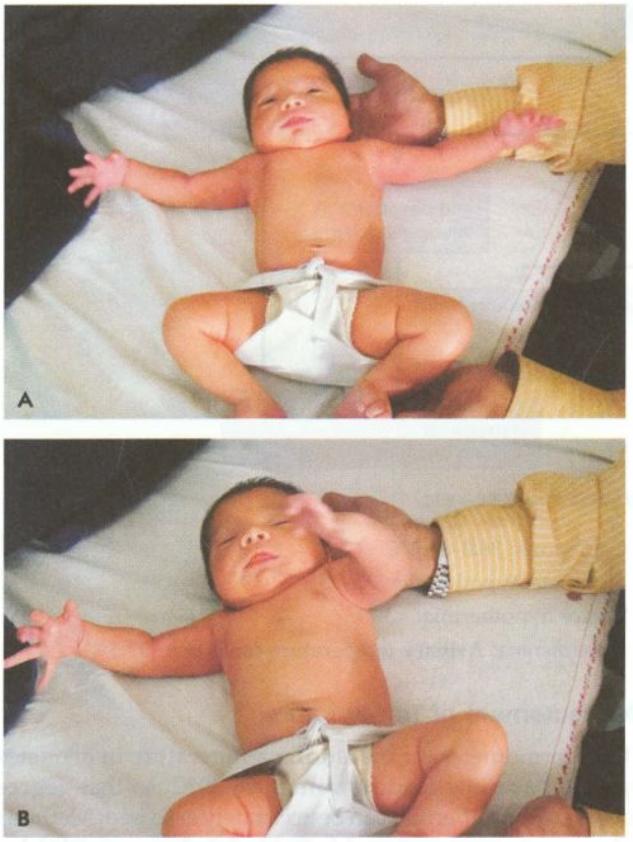
By 28 weeks the infant startles or blinks to loud noise. Sucking and swallowing are important aspects that should be examined as they give insight into the proper functioning of the V, VII, IX, X and XII cranial nerves.

The act of sucking requires the coordinated action of breathing, sucking and swallowing. Suck-swallow coordination so as to accept paladai feeding is present by 32 weeks. Suck-swallow and breathing coordination occurs by 34 weeks when baby can breastfeed. However, perfect coordination of suck-swallow and breathing develops only by 38 weeks of gestation.

Motor examination. By 28 weeks there is minimal resistance to passive manipulation of all the limbs and a distinct flexor tone is appreciated in lower extremities by 32 weeks. By 36 weeks, flexor tone is palpable in both the lower and upper extremities.

Primary neonatal reflexes. Moro reflex is best elicited by the sudden dropping of the baby's head in relation to trunk; the response consists of opening of the hands and extension and abduction of the upper extremities, followed by anterior flexion (embracing) of upper extremities with an audible cry (Figs 8.20A and B). The hand opening is present by 28 weeks, extension and abduction by 32 weeks and anterior flexion by 37 weeks. Moro reflex disappears by 3–6 months in normal infants. The most common cause of depressed or absent Moro reflex is a generalized disturbance of the central nervous system. An asymmetrical Moro reflex is indicative of root plexus injury.

The palmar grasp is clearly present at 28 weeks of gestation and is strong by 32 weeks. This allows the lifting of the baby at 37 weeks of gestation. This becomes less consistent on development of voluntary grasping by 2 months. The tonic neck response is another important response elicited by rotation of the head, that causes extension of the upper extremity on the side to which the face is rotated and flexion of the upper extremity on the side of the occiput (Fig. 8.21). This disappears by 6 to 7 months.



Figs 8.20A and B: Moro reflex (A) Abduction and extension of arms is followed by (B) Adduction and flexion component

THERMAL PROTECTION

Newborn babies are prone to hypothermia as they have poor heat regulating mechanisms. During intrauterine life, the fetal temperature is 0.5°C higher than the maternal temperature due to metabolic reactions that generate heat. After birth, the infant is exposed to outside environment which has lower temperature.

Sources of Heat Loss

Heat loss in a newborn occurs through 4 ways:

i. *Radiation* to surrounding environment not in direct contact with baby
ii. *Convection* to air flowing in surrounding
iii. *Conduction* to substances in direct contact with baby
iv. *Evaporation* of amniotic fluid and moisture from baby's skin to atmosphere

Why are Newborns Susceptible to Hypothermia?

- Large surface area of babies compared to their weight: The head constitutes a significant portion of the newborn's surface area and can be a source of great heat loss
- Limited heat generating mechanisms

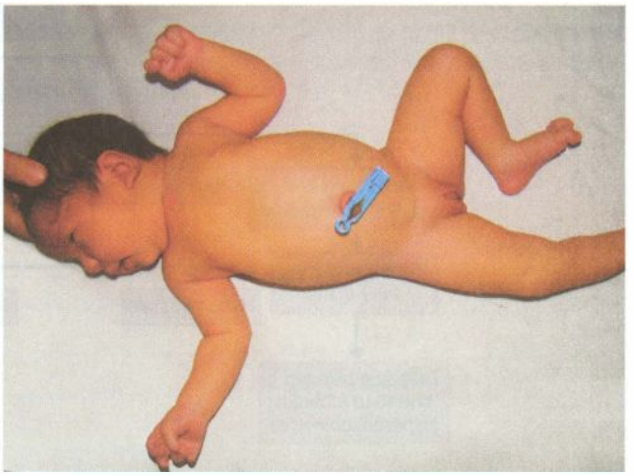


Fig. 8.21: Asymmetrical tonic neck reflex

- Vulnerability to getting exposed, being dependant on others for early detection and rectification

Additional factors that contribute to heat loss in LBW babies include:

- Poor insulation due to lower subcutaneous fat
- Decreased brown fat
- More permeable skin
- Larger surface area than term babies
- Poorer physiological response to hypothermia and early exhaustion of metabolic stores like glucose.

Sources of Heat Production

On exposure to cold and wet environment, the neonate tries to generate heat by increasing physical activity (crying, increased body movements) and by mounting a sympathetic surge that causes vasoconstriction and *non-shivering thermogenesis* in the brown fat. Brown fat is richly vascularized, sympathetically innervated fat collections located in the axillae, groin and nape of the neck, interscapular area and perirenal area. Release of norepinephrine uncouples beta-oxidation in fat that results in heat production. Blood passing through brown fat gets heated up to keep baby warm. Preterm and small for gestational age infants have scanty brown fat stores.

Response to hypothermia. Hypothermia induced peripheral vasoconstriction leads to increased metabolism with excess oxygen consummation and glucose utilization. Switch to anaerobic metabolism in hypothermia causes metabolic acidosis (Fig. 8.22). The acidosis induces pulmonary vasoconstriction and pulmonary hypertension further worsening the hypoxemia. When body temperature drops below 32°C, hemoglobin cannot release oxygen resulting in the blood having a bright red color because of good oxygen content but it cannot be released to tissues (tissue hypoxia). With severe hypothermia, hypoxemia, bradycardia, hypoglycemia and metabolic acidosis contributes towards increased mortality in hypothermic babies.

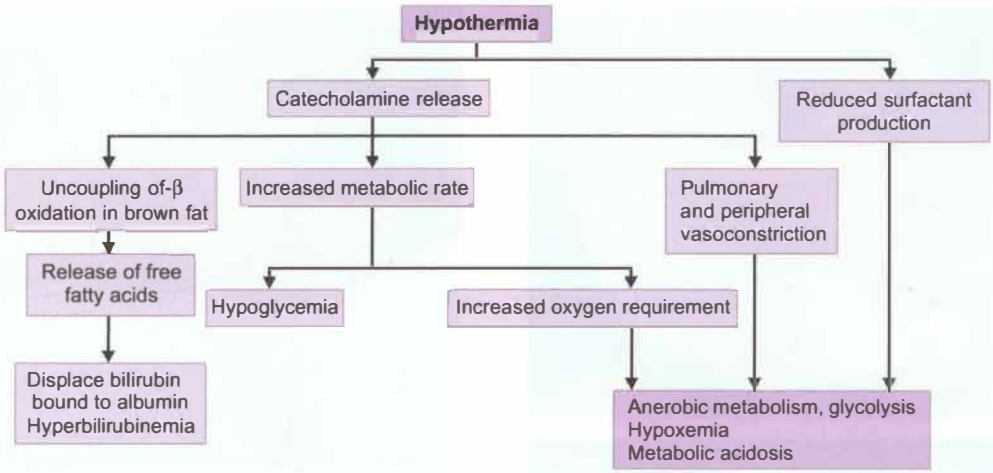


Fig. 8.22: Response to cold stress in sick neonate

Hyperthermia. An immature thermoregulating mechanism and decreased ability to sweat predispose newborns to hyperthermia. Factors like overclothing, high environmental temperature in summers, poor feeding and dehydration are the common factors that can lead to hyperthermia.

Definitions

Thermoneutral environment. Thermoneutral zone refers to narrow range of environmental temperature in which a baby has the lowest basal metabolic rate and oxygen utilization and the baby has normal body temperature. The thermoneutral zone is different for babies of different gestation and postnatal age. Thermoneutral zone is higher for lower gestation and smaller birth weight; lower for clothed babies compared to naked ones and is higher in the earlier hours and days of life than later age. This is because preterm, small, naked and younger neonates need extra warmth to maintain body temperature.

Normal body temperature: 36.5°C to 37.5°C
Hypothermia: Axillary temperature less than 36.5°C
Cold stress: 36.0–36.4°C
Moderate hypothermia: 32–35.9°C
Severe hypothermia: <32°C
Hyperthermia: Axillary temperature more than 37.5°C

Measurement of Temperature

The thermometer for measuring temperature in neonates should have low reading values till 30°C, so that degree of severe hypothermia can be accurately assessed. Methods of measurement are listed in Table 8.9. A reasonable idea can be obtained by touching the baby's hands and feet and abdomen by back of examiner's hand. If everything appears warm, baby has normal temperature. Warm abdomen but cold feet and hands indicate hypothermia. Cold feet and hands as well as the abdomen would indicate that the baby has severe hypothermia.

Frequency of Measurement

The frequency of temperature measurement can be once daily for healthy babies who are otherwise well, two to three times daily for healthy small babies (2 to 2.5 kg),

Table 8.9: Methods of temperature measurement

Name	*Method*	*Timing*	*Comment*
Axillary	Bulb of thermometer is placed in the roof of dry axilla for 3 minutes while holding the baby's arm close to the trunk	Intermittent measurement	Standard method of temperature recording; closely approximates the core temperature
Skin probe	Probe of thermal sensor is placed on the skin over upper abdomen; panel displays the measured temperature	Continuous monitoring	Useful in regulating the heater output in radiant warmer and incubators
Touch	The back of hand is used to appreciate the skin temperature. Temperature is considered *normal* if the baby's abdomen, feet and hands are warm; *cold* if the abdomen is warm but feet and hands are cold; and *hypothermia* if abdomen, feet and hands are cold	Intermittent measurement	Crude method; helps mothers and health workers estimate the baby's temperature quickly

four times daily for very small babies (<2 kg) and every two hour for sick babies. Mother should be encouraged to assess body temperature of the neonate by touching the baby.

Disorders of Body Temperature

Hypothermia may happen as a result of exposure to a cold environment such as low ambient temperature, cold surface, or cold air, or the baby is wet or not clothed adequately. Hyperthermia may result if the infant is exposed to warm environment such as in summers, direct sun exposure, or overheating in the incubator or radiant warmer. Hypothermia as well as hyperthermia can also indicate underlying serious illness.

Hypothermia

Prevention

Warm chain: The strategy for prevention of hypothermia is known as warm chain. The 'warm chain' is a set of ten steps (Table 8.10) aimed at decreasing heat loss, promoting heat gain and ensuring that baby is not exposed to the circumstances that can result in hypothermia.

Table 8.10: Ten steps of warm chain

i. Warm delivery room
ii. Warm resuscitation
iii. Immediate drying
iv. Skin to skin contact
v. Breastfeeding
vi. Bathing postponed
vii. Appropriate clothing
viii. Mother and baby together
ix. Professional alertness
x. Warm transportation

- The birthing room should have ambient temperature of at least 25°C and should be free from drafts of air (keep windows and doors closed).
- After delivery, the baby should be dried immediately, put in skin to skin contact on mother's abdomen and covered by warm and dry linen. The wet towel should be discarded. The baby should be capped and dressed adequately (Fig. 8.23).
- Kangaroo mother care (KMC) is an effective way to keep LBW baby warm.
- Frequent breastfeeding is critical to provide energy to keep the baby warm.
- Bathing and weighing are postponed. Term babies can be sponged after 24 hr of life in summer months. Bathing should be postponed during winters and in sick or LBW babies until the umbilical cord falls off (end of first week). Dressing the baby in multiple layers of warm and light clothes provides better thermal protection than a single layer of heavy woolen clothing.

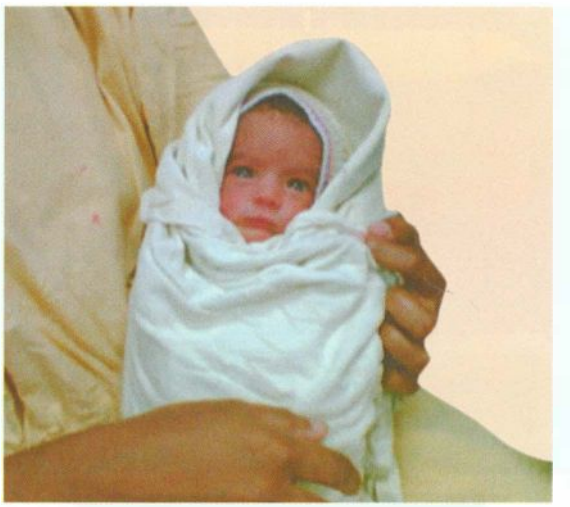


Fig. 8.23: A well clothed baby

- Mother and baby should be kept on the same bed (co-bedding/rooming in).
- Warm transportation: This is the weakest link in the warm chain with greatest possibility of severe and undetected hypothermia.
- Training/awareness of healthcare providers: Unless persons involved in the care of newborns realize the implications of hypothermia it cannot be detected or managed effectively.

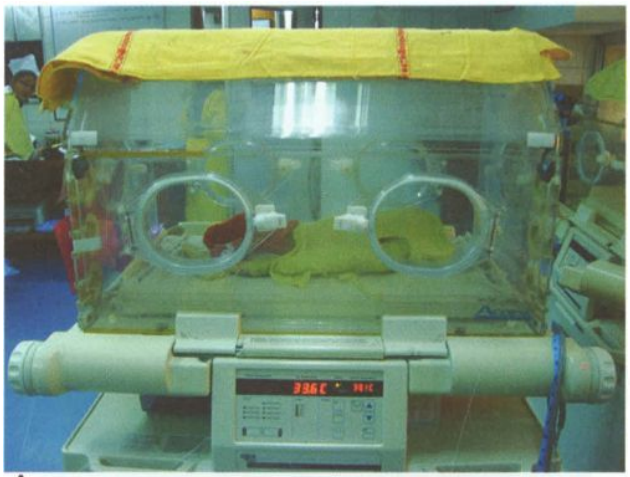
Incubators and radiant warmers. These equipment are used to assist sick and small neonates maintain their normal body temperature (Figs 8.24A and B). Incubator is a transparent acrylic cabin which has warm air circulating around the baby to keep him warm. There is an inbuilt feedback system (servo-control) that controls ambient temperature inside incubator by altering heater output based on baby's temperature and thereby maintains the temperature of baby in the normal range.

A radiant warmer is an open system (as compared to incubator which is a closed cabinet) and the neonate lies on a crib. There is overhead radiant warmer that modulates its heater output based on baby's temperature sensed by a skin probe.

Radiant warmers and incubators should be used in the servo control mode with the abdominal skin temperature maintained at 36.5°C to 37°C depending on the birth weight of the neonate.

Signs and Symptoms

Peripheral vasoconstriction results in acrocyanosis, cool extremities and delayed peripheral capillary refill time (CRT). The baby becomes restless and then lethargic. Chronic or recurrent episodes of hypothermia result in poor weight gain. Cardiovascular manifestations may occur in the form of bradycardia, hypotension, raised pulmonary artery pressure with resultant hypoxemia, tachypnea and distress. Presence of lethargy, poor reflexes,



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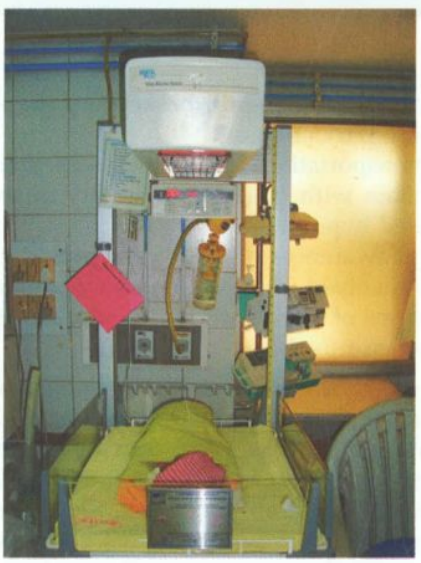


B

Figs 8.24A and B: A very low birth weight (VLBW) baby being cared for in (A) an incubator and (B) radiant warmer. Note that baby is well clothed and the incubator is covered with cloth to prevent excessive light or noise for adequate comfort of the baby

decreased oral acceptance and apnea denotes neurological depression. Abdomen distension, vomiting and feeding intolerance make enteral intake difficult. Acidosis, hypoglycemia, oliguria, azotemia and generalized bleeding can occur in severe cases. Babies who are chronic cold stress do not gain adequate weight.

Management

Methods for temperature maintenance include skin to skin contact, warm room, radiant warmers, incubators and increasing ambient temperature by use of hot air blowers, or a 200 watt bulb.

Cold stress or moderate hypothermia

- Remove the baby from the source that may be causing hypothermia such as cold environment, cold clothes, cold air or wet clothing.
- Initiate skin to skin contact, is possible. If not possible, dress the baby in warm clothing and keep him in a warm room. Alternately a radiant warmer or incubator may be used.
- Monitor temperature frequently. If the temperature of baby is not rising, check if adequate amount of heat being provided. Sepsis should be suspected unresponsive hypothermia.
- Ensure frequent feeding to prevent hypoglycemia. Monitor vitals.

Severe hypothermia

- Remove all wet clothing and place baby in an incubator (air temperature 35–36°C), preheated radiant warmer or thermostatically controlled heated mattress set at 37–38°C. Alternately, one may use a room heater.
- Once baby's temperature reaches 34°C, the rewarming process should be slowed down.
- Temperature is measured every hour for 3 hr. If rise of temperature has been by 0.5°C per hr then heating is considered adequate, and temperature measurement is continued 2 hourly until normal body temperature is attained, and thereafter 3 hourly for 12 hr. If rise of temperature is not adequate, one should check the heating technique.
- Provide oxygen, empirical antibiotics, saline bolus if shock, IV dextrose and vitamin K. Monitor vitals.

Suggested Reading

Guidelines for perinatal care. Second Edition, American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 1998

Thermal protection of the newborn: A practical guide. WHO/FHW/MSM/97.2

FLUID AND ELECTROLYTE MANAGEMENT

Transition from fetal to extrauterine life is accompanied by remarkable changes in body fluid composition. Neonates are born with an excess of total body water (TBW) primarily in the extracellular fluid (ECF) compartment. This excess of TBW is normally lost by diuresis during first week of life. Term neonates lose about 7%–10% of body weight during first 3 to 5 days of life. Preterm neonates have proportionately higher TBW and, therefore, may lose up to 10%–15% of birth weight during first week of life.

The heart, kidneys, the skin and the neuroendocrine system regulate fluid and electrolyte balance in neonates. In neonates, kidneys have a limited capacity to concentrate or dilute urine due to lower glomerular filtration rate and reduced proximal and distal tubular sodium reabsorption. In addition to water loss by the kidneys and gastrointestinal system, additional water losses occur due to evaporation from the skin and respiratory tract (insensible water loss; IWL). IWL is higher in preterm infants owing to thin skin. Fever, increased respiratory rate, radiant warmers and phototherapy increase IWL.

Guidelines for Fluid Therapy

Healthy babies of 1200 g or more should be started on enteral feeding with breast milk. A baby of 1800 g or more would be able to breastfeed directly while a smaller baby may require expressed breast milk fed by suitable alternate route.

Intravenous (IV) fluid therapy. IV fluids are indicated when baby is either small or sick. Babies less than 1200 g or gestation <30 week should be started on IV fluids routinely. Sick babies (irrespective of weight or gestation) such as those with respiratory distress, significant asphyxia, feed intolerance, hemodynamic instability, gastrointestinal malformations (like tracheoesophgeal fistula, intestinal atresia, etc.) or any other severe illness precluding oral feeding should be given IV fluids. Peripheral intravenous line is the most common route used to provide fluids. Fluid requirement is calculated based on birth weight, day of life and the current fluid balance.

Babies with birth weight ≥1500 g. Infants on IV fluids require to excrete a solute load of about 15 mOsm/kg/day in the urine. To excrete this solute load at a urine osmolarity of 300 mOsm/kg/day, the infant would have to pass a minimum of 40 ml/kg/day of urine. Allowing for an additional IWL of 20 ml/kg, the initial fluids should be 60–80 ml/kg/day. The initial fluids should be 10% dextrose with no electrolytes in order to maintain a glucose infusion rate of 4–6 mg/kg/min. (Table 8.11). As the infant grows and receives enteral feeds, the solute load presented to the kidneys increases and the infant requires more fluid to excrete the solute load. Water is also required for fecal losses and for growth purposes. Therefore, the fluid requirements increase by 15–20 ml/kg/day till a maximum of 150 ml/kg/day by the 7th day. Sodium and potassium should be added to IV fluids after 48 hr.

Babies with birthweight <1500 g. The urine output in these babies is similar to a baby of 1500 g or more. However, the fluid requirement is higher due to increased IWL. These babies need 80 ml/kg/day of 10% dextrose on day 1 of life (Table 8.11). The babies should be well dressed including provision of caps and socks to reduce the IWL under the radiant warmer. As the skin matures, the IWL progressively decreases and fluid requirement becomes similar to bigger babies. Fluids need to be increased at 10–15 ml/kg/day up to a maximum of 150 ml/kg/day by 5th to 7th day. Sodium and potassium should be added to IV fluids after 48 hr.

Problems with IV fluid therapy include local and systemic infection, phlebitis, fluid overload and extravasation. Because IV fluid therapy is a major risk factor for nosocomial infection, all asepsis precautions must be followed during insertion of IV cannula or administering fluids. Oral feeds should be started at the earliest possible opportunity when clinical condition of neonate improves and IV fluid should be stopped when oral feeds constitute about two-thirds of daily fluid requirement. IV sites should be inspected frequently to timely detect extravasation.

Calculation of fluids for a 1250 g baby:

Day 1: 100 ml (80 ml/kg) to be infused at 4.2 ml/hr

Day 2: 120 ml (95 ml/kg) to be infused at 5.0 ml/hr

Monitoring of Fluid and Electrolyte Status

Fluid therapy should be monitored every 12 to 24 hr in a baby on IV fluids using following parameters:

Body weight. Serial weight measurements can be used as a guide to estimate the fluid deficit in newborns. Term neonates lose 1–3% of their birth weight daily with a cumulative loss of 5–10% in the first week of life. Preterm neonates lose 2–3% of their birth weight daily with a cumulative loss of 10–15% in the first week of life. Failure to lose weight in the first week of life may be an indicator of excessive fluid administration. However, excessive weight loss (>3% in 24 hr) in the first 5–7 days or later would be non-physiological and would merit correction with fluid therapy.

Clinical examination. The usual physical signs of dehydration are unreliable in neonates. Infants with 10% (100 ml/kg) dehydration may have sunken eyes and fontanel, cold and clammy skin, poor skin turgor and oliguria. Infants with 15% (150 ml/kg) or more dehydration would have signs of shock (hypotension, tachycardia and weak pulses).

Urine output. A well hydrated baby would pass urine at 1 to 3 ml/kg/hr.

Suggested Reading

Chawla D, Agarwal R, Deorari AK, Paul VK. Fluid and electrolyte management in term and preterm neonates. Indian J Pediatr. 2008;75:255–9

Table 8.11: Daily fluid requirements during first week of life (ml/kg/day)

Birth weight	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7 and onwards*
<1500 g	80	95	110	120	130	140	150
≥1500 g	60	75	90	105	120	135	150

KANGAROO MOTHER CARE

Kangaroo mother care (KMC) refers to care of preterm or low birth weight infants by placing the infant in skin-to-skin contact with the mother or any other caregiver. Initially conceived as an alternative to conventional warmer care for LBW infants, KMC has now become standard of care either as an alternative to or an adjunct to technology-based care.

KMC was first suggested in 1978 by Dr Edgar Rey in Bogotá, Colombia. The term kangaroo care is derived from practical similarities to marsupial caregiving, i.e. the infant is kept warm in the maternal pouch and close to the breasts for unlimited feeding.

Components

i. *Kangaroo position.* The kangaroo position consists of skin-to-skin contact between the mother and the infant in a vertical position, between the mother's breasts and under her clothes. The provider must keep herself in a semi-reclining position to avoid the gastric reflux in the infant. The kangaroo position is maintained until the infant no longer tolerates it, as indicated by sweating in the baby or baby refusing to stay in KMC position.

ii. *Kangaroo nutrition:* Kangaroo nutrition is exclusive breastfeeding.

iii. *Kangaroo discharge and followup:* Early home discharge in the kangaroo position from the neonatal unit is one of the original components of the KMC intervention. Mothers at home require adequate support and followup hence a followup program and access to emergency services must be ensured.

Benefits

Physiological Benefits

KMC results in keeping neonates warm and cozy. Babies get protected against cold stress and hypothermia. Physiological parameters such as heart and respiratory rates, oxygenation, sleep patterns get stabilized.

Clinical Benefits

KMC significantly increases milk production in mothers and exclusive breastfeeding rates. KMC improves weight gain in the infants and improves thermal protection. It reduces incidence of respiratory tract and nosocomial infections, improves emotional bonding between the infant and mothers and results in earlier discharge from the hospital.

Criteria for Eligibility

Baby

KMC is indicated in all stable LBW babies (Fig. 8.25). However, sick babies should be cared under radiant warmer initially and KMC should be started once the baby is hemodynamically stable. Short KMC sessions can be initiated during recovery with ongoing medical treatment (IV fluids, oxygen therapy). KMC can be provided while the baby is being fed via orogastric tube or on oxygen therapy.

Mother

All mothers can provide KMC, irrespective of age, parity, education, culture and religion. The mother must be willing to provide KMC. The mother should be free from serious illness to be able to provide KMC. She should receive adequate diet and supplements recommended by her physician. She should maintain good hygiene. Mother would need family's cooperation to deal with her conventional responsibilities of household chores till the baby requires KMC.

Initiation of KMC

Counseling. When baby is ready for KMC, arrange a time that is convenient to the mother and her baby. The first few sessions are important and require extended interaction. Demonstrate to her the KMC procedure in a caring, gentle manner and with patience. Answer her queries and allay her anxieties. Encourage her to bring her mother/mother-in-law, husband or any other member of the family. It helps in building positive attitude of the family and ensuring family support to the mother which is particularly crucial for post-discharge home-based KMC. It is helpful that the mother starting KMC interacts with someone already practicing KMC for her baby.

Mother's clothing. KMC can be provided using any front-open, light dress as per the local culture. KMC works well

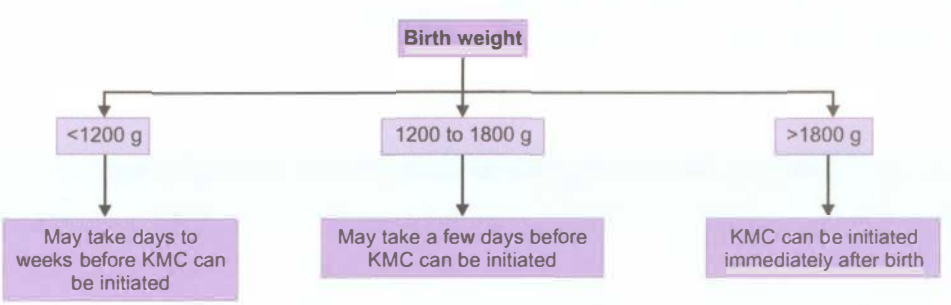
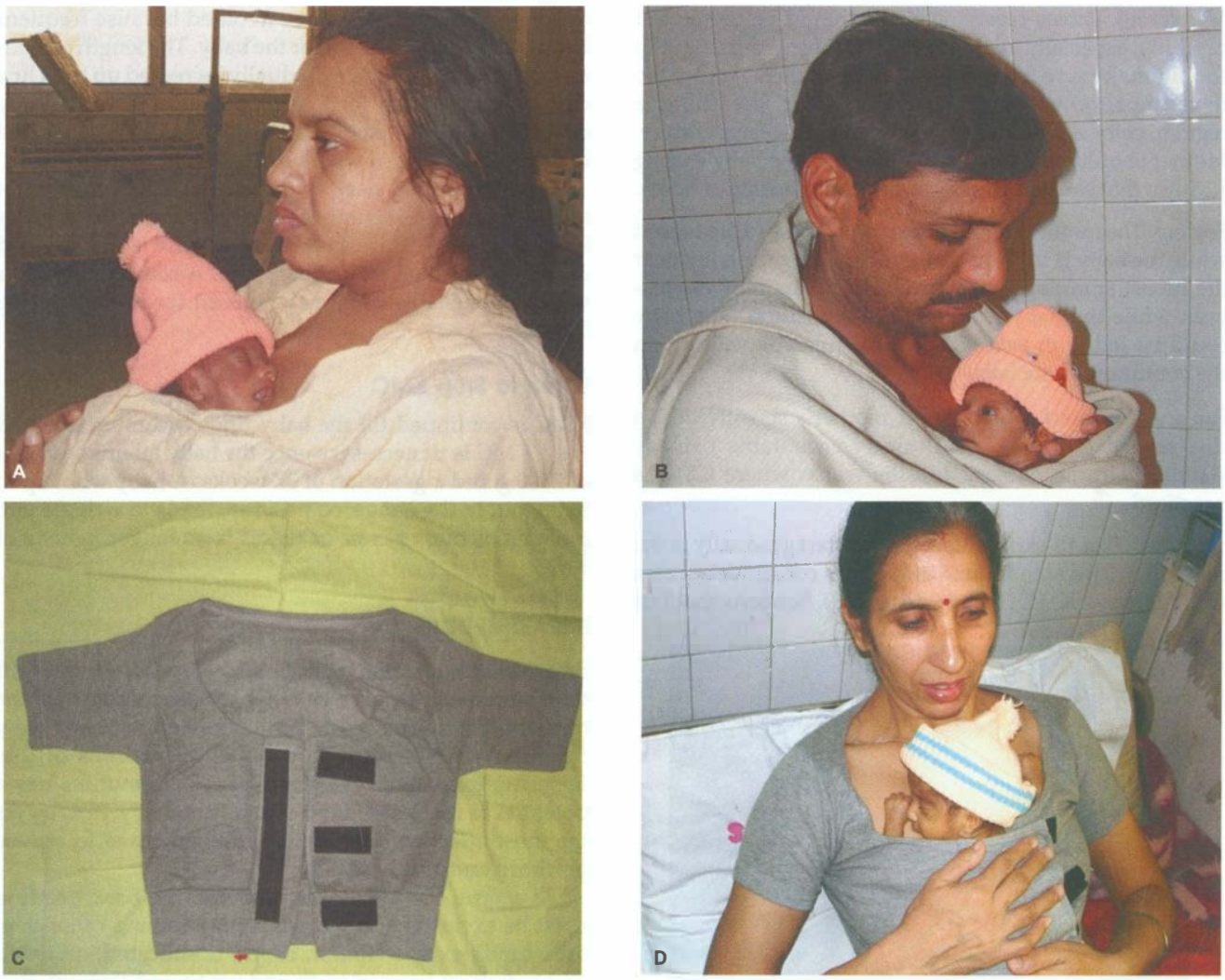


Fig 8.25: Kangaroo mother care (KMC) protocol



Figs 8.26A to D: (A) Mother and (B) father practicing KMC in front open gown and shawl; (C) AIIMS KMC jacket; and (D) mother performing KMC using AIIMS KMC jacket

with blouse and sari, gown or shawl (Fig. 8.26). Suitable apparel that can retain the baby for extended period of time can be adapted locally.

Baby's clothing. Baby is dressed with cap, socks, nappy and front open sleeveless shirt.

Procedure

Kangaroo positioning. The baby should be placed between the mother's breasts in an upright position (Fig. 8.27). The head should be turned to one side and in a slightly extended position. This slightly extended head position keeps the airway open and allows eye to eye contact between the mother and her baby. The hips should be flexed and abducted in a 'frog' position; the arms should also be flexed. Baby's abdomen should be at the level of the mother's epigastrium. Mother's breathing stimulates the baby, thus reducing the occurrence of apnea. Support the baby's bottom with a sling or binder.

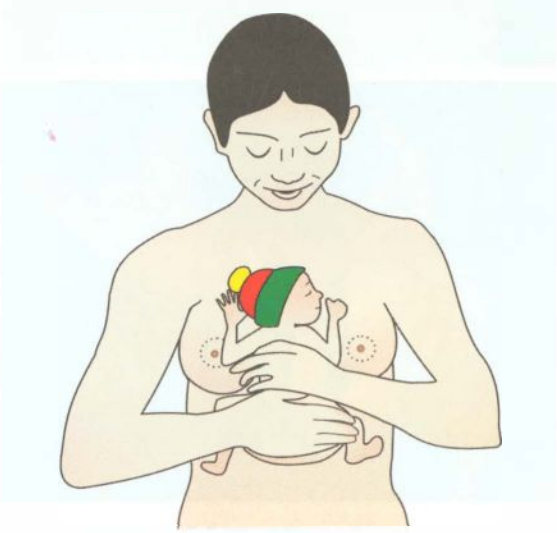


Fig. 8.27: Kangaroo positioning

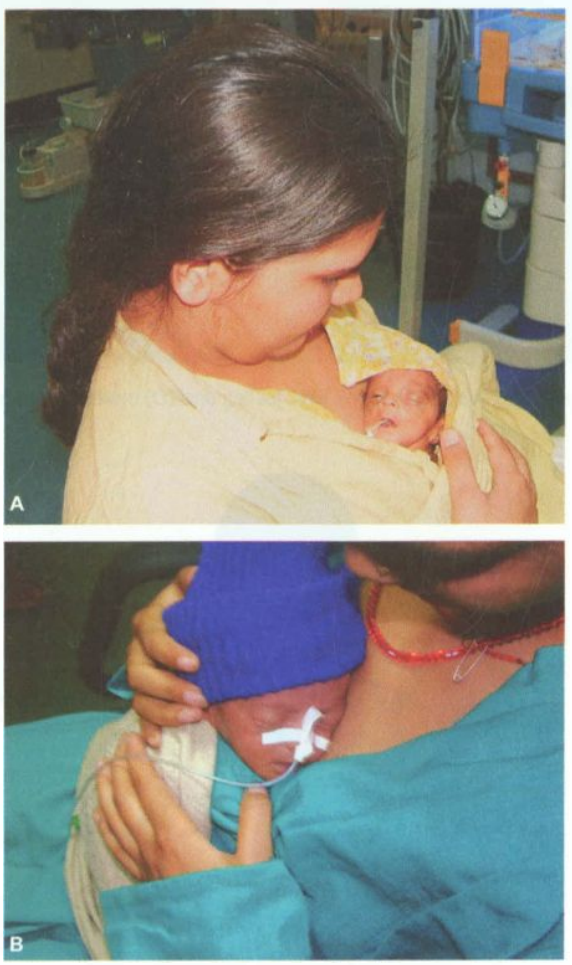
Monitoring. Babies receiving KMC should be monitored carefully, especially during the initial stages. Nursing staff should make sure that baby's neck position is neither too flexed nor too extended, airway is clear, breathing is regular, color is pink and baby is maintaining temperature. Mother should be involved in observing the baby during KMC so that she herself can continue monitoring at home.

Feeding. The mother should be explained how to breastfeed while the baby is in KMC position. Holding the baby near the breast stimulates milk production. She may express milk while the baby is still in KMC position. The baby could be fed with *paladai*, spoon or tube, depending on the condition of the baby.

Privacy. The staff must respect mother's sensitivities in this regard and ensure culturally acceptable privacy standards in the nursery and the wards where KMC is practised.

Duration. Skin-to-skin contact should start gradually in the nursery, with a smooth transition from conventional care to continuous KMC (Figs 8.28A and B). Sessions that last less than one hour should be avoided because frequent handling may be stressful for the baby. The length of skin-to-skin contact should be gradually increased up to 24 hr a day, interrupted only for changing diapers. When the baby does not require intensive care, she should be transferred to the postnatal ward where KMC should be continued.

The mother can sleep with baby in KMC position in reclined or semi-recumbent position about 30 degrees from horizontal. This can be done with an adjustable bed or with pillows on an ordinary bed. A comfortable chair with an adjustable back may be used for resting during the day.



Figs 8.28A and B: Kangaroo mother care being provided in postnatal ward

When to Stop KMC

KMC is continued till the baby finds it comfortable and cosy. KMC is unnecessary once the baby attains a weight of 2500 g and a gestation of 37 weeks. A baby who, upon being put in the kangaroo position, tends to wriggle out, pulls limbs out, or cries or fusses is no longer in need of KMC.

BREASTFEEDING

Breast milk is an ideal food for neonates. It is the best gift that a mother can give to her baby. It contains all the nutrients for normal growth and development of a baby from the time of birth to the first six months of life. Ensuring exclusive breastfeeding for six months has a potential to reduce under-5 mortality rate by 13%, by far the most effective intervention that is known to reduce newborn and child deaths.

To accrue the maximum benefits, the breastfeeding must be exclusive (only breast milk; nothing other than breast milk except vitamin drops, if indicated), initiated within half an hour of birth and continued through first six months after birth. Coverage Evaluation Survey (2009) reported that only 33.5% of infants were breastfeeding started within an hour of birth. Only 36.8% of infants aged 6 to 9 months received exclusive breastfeeding until 6 months of age.

Benefits of Breast Milk

Nutritional superiority. Breast milk contains all the nutrients a baby needs for normal growth and development, in an optimum proportion and in a form that is easily digested and absorbed.

Carbohydrates. Lactose is in a high concentration (6–7 g/dl) in breast milk. The galactose is necessary for formation of galactocerebrosides. Lactose helps in absorption of calcium and enhances the growth of lactobacilli, the good bacteria, in the intestine.

Proteins. The protein content of breast milk is low (0.9–1.1 g/dl) compared to animal milk. Most of the protein is in form of lactalbumin and lactoglobulin (60%), which is easily digested. Human milk contains amino acids like

taurine and cysteine which are necessary for neurotransmission and neuromodulation. These are lacking in cow milk and formula.

Fats. Breast milk is rich in polyunsaturated fatty acids, necessary for the myelination of the nervous system. It also contains omega 2 and omega 6 (very long chain) fatty acids, which are important for the formation of prostaglandins and cholesterol, required as a base for steroid hormones.

Vitamins and minerals. The quantity and bioavailability of vitamins and minerals is sufficient to the needs of the baby in the first 6 months of life.

Water and electrolytes. Breast milk has a water content of 88% and hence a breastfed baby does not require any additional water in the first few months of life even during summer months. The osmolality of breast milk is low, presenting a low solute load to the kidneys.

Immunological superiority. Breast milk contains a number of protective factors which include immunoglobulin–mainly secretary IgA, macrophages, lymphocytes, lactoferrin, lysozyme, bifidus factor and interferon among others. Breastfed babies are less likely to develop infection. A breastfed baby is 14 times less likely to die of diarrhea and almost four times less likely to die of respiratory infection.

Other benefits. Breast milk contains a number of growth factor, enzymes and hormones. The epidermal growth factor in breast milk enhances maturation of the intestinal cells and reduces the risk of allergy in later life. Enzymes like lipases increase the digestion of fats in the milk.

Protection against other illness. Breastfed babies have a lower risk of allergy, ear infections and orthodontic problems. They have a lower risk of diabetes, heart disease and lymphoma in later life.

Mental growth. Babies who are breastfed are better bonded to their mothers. Studies have shown that babies who were breastfed had a higher IQ than those babies who were given other forms of milk.

Benefits to mother. Breastfeeding soon after birth helps uterine involution, reducing chances of postpartum hemorrhage. It provides protection against pregnancy due to lactational amenorrhea. If the mother has been exclusively breastfeeding her baby and has not resumed menses then there is no need for any other contraception during initial 6 months after delivery.

Breastfeeding is most convenient and time saving. It reduces the risk of cancer of breast and ovary. Breastfeeding is the most effective way of shedding extra weight that mother has gained during pregnancy.

Breast Anatomy

The breast is made up of glandular tissue, supporting tissue and fat (Fig. 8.29). The glandular tissue consists of small clusters of sac-like spaces which produce milk. Each sac is lined by network of myoepithelial cells that propel the milk into lactiferous ducts towards nipple. Before reaching the nipple, the ducts widen to form lactiferous sinuses which store milk. The lactiferous sinuses lie beneath the junction of areola and rest of breast.

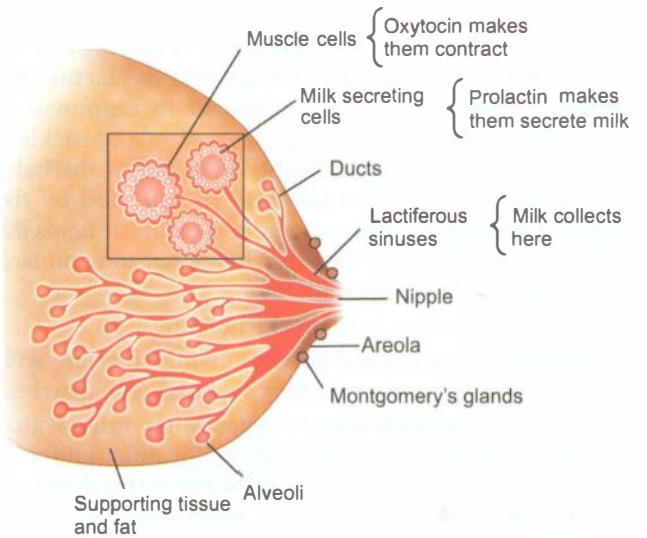


Fig. 8.29: Anatomy of breast

The areola and nipples are extremely sensitive as they are supplied by a rich network of nerve endings. On the areola there are small swellings of glands which produce an oily fluid to keep the nipple skin soft. Since the lactiferous sinuses lie beneath the areola, a baby must suck at the nipple and areola. The gum line of the baby should rest at the junction of areola and rest of breast tissue in order to express milk stored in lactiferous sinuses.

Physiology

Lactogenesis is a complex phenomenon involving many hormones and reflexes. Two hormones are most important, prolactin and oxytocin.

Prolactin reflex (milk secretion reflex). Prolactin produced by the anterior pituitary gland is responsible for milk secretion by the alveolar epithelial cells (Fig. 8.30A). When the baby sucks, the nerve ending in the nipple carry impulse to the anterior pituitary which in turn release prolactin and that acts on the alveolar glands in the breast to stimulate milk secretion.

This cycle from stimulation to secretion is called the *prolactin reflex or the milk secretion reflex*. The more the baby sucks at the breast, the greater is the milk production. The earlier the baby is put to the breast, the sooner this reflex is initiated. The greater the demand more is the production. It is, therefore, important for mothers to feed early, frequently and empty out the breasts completely at each feeding session. Since prolactin is produced during night time, breastfeeding during night is very important for maintenance of this reflex.

Oxytocin reflex (milk ejection reflex). Oxytocin is a hormone produced by the posterior pituitary. It is responsible for *ejection of the milk* from the glands into the lactiferous sinuses. This hormone is produced in response to stimulation to the nerve endings in the nipple by suckling as well as by the thought, sight, or sound of the baby (Figs 8.30B and C). Since this reflex is affected by the mother's emotions, a relaxed, confident attitude helps the milk ejection reflex. On the other hand, tension and lack of confidence hinder the milk flow.

Factors which reduce milk production are:

- Dummies, pacifiers and bottles not only interfere with breastfeeding but also predispose the baby to diarrhea.
- Giving supplements such as sugar water, gripe water, honey, breast milk substitutes or formula, either as *prelacteal* (before initiation of breastfeeding) or supplemental (concurrent to breastfeeding) feeds. Studies have reported that even 1 or 2 supplemental feeds reduce the chances of successful breastfeeding.
- Painful breast conditions like sore or cracked nipples and engorged breast.
- Lack of night feeding, as the prolactin reflex is not adequately stimulated.
- Inadequate emptying of breast such as when baby is sick or small and the mother does not manually express breast milk or when baby is fed less frequently.

Reflexes in the Baby

A baby is born with certain reflexes which help the baby to feed. These include rooting, sucking and swallowing reflexes.

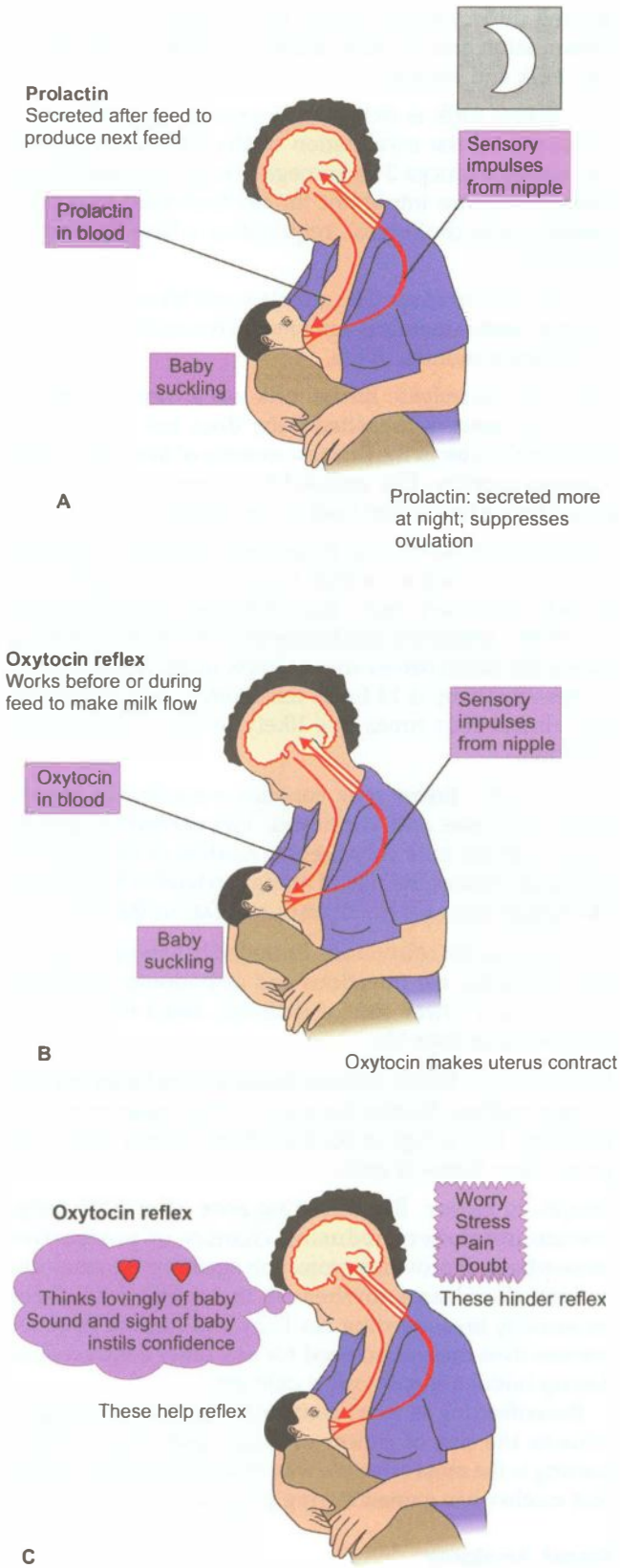
The rooting reflex. When cheek or the side of the mouth is touched, the baby opens her mouth and searches for the nipple. This is called rooting reflex. This reflex helps the baby to find the nipple and in proper attachment to the breast.

The suckling reflex. When baby's palate is touched with nipple, the baby starts sucking movements. This reflex is very strong immediately after birth. The sucking reflex consists of:

- Drawing in the nipple and areola to form an elongated teat inside the mouth.
- Pressing the stretched nipple and areola with the jaw and tongue against the palate.
- Drawing milk from the lactiferous sinuses by wave-like peristaltic movement of the tongue underneath the areola and the nipple and compressing them against the palate above.

To suckle effectively, the baby has to attach (latch) well. Obtaining good attachment at breast is a skill, which both the mother and the baby have to learn.

The method of suckling at the breast and bottle is entirely different. Suckling on a bottle filled with milk is a passive



Figs 8.30A to C: (A) Prolactin and (B) oxytocin reflex; (C) factors which help and hinder oxytocin reflex

process and the baby has to control the flow of milk into the mouth with her tongue. While breastfeeding requires active efforts by the baby. A bottlefed baby develops *nipple confusion* and refuses to feed on the breast. Single session of bottlefeeding lessens the chances of successful breastfeeding. Bottle feeding of babies is fraught with risk of serious infections and consequent ill health.

The swallowing reflex. When the mouth is filled with milk, the baby reflexly swallows the milk. It requires a couple of suckles before baby can get enough milk to trigger swallowing reflex. It requires coordination with breathing. The suckle-swallow-breathe cycle lasts for about one second.

Composition of Breast Milk

The composition of breast milk varies at different time points of lactation to suit the needs of the baby. Milk of a mother who has delivered a preterm baby is different from milk of a mother delivered a term baby.

i. *Colostrum* is the milk secreted during the initial 3–4 days after delivery. It is small in quantity, yellow and thick and contains large amount of antibodies and immune-competant cells and vitamins A, D, E and K.
ii. *Transitional milk* is the milk secreted after 3–4 days until two weeks. The immunoglobulin and protein content decreases while the fat and sugar content increases.
iii. *Mature milk* follows transitional milk. It is thinner and watery but contains all the nutrients essential for optimal growth of the baby.
iv. *Preterm milk* is the milk of a mother who delivers before 37 week. It contains more proteins, sodium, iron, immunoglobulins and calories as per the requirement of preterm baby.
v. *Foremilk* is the milk secreted at the start of a feed. It is watery and is rich in proteins, sugar, vitamins, minerals and water that quenches the baby's thirst.
vi. *Hindmilk* comes later towards the end of feed and is richer in fat that provides more energy and gives a sense of satiety. Thus, the composition of milk also varies during the phase of feeding. For optimum growth, the baby needs both fore as well as hindmilk. Therefore, the baby should be allowed to empty out one breast completely before switching over to the other.

Technique of Breastfeeding

Mothers require substantial assistance to learn the technique of breastfeeding. With correct technique, breastfeeding is natural and a pleasurable experience for the mother. However a variety of breastfeeding problems do occur in large proportion of mothers that require counseling and support from the health providers for their prevention and appropriate treatment. Provision of lactation support services by lactational counsellor or trained health providers greatly increase the success of breastfeeding.

Positioning

Position of the mother. The mother can assume any position that is comfortable to her and the baby. She can sit or lie down. Her back should be well supported and she should not be leaning on her baby (Figs 8.31A to C).


A


B


C

Figs 8.31A to C: Different postures of feeding

Position of baby. Make sure that baby is wrapped properly in a cloth

i. Baby's *whole body is supported* not just neck or shoulders
ii. Baby's *head and body are in one line* without any twist in the neck
iii. Baby's *body turned towards the mother* (abdomens of the baby and the mother touching each other)
iv. Baby's *nose is at the level of the nipple.*

Attachment (Latching)

After proper positioning, the baby's cheek is touched and that initiates rooting reflex. Allow the baby to open his mouth widely and at that point, the baby should be latched on to the breast ensuring that the nipple and most of the areola are within baby's mouth (Fig. 8.32). It is important that the baby is brought on the mother's breast and mother should not lean on to baby.

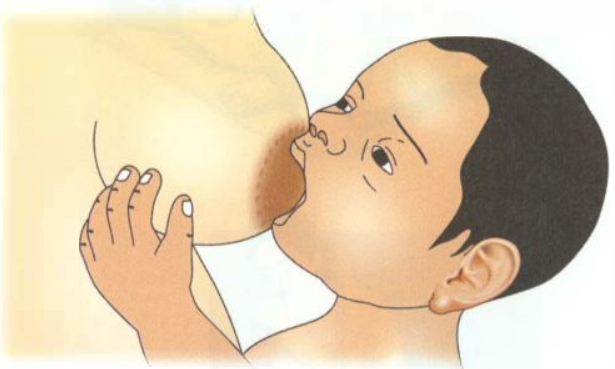


Fig. 8.32: Good attachment

Signs of good attachment

i. The baby's mouth is *wide open*
ii. *Most of the nipple and areola in the mouth*, only upper areola visible, not the lower one
iii. The baby's *chin touches the breast*
iv. The baby's *lower lip is everted*

Effective Suckling

- Baby *suckles slowly and pauses* in between to swallow (suck, suck, suck.. and swallow). One may see throat cartilage and muscles moving and hear the gulping sounds of milk being swallowed.
- Baby's cheeks are full and not hollow or retracting during sucking.

Problems in Breastfeeding

Inverted nipples. Flat or short nipples which become prominent easily on pulling out do not pose difficulty in breastfeeding. However, truly inverted or retracted nipples make latching difficult. As the baby is not able to take nipple and areola in the mouth properly, sucking on the nipples makes them sore and excoriated. Treatment is *started after birth* of the baby. The nipple is manually everted, stretched and rolled out several times a day. A plastic syringe is used to draw out to correct the problem (Fig. 8.33).

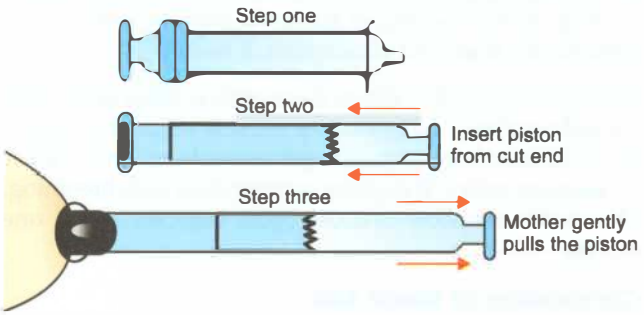


Fig. 8.33: Syringe treatment for inverted/flat nipple

Sore nipple. Nipples become sore when baby *suckles on the nipple rather than areola* because of incorrect attachment. As the baby is unable to express milk, he sucks vigorously in frustration and bites the nipple causing soreness. Frequent washing with soap and water and pulling the baby off the breast while he is still sucking may also result in sore nipple. Treatment consists of *correct positioning and latching* of the baby to the breast. A mother would be able to feed the baby despite sore nipple if the baby is attached properly. Hind milk should be applied to the nipple after a feed and the nipple should be aired and allowed to heal in between feeds. She should be advised not to wash nipple each time before/after feeding. She can clean breast and nipple once daily at time of bathing. There is no need to apply any cream or ointment to the sore nipples.

Breast engorgement. The milk production increases by the second and third day after delivery. If feeding is delayed or infrequent, or the baby is not well positioned at the breast, the milk accumulates in the alveoli. As milk production increases, the amount of milk in the breast exceeds the capacity of the alveoli to store it comfortably. Such a breast becomes swollen, hard, warm and painful and is termed as an 'engorged breast' (Fig. 8.34).

Breast engorgement can be prevented by *early and frequent feeds and correct attachment* of the baby to the breast.

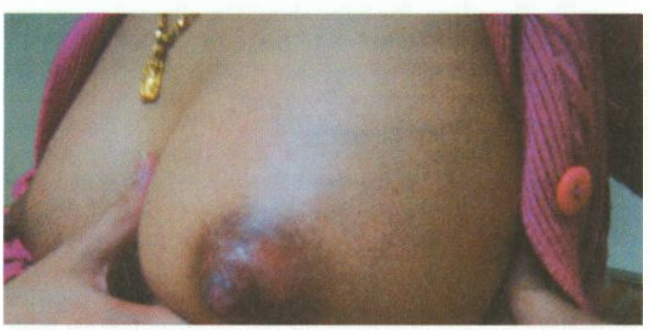


Fig. 8.34: Engorged breast. Note tense and shiny skin; nipple shows excoriation

Treatment consists of local warm water packs, breast massage and analgesics to relieve the pain. Milk should be gently expressed to soften the breast.

Breast abscess. If a congested engorged breast, cracked nipple, blocked duct or mastitis are not treated in the early stages, breast abscess formation can occur. The mother has high grade fever and a raised blood count. She must be treated with analgesics and antibiotics. The abscess may require incision and drainage. Breastfeeding must be continued.

Not enough milk. First make sure that the perception of "not enough milk" is correct. If baby is satisfied and sleeping for 2–3 hr after breastfeeding, passing urine at least 6–8 times in 24 hr and gaining weight, the mother is producing enough milk. There could be a number of reasons for insufficient milk such as incorrect method of breastfeeding, supplementary or bottle feeding, no night breastfeeding, engorgement of breast, any illness, painful condition, maternal stress or insufficient sleep. Try to identify the possible reason and take appropriate actions. Advise mother to take sufficient rest and drink adequate fluids. Feed the baby on demand. Let the baby feed as long as possible on each breast. Advise the mother to keep the baby with her.

Expressed Breast Milk (EBM)

If a mother is not in a position to feed her baby (e.g. ill mother, preterm baby, working mother, etc.), she should express her milk in a clean wide-mouthed container and this milk should be fed to her baby. EBM can be stored at room temperature for 6–8 hr, in a refrigerator for 24 hr and a freezer at –20°C for 3 months.

Method of Milk Expression

Ask the mother to wash her hands thoroughly with soap and water before she expresses. She should make herself comfortable. Gently massage the breast (Fig. 8.35). Hold the container under her nipple and areola. Place her thumb on top of the breast at least 4 cm from the tip of the nipple and the first finger on the undersurface of the breast opposite the thumb. Compress and release the breast tissue between her fingers and thumb a few times.

If the milk does not appear, she should reposition her thumb and finger closer to the nipple and compress and release the breast as before. Compress and release all the way around the breast. Express milk from both breasts.

To maintain adequate lactation, mother should express milk at least 8 to 10 times in 24 hr.

CARE OF LOW BIRTH WEIGHT BABIES

Low birth weight (LBW; birth weight less than 2500 g) babies have higher morbidity and mortality. LBW results from either preterm birth (before 37 completed weeks of gestation) or due to intrauterine growth restriction (IUGR) or both.

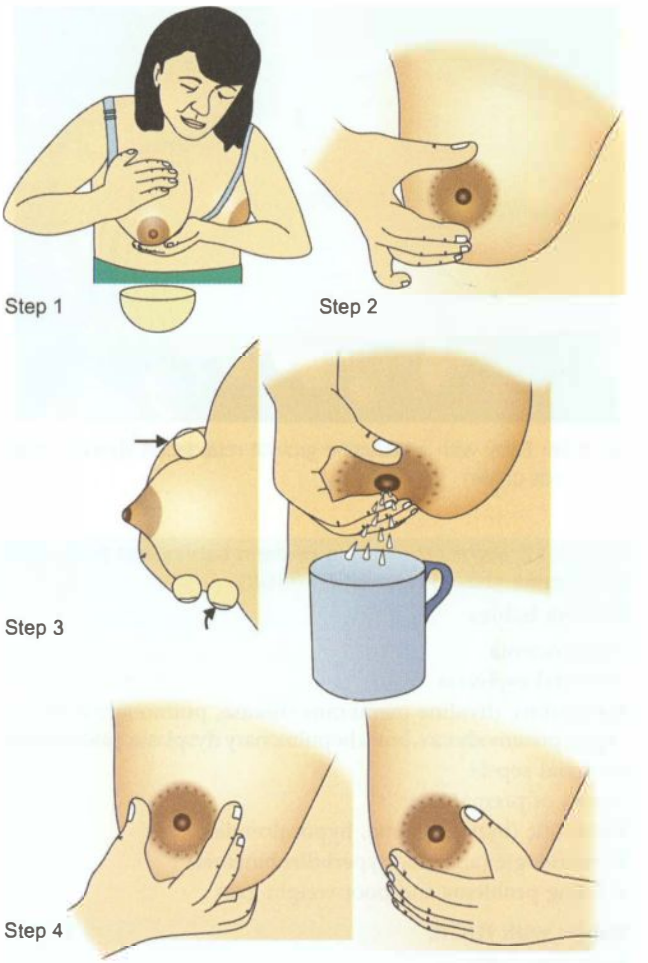


Fig. 8.35: Four steps of breast milk expression. Step 1: Massage the breasts gently toward the nipples; Step 2: Place the thumb and index finger opposite each other just outside the dark circle around the nipple; Step 3: Press back toward the chest, then gently squeeze to release milk; Step 4: Repeat step 3 in different positions around the areola

IUGR is similar to malnutrition and may be present in both term and preterm infants. Neonates affected by IUGR are usually undernourished and have loose skin folds on the face and in the gluteal region (Fig. 8.36), absence of subcutaneous fat and peeling of skin. Problems faced by a preterm and IUGR neonate are different, although the management principles are common to both (Table 8.12).

IUGR (Intrauterine growth restriction). IUGR results when the fetus does not grow as per the normal fetal growth trajectory. IUGR fetal growth restriction results from one or many adverse factors that affect the normal growth pattern of the fetuses. There are two types of IUGR babies:

- *Symmetric IUGR:* When insult on the fetal growth occurs early. The size of the head, body weight and length are equally reduced. Causes include genetic and chromosomal disorders or TORCH infections.

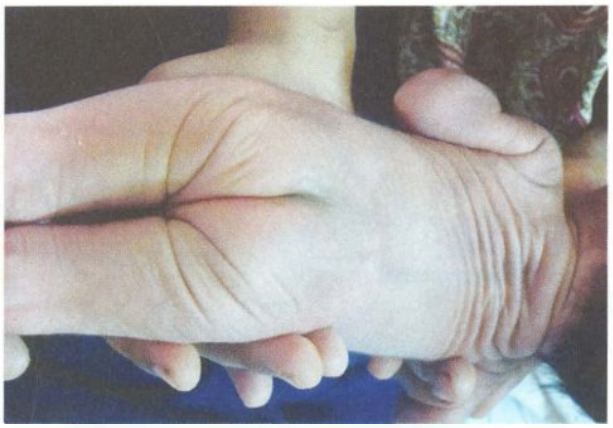


Fig. 8.36: Baby with intrauterine growth retardation showing many loose folds of skin

Table 8.12: Major problems in preterm babies and those with intrauterine growth retardation (IUGR)

Preterm babies
Hypothermia
Perinatal asphyxia
Respiratory (hyaline membrane disease, pulmonary hemorrhage, pneumothorax, bronchopulmonary dysplasia, pneumonia)
Bacterial sepsis
Apnea of prematurity
Metabolic (hypoglycemia, hypocalcemia)
Hematologic (anemia, hyperbilirubinemia)
Feeding problems and poor weight gain
Babies with IUGR
Perinatal asphyxia
Meconium aspiration
Hypothermia
Hypoglycemia
Feed intolerance
Polycythemia
Poor weight gain

- *Asymmetric IUGR:* The insult on the fetal growth occurs during late gestation producing a *brain sparing effect*. Head circumference is relatively preserved compared to length and weight. Causes include placental insufficiency, pregnancy-induced hypertension or maternal medical diseases.

Small for gestational age (SGA): It is a statistical definition and denotes weight of infant being less than 2 standard deviation or less than the tenth percentile of the population norms (plotted on intrauterine growth chart). SGA and IUGR are considered synonymous.

Issues in LBW Care

Besides the pathologies that can affect all neonates irrespective of weight and gestation, LBW may have additional complications requiring special care.

Resuscitation

Problems

- Compromised intrauterine environment with higher chances of perinatal asphyxia
- Preterm babies have immature lungs that may be more difficult to ventilate and are also more vulnerable to lung injury by positive pressure ventilation.
- Immature blood vessels in the brain are prone to hemorrhage
- Thin skin and a large surface area, which contribute to rapid heat loss
- Increased risk of hypovolemic shock caused by small blood volume

Management

- Prepare for high risk of need for resuscitation
- Gentle resuscitation (small tidal volume) using small bags for positive pressure ventilation, use of CPAP
- Take extra care to avoid hypothermia

Temperature Control

Problems

- Higher surface area to body weight ratio
- Low glycogen stores
- Low subcutaneous fat

Management

- Frequent monitoring and educating parents for need to check temperature
- Special attention to maintenance of the warm chain
- Kangaroo mother care

Fluids and Feeding

These have been discussed under the section on feeding.

Infection

Problems

- Immature defenses
- Greater probability of invasive interventions like mechanical ventilation, umbilical vessel catheterization.

Management

- Strict adherence to asepsis, hand hygiene
- Minimal handling of babies
- Low threshold for suspicion of sepsis, adequate and appropriate use of antibiotics
- Decreasing exposure to adults/other children with communicable diseases particularly respiratory.

Metabolic Derangements

Problems

- Low hepatic glycogen stores with rapid depletion in stress places these infants at increased risk of *hypoglycemia*.
- Immature glucose homeostatic mechanisms in premature babies can also lead to decreased inability to utilize glucose and resultant *hyperglycemia*, especially during stressful periods like infection.

- Early onset *hypocalcemia:* Presenting within 3 days of life and is usually asymptomatic, detected on investigation. It is especially seen in premature babies, infants of diabetic mothers and those with birth asphyxia.
- Late onset hypocalcemia presents as classical neonatal tetany, jitteriness and seizures. Feeds with higher phosphate load such as cow milk and some formulae, result in hyperphosphatemia with subsequent hypocalcemia.

Management

This has been discussed in appropriate sections.

Jaundice

Problems

- Larger RBC volume for body weight
- Immaturity of hepatic enzymes and hepatic excretory capacity
- Immature blood brain barrier-increased risk for bilirubin encephalopathy

Management

This has been discussed in section on jaundice.

Hematological Abnormality

Problems

Polycythemia. Placental insufficiency with intrauterine hypoxia leads to stimulation of erythropoiesis and resultant polycythemia, especially seen in IUGR babies. Polycythemia (>65% hematocrit) produces hyperviscosity with decreased organ perfusion. Manifestations include jitteriness, respiratory distress, cardiac failure, feeding intolerance, hypoglycemia, hypocalcemia and hyperbilirubinemia.

Anemia. Accelarated destruction of fetal RBCs, low reticulocyte count and inadequate response of the bone marrow to erythropoietin cause anemia of premaurity. Low iron stores, higher incidence of sepsis and frequent blood sampling in LBW babies further predisposes to risk of severe anemia.

Management

- *Treatment of polycythemia:* Symptomatic infants or those with hematocrit >75% require partial exchange transfusion. For others, management includes increasing the fluid intake.
- *Anemia:*
  - Iron supplementation: All LBW babies should be started of 2–3 mg/kg of iron from 2 months till 2 yr of age.
  - Sampling should be minimized and in small amounts
  - Transfusions may be given as per institution protocol.

Immature Organ Systems in Preterms

Respiratory distress syndrome. This has been described in detail later.

Intraventricular hemorrhage. Preterms have a fragile highly vascular collection of vessels near the lateral ventricle of brain. Respiratory distress, mechanical ventilation or vigorous resuscitation, can cause rupture of these vessels leading to adverse neurological sequelae. Preventive measures include minimal and gentle handling, avoiding rapid changes in intravascular volume such as rapid boluses or infusion of hyperosmolar solutions, avoiding high pressures during ventilation and treating any bleeding diathesis. Treatment is essentially supportive and management of later complications such as hydrocephalus.

Retinopathy of prematurity (ROP). Growth of retinal vessels occurs from the optic disc to the periphery from 18 weeks of gestation till term. Any injury to these vessels due to the still developing vessels of preterm retina when subjected to the premature transition of postnatal life (especially high oxygen saturation as may be used during resuscitation), may pathological proliferation, resulting in retinal damage with vision loss, if left untreated. This complication can be decreased with rational use of oxygen, maintaining a SpO_2 between 85–95% and regular screening for early detection and treatment. Advanced stages of ROP requires peripheral retinal ablation by laser or cryotherapy.

Hearing damage. Preterm infants are at higher risk of hearing loss due to immaturity and complications thereof such as infections or drugs. Adjustment of drug doses according to gestational age, preventing hypoxia, treating jaundice and routine screening for early detection can minimize this complication.

Associated Conditions

An IUGR birth itself might be an indication of a pre-existing problem leading to such occurrence. Examples include intrauterine infections and chromosomal anomalies which result in IUGR. These usually constitute a subgroup of IUGR babies known as symmetrical IUGR. The cause of growth restriction is a condition other than nutritional deficiency and onset occurs early in fetal life with proportionate restriction of head and body, unlike the nutritionally restricted asymmetrical IUGR which has onset in third trimester and has head growth is spared.

Prolonged Hospital Stay

Requirement of frequent monitoring and intervention in these high risk babies results in their separation from parents at birth, and high cost. It is an emotionally and financially trying time for all families. Keeping parents involved in decision making with counseling sessions directed at their concerns helps greatly in management.

Criteria for Discharge

- Screening tests are performed before discharge or on followup, e.g. those for ROP detection in infants <32 weeks and auditory brainstem evoked response (ABER).
- Nutrition supplements including multivitamins, iron, calcium and vitamin D are started.

- Immunization with BCG, Hep B and OPV is given.
- Weight gain should be consistently demonstrated for few days before discharge. Weight, length and head circumference should be recorded at discharge and plotted on a growth chart, which can be used on follow-up to determine if growth is adequate.
- Baby should be feeding well; if on alternate feeding technique like *paladai* feeding, the mother should be confident regarding its details.
- Absence of danger signs and completion of treatment like IV antibiotics. If baby is being discharged on oral medication then parents should be well educated regarding how to administer.
- Methods of temperature regulation, either KMC practice or other methods should be well known to parents.
- All danger signs are explained in detail to parents with information regarding whom and where to contact clearly highlighted.

  The following are the danger signs:
  - History of difficulty in feeding
  - Movement only when stimulated
  - Temperature below 35·5°C or 37·5°C or more
  - Respiratory rate over 60 breaths per minute
  - Severe chest indrawing
  - History of convulsions
- Followup within 3–7 days of discharge to ensure the baby has been adapted well to home environment.

Feeding of LBW Babies

Nutritional management influences immediate survival as well as subsequent growth and development of LBW infants. Early nutrition could also influence the longterm neurodevelopmental outcomes. Malnutrition at a vulnerable period of brain development has been shown to have deleterious effects in experimental animals.

Term infants with normal birth weight require some assistance for feeding in the immediate postnatal period, but they are able to feed directly from mothers' breast. In contrast, feeding of LBW infants, in particular the preterm infants, is relatively difficult because of the following limitations:

i. Though majority of these infants are born at term, a significant proportion are born premature with inadequate feeding skills. They might not be able to breastfeed and hence would require other methods of feeding such as spoon or gastric tube feeding.
ii. They are prone to have significant illnesses in the first few weeks of life, the underlying condition often precludes enteral feeding.
iii. Preterm infants have higher fluid requirements in the first few days of life due to excessive insensible water loss.
iv. Since intrauterine accretion occurs mainly in the later part of the third trimester, preterm infants (particularly those born before 32 weeks of gestation) have low body stores of various nutrients at birth which necessitates supplementation in the postnatal period.
v. Because of the gut immaturity, they are more likely to experience feed intolerance necessitating adequate monitoring and treatment.

Methods

Direct and exclusive breastfeeding is the goal of feeding all LBW infants. However, because of the various limitations, not all LBW infants would be able to accept breastfeeding at least in the initial few days after birth. These infants have to be fed by either spoon/*paladai* or intragastric tube (gavage feeding). Those babies who cannot accept oral feeds by even these methods would require intravenous (IV) fluids.

The appropriate method of feeding in a given LBW infant is decided based upon the following factors:

- Whether the infant is sick or not; and
- Feeding ability of the infant (which depends upon the gestational maturity).

Level of Sickness

It is essential to categorize LBW infants into two major groups, *sick* and *healthy*, before deciding the initial method of feeding.

Sick infants. This group constitutes infants with respiratory distress requiring assisted ventilation, shock, seizures, symptomatic hypoglycemia, electrolyte abnormalities, renal/cardiac failure, surgical conditions of gastrointestinal tract, necrotizing enterocolitis (NEC), hydrops. These infants are usually started on IV fluids. Enteral feeds should be initiated as soon as they are hemodynamically stable with the choice of feeding method based on the infants' gestation and clinical condition (*see* below).

It is important to realize that enteral feeding is important even for sick neonates. Oral feeds should not be delayed in them without any valid reason. Even infants with respiratory distress and/or on assisted ventilation can be started on enteral feeds once the acute phase is over and the infants' color, saturation and perfusion have improved. Similarly, sepsis (unless associated with shock/sclerema/NEC) is not a contraindication for enteral feeding.

Healthy LBW infants. Enteral feeding should be initiated immediately after birth in healthy LBW infants with the appropriate feeding method determined by their oral feeding skills and gestation.

Ability to Feed

Breastfeeding requires effective sucking, swallowing and a proper coordination between suck/swallow and breathing. These complex skills mature with increasing gestation. A robust sucking pattern is not present until

32–34 weeks gestation. A coordination between sucking, swallowing and breathing does not mature until 34 weeks of gestation. This fully matures by 37 weeks of gestation. The maturation of oral feeding skills and the choice of initial feeding method at different gestational ages are summarized in Table 8.13.

However, it is important to remember that *not all* infants born at a particular gestation would have same feeding skills. Hence, the ideal way in a given infant would be to evaluate if the feeding skills expected for his/her gestation are present and then decide accordingly (Fig. 8.37).

All stable LBW infants, irrespective of their initial feeding method should be put on their mothers' breast. The immature sucking observed in preterm infants born before 34 weeks might not meet their daily fluid and nutritional requirements but helps in rapid maturation of their feeding skills and also improves the milk secretion in their mothers (*non-nutritive sucking*).

Figs 8.38A and B show the method of *paladai* and intragastric tube feeding in babies.

Progression of Oral Feeds

All LBW infants, irrespective of their gestation and birth weight, should ultimately be able to feed directly from the mothers' breast. For preterm LBW infants, the progression to direct and exclusive breastfeeding are summarized in Fig. 8.39.

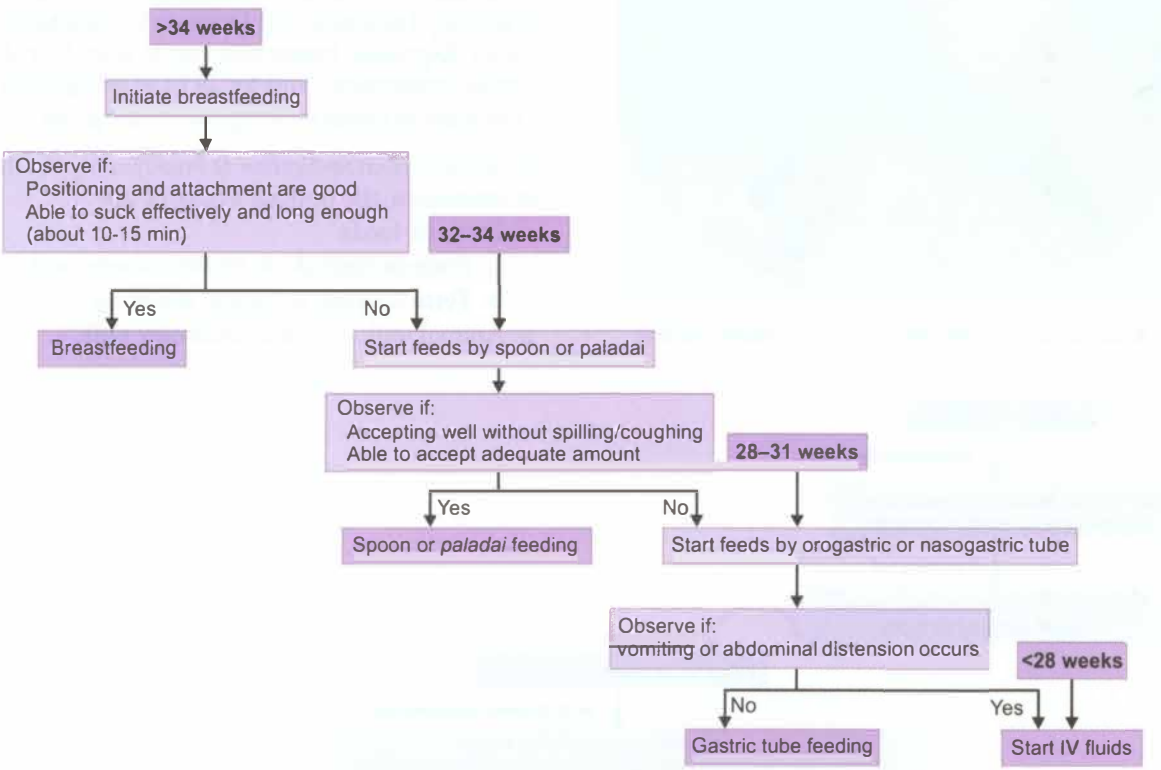
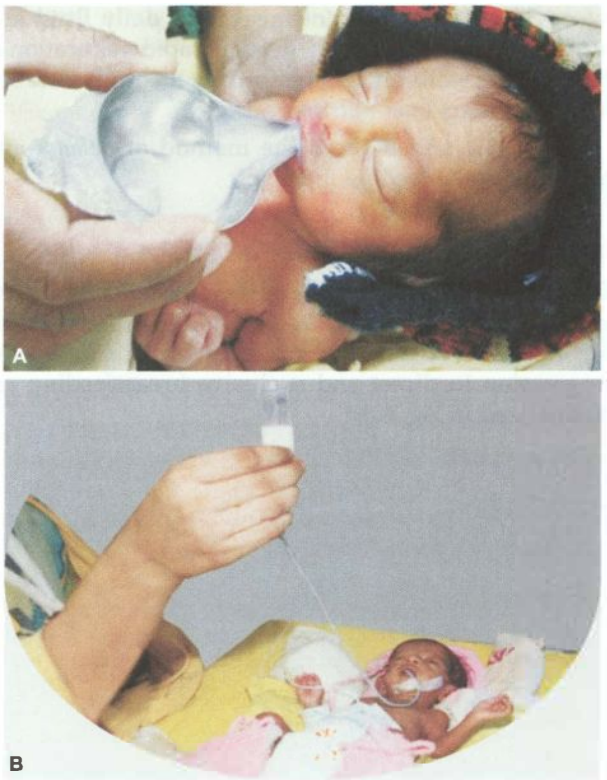


Fig. 8.37: Choosing initial methods of feeding

Table 8.13: Maturation of oral feeding skills and the choice of initial feeding method in LBW infants

Gestational age, weeks	*Maturation of feeding skills*	*Initial feeding method*
< 28 week	Inadequate sucking efforts Lack of propulsive gut motility	Intravenous fluids
28–31 week	Sucking bursts develop Lack of coordination between suck/swallow and breathing	Orogastric or nasogastric tube feeding with occasional spoon or *paladai* feeding
32–34 week	Slightly mature sucking pattern Coordination between breathing and swallowing begins	Feeding by spoon or *paladai*
>34 week	Mature sucking pattern Coordination between breathing and swallowing	Breastfeeding



Figs 8.38A and B: (A) Paladai feeding; (B) Gavage feeding

Term LBW infants started on IV fluids (because of their sickness) can be put on the breast once they are hemodynamically stable.

Choice of Milk

All LBW infants, irrespective of their initial feeding method should receive only breast milk. This can be ensured by giving expressed breast milk (mothers' own milk) for those infants fed by *paladai* or gastric tube.

Expressed breast milk (EBM). All mothers should be counseled and supported in expressing their own milk for feeding their preterm infants. Expression should ideally be initiated within hours of delivery so that the infant gets the benefits of feeding colostrum. Thereafter, it should be done 2–3 hourly so that the infant is exclusively breastfed and lactation is maintained in the mother. Expressed breast milk can be stored for about 6 hr at room temperature and for 24 hr in refrigerator.

The steps of breast milk expression are given in Fig. 8.35.

Sick mothers/contraindication to breastfeeding. In these rare circumstances, the options available are

i. Formula feeds:
   a. Preterm formula in VLBW infants, and
   b. Term formula in infants weighing >1500 g at birth
ii. Animal milk, e.g. undiluted cow milk

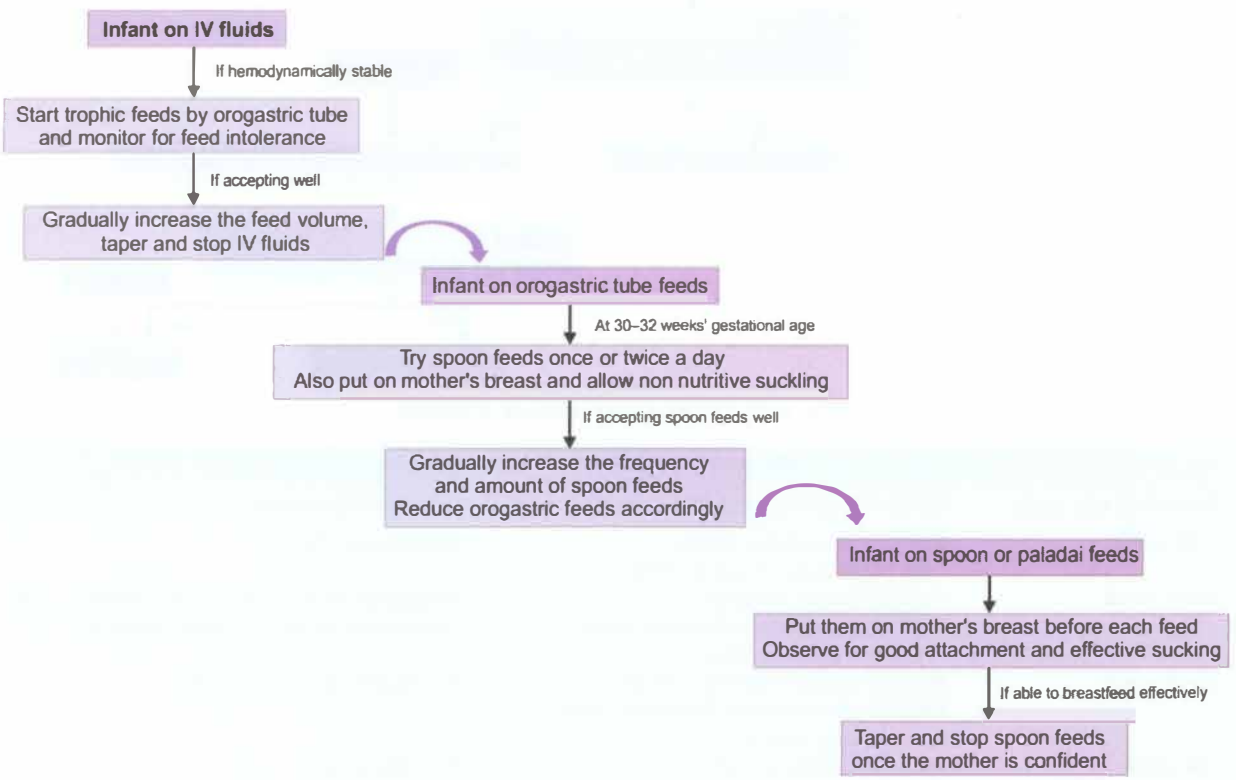


Fig. 8.39: Progression of oral feeding in preterm LBW infants. Term and near-term sick infants started on intravenous (IV) fluids can be initiated on breastfeeding once they are hemodynamically stable

Once the mother's condition becomes stable (or the contraindication to breastfeeding no longer exists), these infants should be started on exclusive breastfeeding.

How Much to Feed?

Infants who are breastfed Infants who are able to suckle effectively at the breast should be breastfed on demand. Small babies usually demand to feed every 2–3 hr, sometimes more frequently. A small infant, who does not demand to be fed for 3 hr or more, can be offered the breast and encouraged to feed.

Infants who are fed by spoon/paladai or by intragastric tube It is essential to know how much to feed, the amount of expressed breast milk to be given, for those infants who are on alternative methods of feeding like gavage or spoon feeding.

The daily fluid requirements of neonates have been discussed in the section of fluids and electrolytes. Preterm infants need more fluids in the initial weeks of life because of the high insensible water loss. It is usual clinical practice to provide VLBW infants (<1500 g) about 80 ml/kg fluids on the first day of life and increase by 10–15 ml/kg/day to a maximum of 160 ml/kg/day by the end of the first week of life. LBW infants ≥1500 g are usually given about 60 ml/kg fluids on the first day of life and fluid intake is increased by about 15–20 ml/kg/day to a maximum of 160 ml/kg/day by the end of the first week of life. After deciding the total daily fluid requirement, the individual feed volume to be given every 2 or 3 hr (by OG tube or *paladai)* can be determined.

Nutritional Supplementation

LBW infants, especially those who are born preterm, require supplementation of various nutrients to meet their high demands. Since the requirements of VLBW infants differ significantly from those with birth weights of 1500–2499 g, supplementation regimes for these two groups have been discussed separately.

Supplementation for infants with birth weights of 1500–2499 g These infants are more likely to be born at term or near term gestation (≥34 week) and are more likely to have adequate body stores of most nutrients. Therefore, they do not require multinutrient supplementation (unlike VLBW infants). However, vitamin D and iron should be supplemented in them (Table 8.14).

Supplementation in VLBW infants These infants who are usually born before 32–34 week gestation have inadequate body stores of most of the nutrients. Since EBM has inadequate amounts of protein, energy, calcium, phosphorus, trace elements (iron, zinc) and vitamins D, E and K, it is often not able to meet the daily recommended intakes of these infants. Hence, these infants need multinutrient supplementation till they reach term gestation (40 weeks, i.e. until the expected date of delivery). The following nutrients have to be added to the expressed breast milk in them:

i. Calcium and phosphorus (140–160 mg/kg/day and 70–80 mg/kg/day respectively for infants on EBM)
ii. Vitamin D (400 IU/day), vitamin B complex and zinc (about 0.5 mg/day) usually in the form of multivitamin drops
iii. Folate (about 50 µg/kg/day)
iv. Iron (2 mg/kg/day)

Multinutrient supplementation can be ensured by one of the following methods:

i. Supplementing individual nutrients, e.g. calcium, phosphorus, vitamins, etc. These supplements should be added at different times in the day to avoid abnormal increase in the osmolality.
ii. By fortification of expressed breast milk with human milk fortifiers (HMF): Fortification increases the nutrient content of the milk without compromising its other beneficial effects. Experimental studies have shown that the use of fortified human milk results in net nutrient retention that approaches or is greater than expected intrauterine rates of accretion in preterm infants. Preterm VLBW infants fed fortified human milk do not require any supplementation other than iron.

Fortification or supplementation of minerals and vitamins should be continued only till term gestation (40 weeks) in VLBW infants; after this period, only vitamin D and iron needs to be supplemented (similar to infants with birth weights of ≥1500 g).

Growth Monitoring of LBW Infants

Regular growth monitoring helps in assessing the nutritional status and adequacy of feeding in LBW infants; it also identifies those infants with inadequate weight gain.

All LBW infants should be weighed daily till the time of discharge from the hospital. Other anthropometric parameters such as length and head circumference should be recorded weekly.

Both term and preterm LBW infants tend to lose weight (about 10% and 15% respectively) in the first 7 days of life; they regain their birth weight by 10–14 days.

Table 8.14: Nutritional supplements for infants with birth weight between 1500 g and 2499 g

Nutrients	*Method of supplementation*	*Dose*	*Duration*
Vitamin D	Multivitamin drops or syrup	400 IU/day	2 weeks to 1 yr of age
Iron	Iron drops or syrup	2 mg/kg/day (maximum 15 mg)	6–8 weeks to 1 yr of age

Thereafter, the weight gain should be at least 15–20 g/kg/day till a weight of 2–2.5 kg is reached. After this, a gain of 20 to 40 g/day is considered appropriate.

Growth charts. Using a growth chart is a simple but effective way to monitor the growth. Serial plotting of weight and other anthropometric indicators in the growth chart allows the individual infant's growth to be compared with a reference standard. It helps in early identification of growth faltering in these infants.

The two postnatal charts that are most commonly used for growth monitoring of preterm VLBW infants are: Wright's and Ehrenkranz' charts. Once the preterm LBW infants reach term gestation (40 week), WHO growth charts should be used for growth monitoring.

Management of Inadequate Weight Gain

Inadequate weight gain is a common and pertinent problem in LBW infants. It starts at the time of initial admission and continues after discharge resulting in failure to thrive and wasting in the first year of life. The common causes are summarized in Table 8.15.

Table 8.15: Causes of inadequate weight gain

Inadequate intake
Breastfed infants
Incorrect feeding method (improper positioning or attachment)*
Less frequent breastfeeding, not feeding in the night hours*
Infants on spoon or paladai feeds
Incorrect method of feeding* (e.g. excess spilling)
Incorrect measurement or calculation
Infrequent feeding*
Not fortifying the milk in VLBW infants
Increased demands
Hypothermia or cold stress*
Chronic illnesses, bronchopulmonary dysplasia
Medications such as corticosteroids

*Common causes

Management of inadequate weight gain consists of the following steps:

i. Proper counseling of mothers and ensuring adequate support for breastfeeding their infants; including an assessment of positioning/attachment and managing sore or flat nipple.
ii. Explaining the frequency and timing of both breast-feeding and spoon or *paladai* feeds: Infrequent feeding is one of the commonest causes of inadequate weight gain. Mothers should be properly counseled regarding the frequency and the importance of night feeds. A time-table where mother can fill the timing and amount of feeding is very helpful in ensuring frequent feeding.
iii. Giving EBM by spoon or *paladai* feeds after breast-feeding also helps in preterm infants who tire out easily while sucking from the breast.
iv. Proper demonstration of the correct method of expression of milk and *paladai* feeding: It is important to observe how the mother gives *paladai* feeds; the technique and amount of spillage should be noted. This should be followed by a practical demonstration of the proper procedure.
v. Initiating fortification of breast milk when indicated

Suggested Reading

Nutrition. In: Edmond K, Bahl R (Eds). Optimal feeding of low-birth-weight infants—Technical Review. World Health Organization 2006; p42

Sankar MJ, Agarwal R et al. Feeding of low birth weight infants. Indian J Pediatr 2008;75:459–69

INFECTIONS IN THE NEONATES

Infection by bacteria constitutes a common morbidity and accounts for nearly one-third of total neonatal deaths. Infections can be superficial and systemic.

Superficial Infections

Omphalitis. Any redness or induration around the umbilicus or pus drainage from it should alert the clinician to omphalitis. *Omphalitis* starts as a local infection of the umbilicus, usually from unclean handling or application of unclean substances to the cord. It can spread to cause life-threatening systemic sepsis.

Local infection. When the redness extends to less than 1 cm of surrounding area and there is absence of any sign of sepsis. Local cleaning with antiseptic solution, followed by application of 0.5% gentian violet four times a day till redness subsides would take care

Severe infection. When area of redness extends beyond 1 cm of surrounding tissue or there are signs of sepsis local therapy plus systemic antibiotic should be started as in management of septicemia.

Oral thrush. White patchy lesions on the oral mucosa and tongue can occur in healthy newborns. True oral thrush lesions are difficult to wipe off and leave hemorrhagic points when removed. Local nystatin or clotrimazole application four times a day after feed is recommended.

Conjunctivitis. Conjunctivitis is caused by a variety of bacterial, viral and chalamydial infections. Infection should be differentiated from sticky eyes and blocked nasolacrimal duct. Sticky eyes generally manifests as mucoid discharge without any signs of inflammation and requires cleaning with saline.

Blocked nasolacrimal duct manifests as persistent or intermittent discharge which can be mucopurulent. It requires massage to relieve obstruction and instillation of antibitiocs. Conjunctivitis manifests as purulent discharge and signs of inflammation and requires local instillation

of antibiotics. Gonococcal conjuctivtis can result in blindness and requires timely systemic antibiotics therapy.

Systemic Infections (Neonatal Sepsis)

When pathogenic organisms gain access into the blood stream, they may cause an overwhelming infection without much localization (septicemia), or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis). Systemic bacterial infections are known by the generic term neonatal sepsis (NNS), which incorporates septicemia, pneumonia and meningitis.

Etiology

Escherichia coli, *Staphylococcus aureus* and *Klebsiella* sp. are the predominant organisms. Organisms like *Acinetobacter*, *Pseudomonas* and coagulase negative staphylococci are also important pathogens in hospital acquired infections.

Early Versus Late Sepsis

Early-onset sepsis (EOS) (less than 72 hr) infections are caused by organisms prevalent in the maternal genital tract or in the delivery area. The predisposing factors include LBW, prolonged rupture of membranes, foul smelling liquor, multiple per vaginal examinations, maternal fever, difficult or prolonged labor and aspiration of meconium. EOS frequently manifests as pneumonia and less commonly as septicemia or meningitis.

Late-onset sepsis (LOS) (72 hr or later) infections are caused by the organisms thriving in the external environment of the home or the hospital. The infection is often transmitted through the hands of the care-providers. The presentation is that of septicemia, pneumonia or meningitis. The predisposing factors include LBW, lack of breastfeeding, poor cord care, superficial infections (pyoderma, umbilical sepsis), aspiration of feeds and disruption of skin integrity with needle pricks and use of intravenous fluids.

Clinical Features

NNS often manifests with vague and ill-defined symptoms and, therefore, requires high index of suspicion for early diagnosis. An early but non-specific manifestation is alteration in the established feeding behavior. The baby, who had been active and sucking normally, refuses to suck and becomes lethargic, or unresponsive. Poor cry, hypothermia, abdominal distension, vomiting and apneic spells are other common manifestations. Diarrhea is uncommon. Fast breathing, chest retractions and grunt indicate pneumonia. Most cases of meningitis do not have any distinct clinical picture per se, making it mandatory to suspect meningitis in all cases suspected of sepsis. Though the presence of excessive or high-pitched crying, fever, seizures, blank look, neck retraction or bulging anterior fontanel are suggestive of meningitis. Shock, bleeding, sclerema and renal failure are indicators of overwhelming sepsis.

Diagnosis of sepsis is fraught with poor specificity. A host of conditions like hypothermia, hyperthermia, hypoglycemia, hypoxia, late metabolic acidosis, congestive heart failure and even simple conditions like nasal block may mimic sepsis. A careful clinical examination and relevant investigations are necessary to differentiate these conditions from NNS and avoid unnecessary antibiotics therapy. Babies who are clinically stable can be observed, without admission and intravenous antibodies, while providing good supportive care (Fig. 8.40).

Investigations

No investigation is required to start treatment in a sick baby who has high probability of sepsis. Blood culture provides definitive diagnosis of NNS and should be taken before starting antimicrobial therapy. After cleaning the skin (alcohol, povidone-iodine and again alcohol, a specimen of 0.5 to 1.0 ml of blood can be taken in a small culture media bottle containing 5 to 10 ml of the liquid broth.

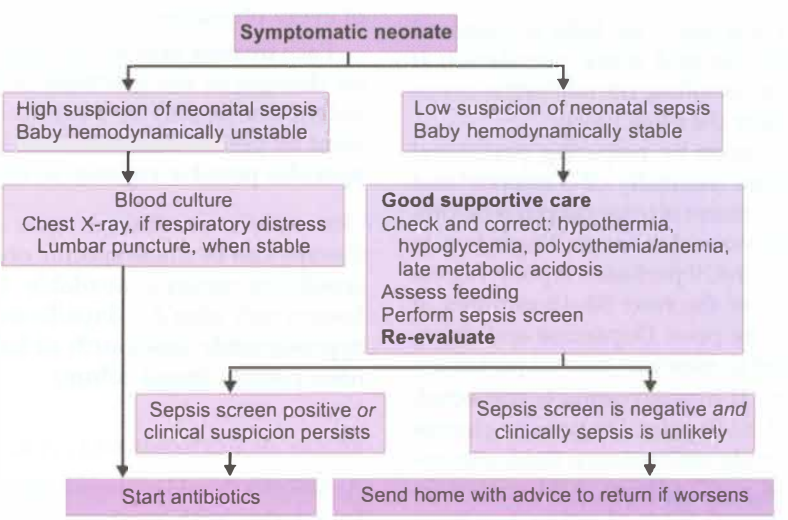


Fig 8.40: Approach to neonate suspected of sepsis

Sepsis screen should be performed in equivocal cases. A panel of tests (sepsis screen) consisting of total leukocyte count (TLC; <5000/mm^3), absolute neutrophil count (ANC; <1800/mm^3), immature to total neutrophil ratio (I/T ratio; more than 20%), CRP (more than 1 mg/dl) and micro ESR (15 mm or more in the first hour) constitutes a useful sepsis screen for clinically doubtful cases. Sepsis screen is considered positive if two of these parameters are positive. Value of sepsis screen is more for exclusion of diagnosis of NNS.

Lumbar puncture should be performed in all cases suspected of NNS except in asymptomatic babies being investigated for maternal risk factors. Table 8.16 provides gestation specific cut offs for values of various parameters in cerebrospinal fluid.

Table 8.16: Normal CSF examination in neonates [(mean (range)]

Test	*Term*	*Preterm*
Cells		
Leukocytes	7 (0–32)	9 (0–29)
Polymorphonuclear cells	61%	57%
Protein (mg/dl)	90 (20–170)	115 (65–150)
Glucose (mg/dl)	52 (34–119)	50 (24–63)

Treatment

Institution of prompt treatment is essential for ensuring optimum outcome of neonates with sepsis who often reach the health care facilities late and in a critical condition. Supportive care and antibiotics are the two *equally important* components of treatment. Antibiotics take at least 12 to 24 hr to show any effect, optimum supportive care improves the outcomes in sick septic babies.

Supportive care Good supportive care requires meticulous attention to various aspects:

- Provide warmth; ensure normal temperature (36.5°–37.5°C).
- Start oxygen by hood or mask, if the baby is cyanosed or grunting. Provide bag and mask ventilation if breathing is inadequate. Instilling normal saline drops in nostrils may help clear the nasal block.
- Assess peripheral perfusion by palpating peripheral pulses, capillary refill time (normally <2–3 seconds) and skin color. Serial measurement of urine output is helpful for this purpose. Infuse normal saline or Ringer lactate 10 ml/kg over 5–10 minutes, if perfusion is poor. Repeat the same 1–2 times over the next 30–45 minutes, if perfusion continues to be poor. Dopamine and dobutamine may be required to maintain normal perfusion.
- Insert intravenous line. If hypoglycemia is suspected, infuse glucose (10%) 2 ml/kg stat. Do not use glucose boluses routinely. Provide maintenance fluid, electrolytes and glucose (4–6 mg/kg/min). Add potassium to IV fluids once normal flow of urine has been documented.
- Ensuring optimal nutrition is extremely helpful in sick babies. Enteral feeds should be initiated early if there is no abdominal distension and baby is hemodynamically stable. Feed mother's milk. Consider parenteral nutrition, if baby is not expected to receive enteral feeds for prolonged period.
- Administer vitamin K 1 mg intramuscularly.
- Transfuse packed cells, if baby has a low hematocrit (less than 35–40%). *Do not use blood/plasma transfusion on routine basis for 'boosting' immunity.*

Specific care *Antimicrobial therapy* constitutes the mainstay of treatment of sepsis. In a seriously sick neonate suspected of sepsis, appropriate antibiotics therapy should be initiated without any delay after obtaining blood samples for culture and sepsis screen. One need not await for the results of sepsis screen for antibiotics treatment. However, in a baby who is otherwise stable or suspected of sepsis because of maternal risk factors, it is desirable to await results of sepsis screen before initiation of antibiotics. Since symptoms suggestive of sepsis may be caused by a variety of other illnesses, confirmation of sepsis by sepsis screen may help avoiding unnecessary antibiotics therapy.

Empiric therapy when etiologic agent is not known. The empiric therapy of NNS should cover the major causative pathogens while awaiting reports of culture studies.

Since the antimicrobial spectrum and susceptibility profile is different in different settings, there cannot be a universal policy of empiric regimen. Antibiotics are often used in neonates on the slightest suspicion of sepsis because of the grave and fulminant nature of neonatal sepsis. But unbridled overuse of antibiotics is associated with the serious risk of emergence of resistant strains of pathogens. Most newborn units in the country are facing the problem of overwhelming resistance to practically all antibiotics including third generation cephalosporins. Rational use of antibiotics is, therefore, the responsibility of every physician.

Each treating unit should adopt a suitable policy. Based on changes in the spectrum of etiologic agents and the antibiotics sensitivity pattern, the choice of antibiotics must be periodically reviewed and modified. Table 8.17 provides possible regimen of empiric antibiotics.

Therapy after an etiologic agent is known. Antimicrobial therapy can be made specific once a positive culture and sensitivity report is available. However, this would be known only after 2–3 days. Even in best institutions, only approximately one-fourth of babies suspected of sepsis have positive blood culture.

Mode of Administration and Dosage

Antibiotics should preferably be administered parenterally. In a baby with septicemia or pneumonia (but not meningitis), who has received intravenous ampicillin and

Table 8.17: Choice of initial antibiotic therapy

Clinical situation	*Septicemia and pneumonia*	*Meningitis*
Community acquired; resistant strains unlikely	Ampicillin or penicillin and gentamicin (First line)	Cefotaxime and gentamicin
Hospital acquired or when there is a low to moderate probability of resistant strains	Ampicillin or cloxacillin and amikacin (Second line)	Cefotaxime and amikacin
Hospital acquired sepsis or when there is a high probability of resistant strains	Cefotaxime and amikacin (Third line)	Cefotaxime and amikacin

Therapy might be modified based on culture report

gentamicin initially and is clinically well after 3 days, the physician may consider an individual basis switching over to oral amoxycillin along with single-dose intramuscular gentamicin therapy for the rest of the course.

Monitoring

Intensive care and monitoring is the key determinant of improved survival of neonates. The elements of monitoring in sepsis are not different from those in other life-threatening conditions. Proper monitoring of sick babies enables care providers detection of complications at the earliest. The periodicity of documenting the various parameters should be individualized.

Prognosis

The outcome depends upon weight and maturity of the infant, type of etiologic agent, its antibiotic sensitivity pattern; and adequacy of specific and supportive therapy. The early-onset septicemia carries higher risk of adverse outcomes. The reported mortality rates in neonatal sepsis in various studies from India ranges between 45–58%. The institution of sepsis screen for early detection of infection, judicious and early antimicrobial therapy, close monitoring of vital signs and intensive supportive care are the most crucial factors responsible for a better outcome.

Suggested Reading

Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr. 2008 Mar;75:261–6

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) occurs among smaller premature infants, often those less than 32 week. The clinical picture mimicks neonatal septicemia because of the presence of abdominal distension, apnea, bradycardia, instability of temperature, cyanosis and lethargy.

NEC is believed to result from interaction of several factors such as gut immaturity, mucosal injury due to hypoxia-ischemia, milk feeding and infection. Antenatal steroids and breastfeeding protect against NEC. Delaying enteral feeding does not prevent NEC.

Clinical Features

The illness usually develops after the first week of life. The course may be very fulminant with death occurring in a few hours, mortality rate being around 40–50%.

Clinical manifestations may be described in three stages:

Stage 1. Suspected NEC: Unstable temperature, apnea, bradycardia, lethargy, mild abdominal distension, vomiting. Frank or occult, blood may be present in stools. X-ray shows mild intestinal distension.

Stage 2. Clinical signs as similar to stage 1. Bowel sounds are diminished with or without abdominal tenderness. Pneumatosis intestinalis (gas in intestinal wall) and dilatation of intestines are seen on abdominal X-ray (Fig. 8.41).

Stage 3. In addition to the above, the infant is severely sick with hemodynamic instability. There are frank signs of peritonitis with abdominal wall redness. Pneumoperitoneum may occur due to intestinal perforation.

Management

Oral feeding should be withheld. A nasogastric tube is inserted to relieve distension and to aspirate stomach contents. Fluids and electrolytes in adequate quantities should be administered. Parenteral nutrition may be administered.

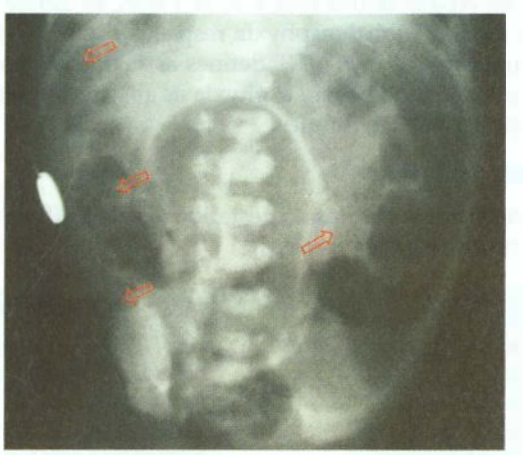


Fig. 8.41: Necrotizing enterocolitis showing dilated bowel loops and pneumatosis intestinalis (arrows)

The blood, cerebrospinal fluid, urine and stools are cultured. Shock is managed by replacement of fluids and use of vasopressor agents. Plasma and platelet transfusion may be necessary to prevent bleeding tendency.

Perforation is suggested if there is free intra-abdominal gas and liver dullness is obliterated. Surgical intervention is required in these cases.

Sequelae

Intestinal strictures may develop in survivors. These manifest with bloody stools, vomiting and abdominal distention. Shortened bowel leads to malabsorption.

PERINATAL ASPHYXIA

Perinatal asphyxia is an insult to the fetus or newborn due to a lack of oxygen (hypoxia) and/or a lack of perfusion (ischemia) to various organs. It is often associated with tissue lactic acidosis and hypercarbia.

There is no universally accepted definition of perinatal asphyxia. The American Academy of Pediatrics Committee on Fetus and Newborn has suggested essential criteria (Tables 8.18 and 8.19) for defining perinatal asphyxia.

Table 8.18: Essential criteria for perinatal asphyxia

Prolonged metabolic or mixed acidemia (pH <7.0) on an umbilical arterial blood sample
Persistence of Apgar score of 0–3 for >5 min
Neurological manifestations, e.g. seizures, coma, hypotonia or hypoxic ischemic encephalopathy (HIE) in the immediate neonatal period
Evidence of multiorgan dysfunction in the immediate neonatal period

In the absence of such quantification, it is better to use the term 'neonatal depression', which refers to a condition of the infant in the immediate postnatal period (approximately 1st hr) without making any association with objective evidence.

National Neonatology Forum of India (NNF) and WHO use an Apgar of 0–3 and 4–7, at 1 min, to define severe and moderate birth asphyxia respectively (1985). For the community settings NNF defines asphyxia as absence of cry at 1 min and severe asphyxia as absent or inadequate breathing at five minutes.

Neuropathology

These differ according to gestation (Table 8.20) and are of the following main types:

Table 8.20: Neurological patterns of hypoxic ischemic encephalopathy

Premature newborns
Selective subcortical neuronal necrosis
Periventricular leukomalacia
Focal and multifocal ischemic necrosis
Periventricular hemorrhage or infarction
Term newborns
Selective cortical neuronal necrosis
Status marmoratus of basal ganglia and thalamus
Parasagittal cerebral injury
Focal and multifocal ischemic cerebral necrosis

Term

Selective neuronal necrosis involves cerebral cortex, hippocampus, basal ganglia, cerebellum and anterior horn cells of spinal cord. Seen predominantly in term infants and depending on site, this manifests clinically as diminished consciousness, seizures and abnormalities of feeding, breathing, etc. Parasagittal area is a watershed area for many arteries and is vulnerable to ischemia resulting in proximal limb weakness (upper >lower) that later may develop into spastic quadriparesis. Status marmoratus is a variant of selective neuronal necrosis involving basal ganglia and thalamus, having longterm sequelae such as choreoathetosis, spastic quadriparesis and retardation. Focal necroses are commonly thromboembolic and involve the left middle cerebral artery.

Preterm

Selective neuronal necrosis is rare in preterms; diencephalic neuronal necrosis restricted to thalamus and brainstem with or without hypothalamus and lateral geniculate body is seen. Hypoxia and acidosis followed by hyperoxia demonstrates a unique pattern of injury involving pontine nucleus and subiculum of the hippocampus.

Periventricular leukomalacia (PVL) results from hypoxic-ischemic insult leading to coagulative necrosis and infarction of periventricular white matter that is the watershed area between various arteries. Two areas frequently involved are the posterior white matter, involving the occipital radiation at trigone and anteriorly around the foramen of Munro. Relative sparing of the cerebral cortex is seen due to its rich supply of arteries. Longterm sequelae of PVL include spastic diplegia and

Table 8.19: Multiorgan dysfunction in perinatal asphyxia

Central nervous system	Hypoxic ischemic encephalopathy, cerebral edema, longterm neurological sequelae
Pulmonary	Pulmonary hypertension, meconium aspiration, surfactant disruption
Renal	Acute renal failure
Metabolic	Metabolic acidosis, hypoglycemia, hypocalcemia, hyponatremia
Gastrointestinal	Necrotizing enterocolitis, hepatic dysfunction
Hematological	Thrombocytopenia, disseminated intravascular coagulation

quadriplegia (lower limbs >upper limbs) and visual impairment. Posthemorrhagic infarcts are usually associated with severe intraventricular bleeds and result from venous infarction due to occlusion of medullary and terminal veins by the large bleed. Other lesions include small infarcts secondary to blocking of end arteries resulting in porencephaly, hydrancephaly or multicystic encephalomalacia.

Diagnosis and Approach

Hypoxia is an evolving process that starts at the onset of the insult and continues after resuscitation and thereafter manifests in form of sequelae. Management thus depends on which point in this evolution it is detected; with the preventive approach beginning in the prenatal period and then continuing in the form of a long followup much after the stabilization of the initial condition.

A wide spectrum of clinical manifestations is seen depending on the severity of injury. These manifestations change over time and are clinically noted in babies of gestational age more than 36 weeks by classification on the basis of Levenestages of HIE (Table 8.21).

HIE staging helps predict evolution of the disease and longterm outcome. Babies with stage 1 has uniformly good prognosis. Adverse neurological outcomes are present in 20% of babies with stage 2 HIE. In stage 3 HIE, half of the neonates die and remaining half tend to have poor neurodevelopment outcomes.

Post-Resuscitation Management of an Asphyxiated Baby (Fig. 8.42)

i. *Temperature:* Maintain normal temperature of the baby and avoid hyperthermia. In resourceful setting, moderate induced hypothermia (core temperature of 33° to 34°C) reduces the death or severe neurodevelopmental handicap. However, the efficacy and safety of therapeutic hypothermia has not been proved in resource restricted setting (in absence of intensive care).

ii. *Oxygen:* Both hypoxia and hyperoxia can damage neurons. Oxygen saturations are maintained between 90% to 95%. CO_2 concentration in ventilated babies should be maintained between 40 and 50 mm Hg as hypocarbia as well as hypercarbia are detrimental to brain.

iii. *Perfusion:* Cerebral perfusion in asphyxiated babies is in 'pressure passive' state means there is loss of autoregulation and blood supply to the brain is entirely dependant on BPs; it decreased when BP falls and increases when BP rises. Therefore, to maintain normal perfusion pressure, a systemic mean arterial

Table 8.21: Levene classification for hypoxic ischemic encephalopathy

Feature	*Mild*	*Moderate*	*Severe*
Consciousness	Irritablity	Lethargy	Comatose
Tone	Hypotonia	Marked hypotonia	Severe hypotonia
Seizures	No	Yes	Prolonged
Sucking/respiration	Poor suck	Unable to suck	Unable to sustain spontaneous respiration

Modified from: Levene MI.The asphyxiated newborn infant. In Levene MI, Lilford RJ, ed. Fetal and neonatal neurology and neurosurgery. Churchill Livingstone, Edinburgh 1995;405–26

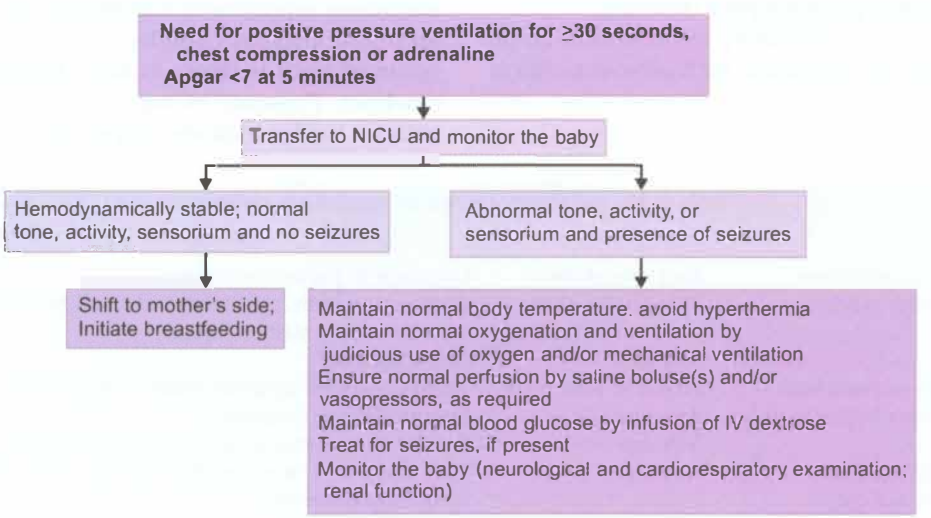


Fig 8.42: Post-resuscitation management of an asphyxiated baby

pressure of 45–50 mm Hg (term), 35–40 (1–2 kg weight) and 30–35 mm Hg (<1 kg weight) is required. Judicious use of fluid boluses and use of vasopressors help maintain BP. Hyperviscosity due to polycythemia should be corrected by partial exchange.

iv. *Glucose:* Levels between 75–100 mg/dl are recommended. Hyperglycemia enhances cerebral edema and compromise perfusion, while hypoglycemia potentiates excitotoxic damage. Hypoglycemia is commonly seen in asphyxiated infants and the infant must be regularly monitored.

v. *Metabolic profile:* Hypocalcemia and electrolyte disturbances should be regularly looked for until stabilization of baby and corrected as indicated.

vi. *Seizures:* 20%–50% of infants with HIE develop seizures during day 1 or 2. Seizures are commonly subtle or focal or multifocal. Metabolic disturbances such as hypoglycemia, hypocalcemia and hyponatremia must be ruled out. Seizures should be treated with antiepileptic drugs (AEDs) such as phenobarbitone and phenytoin. The seizures may be intractable initially but usually tend to burn out by 48 hr. Subtle seizures lasting for brief duration need not be treated.

Once the baby is seizure free for 3–4 days, AEDs are stopped in the same order as they were started, except phenobarbitone. Phenobarbitone is stopped at discharge if neurological examination is normal and baby is feeding well on breast. If neurological examination is not normal, then phenobarbitone is continued until one month. At one month if baby is normal neurologically, phenobarbitone is tapered off over a couple of days. If neurological function is abnormal but EEG shows no seizure activity, tapering of phenobarbitone may still be tried. If EEG shows seizure activity, reevaluation is done at 3 months.

8

Prognosis

The following features predict a poor outcome:

- Lack of spontaneous respiratory effort within 20–30 minutes of birth is associated with almost uniform mortality
- HIE stage 3
- Abnormal neurological findings persisting beyond the first 7–10 days of life
- Oliguria (<1 ml/kg/day) during the first 36 hr

Thus all these babies should have regular followup with monitoring of neurodevelopmental milestones to detect any deficits early and to intervene effectively.

Suggested Reading

Agarwal R, Jain A, Deorari AK, Paul VK.Post-resuscitation management of asphyxiated neonates. Indian J Pediatr 2008;75:175–80

RESPIRATORY DISTRESS

Respiratory distress in the neonate is a common problem and it can be a serious neonatal emergency. Respiratory distress is said to be present when tachypnea (RR >60 per min) is accompanied by chest retractions and or grunt. It can be due to respiratory (Table 8.22) and non-respiratory causes (Table 8.23). Early recognition and prompt treatment is essential to improve outcomes.

Approach

Respiratory distress in a neonate can be recognized by the presence of varying combinations of tachypnea (RR >60/min), chest retractions, grunting, flaring of ala enasi and cyanosis. The gestation, age at onset, severity of distress and presence of associated clinical features help in arriving at diagnosis. It should be noted that chest retractions are mild or absent in respiratory distress due to non-respiratory causes.

Respiratory causes. Conditions listed in Tables 8.22 and 8.23 can occur both in preterm and term babies. However, if a preterm baby has respiratory distress within the first few hours of life the most likely cause is respiratory distress syndrome (RDS). Similarly if a term baby born to a mother with meconium stained liquor develops respiratory distress within the first 24 hr, the most likely cause is meconium aspiration syndrome (MAS). A term baby with uncomplicated birth developing tachypnea in the first few hours of birth is likely to have transient tachypnea of newborn. Presence of suprasternal recessions with or without stridor indicates upper airway obstruction.

Table 8.22: Pulmonary causes of respiratory distress

Cause	*Time of onset*	*Remarks*
Respiratory distress syndrome	First 6 hr of life	Common in preterm neonates
Meconium aspiration syndrome	First few hr of life	Common in term, post-term and small for date babies; history of meconium stained liquor
Pneumonia	Any age	Often bacterial
Transient tachypnea of newborn	First 6 hr after birth	Tachypnea with minimal distress; lasts for 48–72 hr
Persistent pulmonary hypertension	Any age	Severe distress; cyanosis
Pneumothorax	Any age	Sudden deterioration; usually during assisted ventilation
Tracheoesophageal fistula, diaphragmatic hernia, lobar emphysema	Any age	May show associated malformations; polyhydramnios in esophageal atresia

Table 8.23: Non-pulmonary causes of rapid breathing

Cardiac	Congestive heart failure; congenital heart disease
Metabolic	Hypothermia, hypoglycemia, metabolic acidosis
Central nervous system	Asphyxia, cerebral edema, hemorrhage
Chest wall	Asphyxiating thoracic dystrophy, Werdnig-Hoffman disease

Cardiac disease. Cardiac etiology for respiratory distress should be suspected if a neonate with distress has cyanosis or hepatomegaly. Congenital heart disease and cardiomyopathies or rhythm disorders can present as congestive cardiac failure in the neonatal period. Transposition of great vessels (TGV) and hypoplastic left heart syndrome usually present on day one with progressive distress. Most other cardiac conditions present after the first week of life. A preterm neonate having a systolic murmur with tachypnea and hepatomegaly is likely to have patent ductus arteriosus (PDA).

Neurological causes. Neonates with birth asphyxia, cerebral hemorrhage, or meningitis can present with tachypnea and respiratory distress. These neonates are usually lethargic with poor neonatal reflexes.

Respiratory Distress Syndrome (RDS) or Hyaline Membrane Disease (HMD)

RDS is common in preterm babies less than 34 weeks of gestation. The overall incidence is 10–15% but can be as high as 80% in neonates <28 weeks. In addition to prematurity, asphyxia, acidosis, maternal diabetes and cesarean section can increase the risk of RDS.

Etiopathogenesis

In RDS, the basic abnormality is surfactant deficiency. Surfactant is a lipoprotein containing phospholipids like phosphatidylcholine and phosphatidylglycerol and proteins. Surfactant is produced by type II alveolar cells of lungs and helps reduce surface tension in the alveoli. In the absence of surfactant, surface tension increases and alveoli tend to collapse during expiration. During inspiration more negative pressure is needed to keep alveoli patent. There is inadequate oxygenation and increased work of breathing. Hypoxemia and acidosis result in pulmonary vasoconstriction and right to left shunting across the foramen ovale. This worsens the hypoxemia and the neonate eventually goes into respiratory failure. Ischemic damage to the alveoli causes transudation of proteins into the alveoli that forms hyaline membrane. Surfactant production starts around 20 weeks of life and peaks at 35 week gestation. Therefore any neonate less than 35 week is prone to develop RDS.

Clinical Features

Respiratory distress usually occurs within the first 6 hr of life. Clinical features include tachypnea, retractions, grunting, cyanosis and decreased air entry. Diagnosis can be confirmed by chest X-ray. Radiological features include reticulogranular pattern, ground glass opacity, low lung volume, air bronchogram (Fig. 8.43) and white out lungs in severe disease.

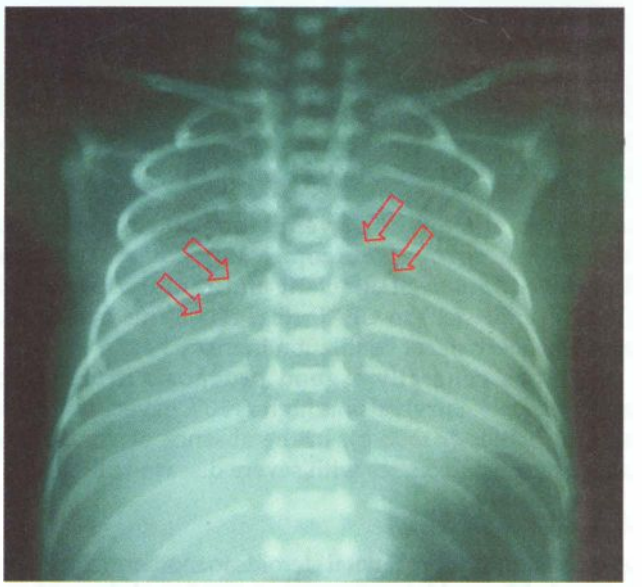


Fig. 8.43: Moderate to severe hyaline membrane disease. Note homogenous opacification of lungs obscuring heart borders and presence of air bronchogram (arrows)

Management

Neonates suspected to have RDS need to be cared for in neonatal intensive care unit with IV fluids and oxygen. Mild to moderate RDS can be managed with continuous positive airway pressure (CPAP). CPAP is a non invasive modality of support where a continuous distending pressure (5–7 cm of water) is applied at nostril level to keep the alveoli open in a spontaneously breathing baby (Fig. 8.44). This is an excellent modality of respiratory support which minimizes lung injury and other complications such as air leak and sepsis. Preterm babies developing severe RDS often require mechanical ventilation. Preterm babies are at risk of lung injury by excessive pressure and high oxygen. High saturations of oxygen (above 95%) can produce retinopathy of prematurity (ROP) which can blind the infant.

Since surfactant deficiency is the basis of RDS, exogenous surfactant is recommended as the treatment of choice in neonates with RDS. Surfactant is indicated in all neonates with moderate to severe RDS. The route of administration is intra tracheal. It can be given as a rescue treatment (when RDS actually develops) or prophylactically (all neonates less than 28 weeks irrespective of presence or absence of RDS). Surfactant decreases duration

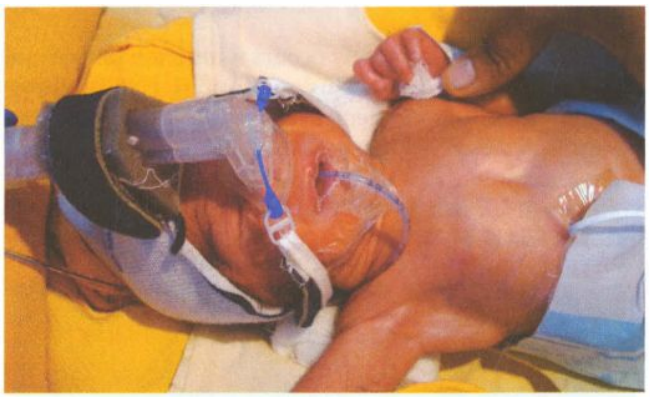


Fig. 8.44: Continuous positive airway pressure being provided to a preterm baby

and level of support of ventilation in neonates and therefore improves outcome. Many babies can be INtubated, given SURfactant and rapidly Extubated (InSurE approach) to CPAP (Fig. 8.44). This avoids the need for mechanical ventilation in many neonates.

RDS has generally a good prognosis if managed appropriately. Survival is as high as 90% in very low birth weight babies (<1500 g). In the absence of ventilatory support, most neonates with severe disease will die.

Prevention of RDS

Administration of antenatal steroids to mothers in preterm labor (<35 week) has been a major breakthrough in management of preterm infants. Antenatal steroids reduces RDS, intraventricular hemorrhage and mortality in preterm neonates (Table 8.24).

Table 8.24: Benefits of administering antenatal glucocorticoids

Reduction in neonatal mortality by 40%
Reduction in respiratory distress by 50%
Reduction in intraventricular hemorrhage by 50%
Reduction in occurrence of patent ductus arteriosus, necrotizing enterocolitis, hemodynamic instability

8

Meconium Aspiratrion Syndrome (MAS)

Meconium staining of amniotic fluid (MSAF) occur in 10%–14% of pregnancies. Neonates born through MSAF can aspirate the meconium into the lungs and develop respiratory distress (meconium aspiration syndrome; MAS). Aspirated meconium can block the large and small airway causing areas of atelectasis and emphysema which can progress to develop air leak syndromes like pneumothorax. Presence of atelectasis and emphysema can cause ventilation perfusion mismatch in these babies that can progress to respiratory failure. Meconium also induces chemical pneumonitis.

Clinical Features and Course

MAS usually occurs in term or post term babies and small for dates babies. Infants usually develops respiratory distress in the first few hours of life that often deteriorates in subsequent 24–48 hr. If untreated, distress can progress to respiratory failure. Complications include pneumothorax, other air leak syndromes (pneumopericardium, pneumomediastinum) and persistent pulmonary hypertension. Chest X-ray shows bilateral heterogeneous opacities, areas of hyperexpansion and atelectesis and air leak (Fig. 8.45).

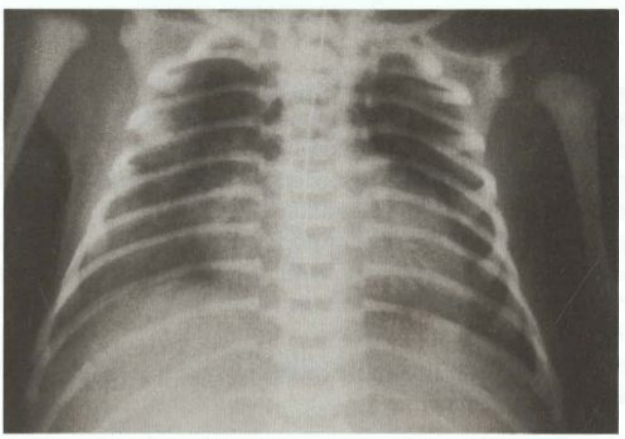


Fig. 8.45: Meconium aspiration syndrome. Note hyperexpansion of lungs and heterogeneous opacities in right lung

Management

Clinical course in these babies can be complicated by severe pulmonary hypertension. A good supportive care in terms of maintenance of normal body temperature, blood glucose and calcium levels, ensuring analgesia and avoiding unnecessary fiddling pay good dividends. Oxygenation and ventilation is maintained by judicious use of oxygen and mechanical ventilation. With ventilatory support, 60–70% neonates survive, but in the absence of ventilatory support, mortality is high in severe disease.

Persistent Pulmonary Hypertension (PPHN)

It is caused by a persistent elevation in pulmonary vascular resistance resulting in right to left shunt across the foramen ovale and/or ductus. The disease is more common in term and post-term babies and occurs as a result of persistent hypoxia and acidosis. Hypoxia and hypercarbia cause pulmonary vasoconstriction. This increases pulmonary vascular pressure and results in right to left shunting.

Common causes include asphyxia, respiratory distress due to MAS, RDS, diaphragmatic hernia, etc. Primary pulmonary hypertension can also occur because of an abnormal pulmonary vasculature secondary to chronic intrauterine hypoxia.

The neonate usually presents with severe respiratory distress and cyanosis. It is often difficult to differentiate PPHN from cyanotic congenital heart disease. Echocardiography helps in ruling out congenital heart disease and may demonstrate right to left shunt across the foramen ovale.

Ventilatory support is mandatory. Nitric oxide, a selective pulmonary vasodilator is an effective therapy.

Pneumonia

Pneumonia is a common cause of respiratory distress in both term and preterm babies and is caused by bacteria such *E. coli*, *S. aureus* and *K. pneumoniae*. Neonatal pneumonia may be due to aspiration or occasionally due to viral or fungal infection. Though group B streptococcal pneumonia is common in the West, it is uncommonly reported in India.

The neonate has features suggestive of sepsis in addition to respiratory distress. Chest X-ray shows pneumonia (Fig. 8.46), blood counts are raised and blood culture may be positive. Treatment includes supportive care and specific antibiotic therapy. Ampicillin or cloxacillin with gentamicin is usually used. If the pneumonia is due to hospital acquired infection, antibiotics like cephalosporins with amikacin may have to be used.

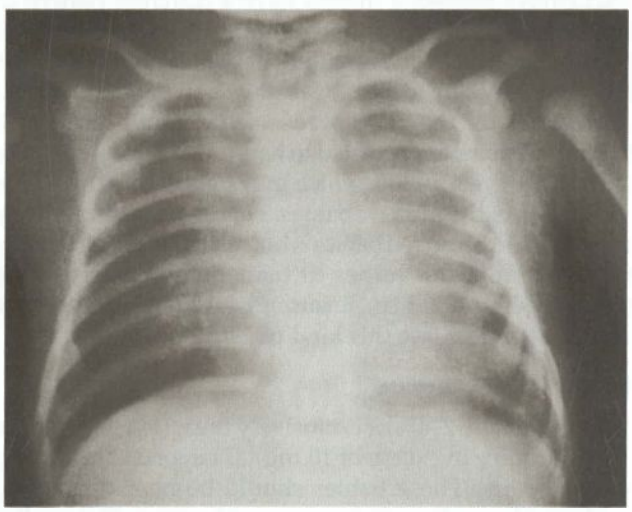


Fig. 8.46: Pneumonia. Note heterogeneous opacities in both the lung fields

Transient Tachypnea of Newborn (TTN)

Transient tachypnea of the newborn is a benign self-limiting disease occurring usually in term neonates and is due to delayed clearance of lung fluid. These babies have tachypnea with minimal or no respiratory distress. Chest X-ray may show hyperexpanded lung fields, prominent vascular marking and prominent interlobar fissure (Fig. 8.47). Oxygen treatment is often adequate. Prognosis is excellent.

Surgical Problems

Tracheoesophageal fistula (TEF) should be suspected in any neonate with excessive frothing. Diagnosis can be confirmed by a plain X-ray with a red rubber catheter (not infant feeding tube, it is soft and gets coiled up) inserted in stomach; the catheter generally stops at 10th thoracic

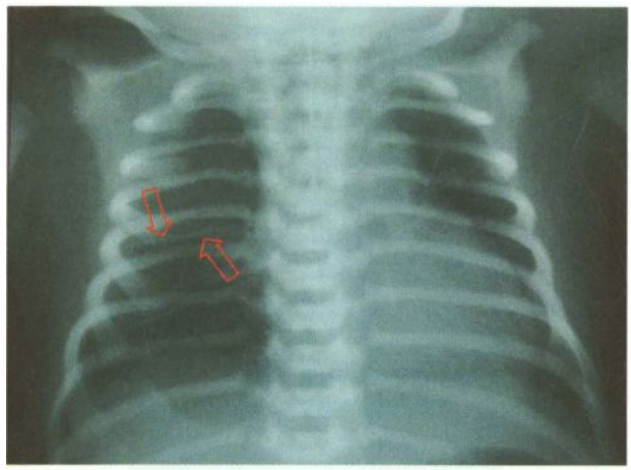


Fig. 8.47: Transient tachypnea of newborn. Note hyperinflated lungs, prominent bronchovascular markings and horizontal fissure (arrow)

vertebrae in presence of esophageal atresia. Presence of gastric bubble suggest concomitant TEF.

Diaphragmatic hernia should be suspected in any neonates who has severe respiratory distress and has a scaphoid abdomen. This condition can be detected during antenatal ultrasonography. Chest X-ray shows presence of bowel loops in the thoracic cavity.

Chronic Lung Disease (CLD) or Bronchopulmonary Dysplasia (BPD)

CLD occurs because of barotrauma and oxygen toxicity that causes damage to the alveolar cells, interstitium and blood vessels. Inflammatory mediators are released and there is increased permeability causing leakage of water and protein. In later stages, there is fibrosis and cellular hyperplasia. Severe lung damage leads to respiratory failure. These babies continue to require prolonged oxygen therapy or ventilatory support.

Pneumothorax

Presence of air in the pleural cavity (pneumothorax) is most common in babies with meconium aspiration syndrome and those being ventilated (Fig. 8.48). Transillumination of the chest can help in diagnosis. Needle aspiration or chest tube drainage is a life saving procedure in this situation.

Apnea

Apnea is defined as cessation of respiration for 20 seconds with or without bradycardia and cyanosis or for shorter periods if it is associated with cyanosis or bradycardia. Apnea is a common problem in preterm neonates. It could be central, obstructive or mixed.

Apnea of prematurity occurs in preterm neonates between the second to fifth days of life and is because of the immaturity of the developing brain. Central apnea can also occur because of pathological causes like sepsis, metabolic problems (hypoglycemia, hypocalcemia),

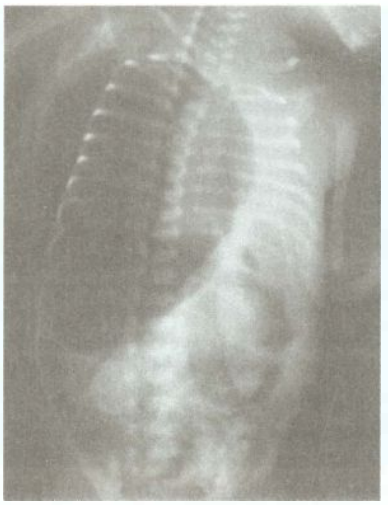


Fig. 8.48: Tension pneumothorax on right side displacing the mediastinum and pushing down the diaphragm

temperature instability, respiratory distress, anemia and polycythemia. Obstructive apnea can occur because of block to the airway by secretion or improper neck positioning.

Treatment is supportive and involves correction of underlying cause. Apnea of prematurity is treated with aminophylline or caffeine. Prognosis is good in apnea of prematurity. In other cases it depends on the underlying cause.

Suggested Reading

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8

JAUNDICE

Jaundice is an important problem in the first week of life. High bilirubin levels may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns. Nearly 60% of term newborn becomes visibly jaundiced in the first week of life. In most cases, it is benign and no intervention is required. Approximately 5–10% of them have clinically significant jaundice requiring use of phototherapy or other therapeutic options.

Physiological Versus Pathological Jaundice

Physiological jaundice represents physiological immaturity of the neonates to handle increased bilirubin production. Visible jaundice usually appears between 24–72 hr of age. Total serum bilirubin (TSB) level usually peaks by 3 days of age and then falls in term neonates. TSB levels are below the designated cut-offs for phototherapy. It does not require any treatment.

Pathological jaundice is referred to as an elevation of TSB levels to the extent where treatment of jaundice is more likely to result into benefit than harm. There is no clear cut demarcation between pathological and physiological jaundice. TSB levels have been arbitrarily defined as pathological if it exceeds 5 mg/dl on first day, 10 mg/dl on second day, or 15 mg/dl thereafter in term babies. Such jaundice warrants investigation for the cause and therapeutic intervention such as phototherapy. Appearance of jaundice within 24 hr, TSB levels above the expected normal range, presence of clinical jaundice beyond 3 weeks and conjugated bilirubin (dark urine staining the nappy) would be categorized under this category.

Breastfeeding Jaundice

Exclusively breastfed infants have a different pattern of physiological jaundice as compared to artificially-fed babies. Jaundice in breastfed babies usually appears between 24–72 hr of age, peaks by 5–15 days of life and disappears by the third week of life. One-third of all breastfed babies are detected to have mild clinical jaundice in the third week of life, which may persist into the 2nd to 3rd month of life in a few babies. This increased frequency of jaundice in breastfed babies is not related to characteristics of breast milk but rather to inadequate breastfeeding (breastfeeding jaundice). Ensuring optimum breastfeeding would help decrease this kind of jaundice.

Breast Milk Jaundice

Approximately 2–4% of exclusively breastfed term babies have jaundice in excess of 10 mg/dl beyond third-fourth weeks of life. These babies should be investigated for prolonged jaundice. A diagnosis of breast milk jaundice should be considered if this is unconjugated (not staining nappies); and other causes for prolongation such as inadequate feeding, continuing hemolysis, extravasated blood, G6PD deficiency and hypothyroidism have been ruled out. Mothers should be advised to continue breastfeeding at frequent intervals and TSB levels usually decline over a period of time. Some babies may require phototherapy. Breastfeeding should not be stopped either for diagnosis or treatment of breast milk jaundice.

Clinical Estimation

Originally described by Kramer, dermal staining of bilirubin may be used as a clinical guide to the level of jaundice. Dermal staining in newborn progresses in a cephalocaudal direction. The newborn should be examined in good daylight. The skin of forehead, chest, abdomen, thighs, legs, palms and soles should be blanched with digital pressure and the underlying color of skin and subcutaneous tissue should be noted.

Serum levels of total bilirubin are approximately 4–6 mg/dl (zone 1), 6–8 mg/dl (zone 2), 8–12 mg/dl (zone 3), 12–14 mg/dl (zone 4) and >15 mg/dl (zone 5) (Fig. 8.49). Yellow staining of palms and soles is a danger sign and requires urgent serum bilirubin estimation and further management. In general, the estimation of bilirubin levels by dermal zones is unreliable particularly at higher TSB levels, after phototherapy and when it is carried out by an inexperienced observer. Total serum bilirubin can be assessed non invasively by a transcutaneous handheld device.

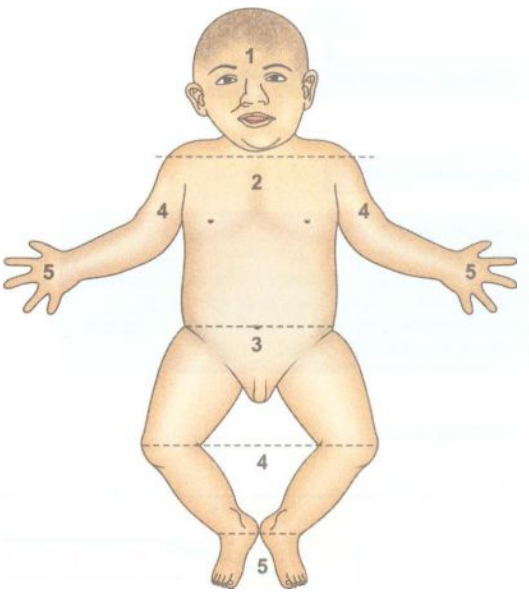


Fig. 8.49: Dermal zones for estimation of total serum bilirubin levels

Measurement of Bilirubin Levels

Newborns detected to have yellow discoloration of the skin beyond the legs, or when their clinically assessed TSB levels approach phototherapy range, should have lab confirmation of total serum bilirubin. TSB assessment has a marked interlaboratory variability.

Causes

Important causes of jaundice in neonates include:

i. Hemolytic: Rh incompatibility, ABO incompatability, G6PD deficiency, thalassemias, hereditary spherocytosis
ii. Non-hemolytic: prematurity, extravasated blood, inadequate feeding, polycythemia, idiopathic, breast milk jaundice

Risk factors for development of severe hyper bilirubinemia include:

i. Jaundice observed in the first 24 hr
ii. Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g. G6PD deficiency).
iii. Gestational age 35–36 weeks.
iv. Previous sibling received phototherapy.
v. Cephalohematoma or significant bruising.
vi. If breastfeeding is inadequate with excessive weight loss

Approach to a Jaundiced Neonate

All the neonates should be visually inspected for jaundice every 12 hr during initial 3 to 5 days of life (Fig. 8.50). Transcutaneous bilirubin (TcB) can be used as an aid for initial screening of infants. Visual assessment (when performed properly) and TcB have reasonable sensitivity for initial assessment of jaundice.

As a first step, serious jaundice should be ruled out. Phototherapy should be initiated if the infant meets the criteria for serious jaundice. Total serum bilirubin should be determined subsequently in these infants to determine further course of action.

Management

Investigations

The aim of performing investigations is to confirm the level of jaundice, identify the cause and follow response to treatment.

First line

- Total serum bilirubin (and its fractions, if jaundice is prolonged or there is yellow staining of nappies): All cases with suspected pathological levels either clinically or by trancutaneous measurements need confirmation by blood examination of serum bilirubin levels.
- Blood groups of mother and baby (if the mother is 'O' or Rh negative): detects any incompatibility
- Peripheral smear: evidence of hemolysis

Second line

- Direct Coombs test: detects presence of antibody coating on fetal RBC
- Hematocrit: decreased in hemolysis
- Reticulocyte count: increased in hemolysis
- G6PD levels in RBC
- Others: sepsis screen; thyroid function test; urine for reducing substances to rule out galactosemia; specific enzyme/genetic studies for Crigler-Najjar, Gilbert and other genetic enzyme deficiencies

Physiological Jaundice

The parents should be explained about the benign nature of jaundice. The mother should be encouraged to breastfeed frequently and exclusively. Mother should be told to bring the baby to the hospital if the baby looks deep yellow or palms and soles have yellow staining. There is no use to expose the baby to direct sunlight to reduce hyperbilirubinemia.

Any newborn discharged prior to 72 hr of life should be evaluated again in the next 48 hr for assessment of adequacy of breastfeeding and progression of jaundice.

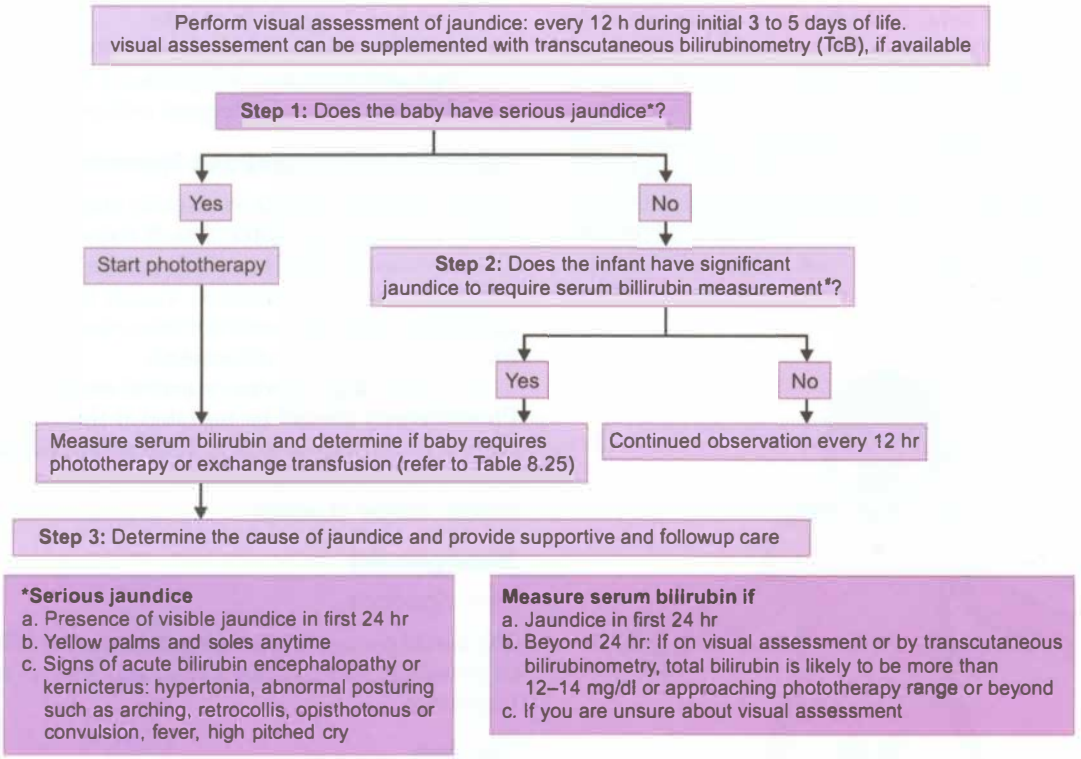


Fig 8.50: Approach to an infant with jaundice

Pathological Jaundice

Term and near term neonates The American Academy of Pediatrics (AAP), has laid down criteria for managing babies with elevated serum bilirubin (Figs 8.51 for phototherapy and 8.52 for exchange transfusion). Both the Figs have age in hours on the X-axis and TSB levels on Y-axis. There are three curves on each Fig. representing three risk categories of babies defined by gestation and other risk factors. Risk factor refer to hemolysis, asphyxia, acidosis, low albumin level, G6PD deficiency, hypothemia and sickness.

Preterm neonates Table 8.25 provides cutoffs for exchange transfusion and phototherapy in preterm neonates below 35 weeks of gestation.

Table 8.25: Suggested TSB cut-offs for phototherapy and exchange transfusion in preterm infants <35 weeks

Gestation (completed weeks)	*Phototherapy*	*Exchange transfusion*
<28	5–6	11–14
28 to 29	6–8	12–14
30 to 31	8–10	13–16
32 to 33	10–12	15–18
34	12–14	17–19

Use postmenstrual age (for phototherapy for example, when a 29 week infant is 7 days old, use the TSB level for 30 weeks).
(Adapted with permission from Maisels et al, Jour Perinatol, 2012)

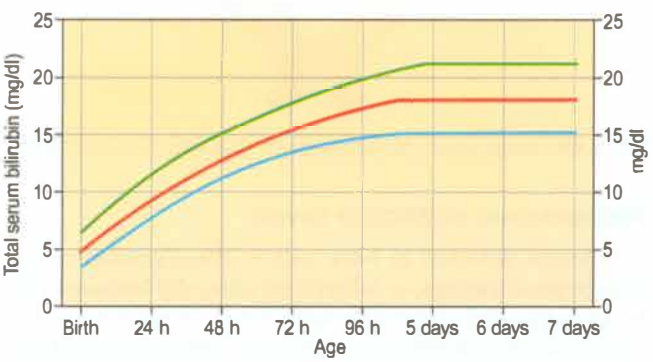


Fig. 8.51: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation. — Infants at lower risk (>38 week and well) — Infants at medium risk (>38 week + risk factors or 35–37 6/7 week and well) — Infants at higher risk (35–37 6/7 week + risk factors)

Prolonged Jaundice Beyond 3 Weeks

This is defined as persistence of significant jaundice (10 mg/dl) beyond three weeks in a term baby. The common causes include inadequate feeding, breast milk jaundice, extravasated blood (cephalohematoma), ongoing hemolytic disease, G6PD deficiency and hypothyroidism. One should rule out cholestasis by noting the urine and stool color and checking the level of direct bilirubin. If the baby has dark urine or significant jaundice, investigations should be initiated to rule out:

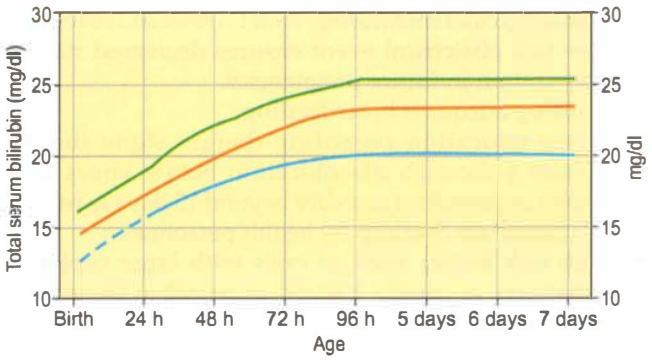


Fig. 8.52: Guidelines for exchange transfusion in infants 35 or more weeks' gestation. — Infants at lower risk (> 38 week and well) — Infants at medium risk (> 38 week + risk factors or 35–37 6/7 week and well) — Infants at higher risk (35–37 6/7 week + risk factors) (Adapted from AAP 2004)

i. Cholestasis (stool color, urine color, direct and indirect bilirubin levels)
ii. Ongoing hemolysis, G6PD screen
iii. Hypothyroidism
iv. Urinary tract infection

Phototherapy Phototherapy remains the mainstay of treating hyperbilirubinemia in neonates. Photocopy is highly effective and carries an excellent safety track record of over 50 yr. It acts by converting insoluble bilirubin (unconjugated) into soluble isomers that can be excreted in urine and feces. Many review articles have provided detailed discussion on phototherapy related issues. The bilirubin molecule isomerizes to harmless forms under blue-green light (460–490 nm); and the light sources having high irradiance in this particular wavelength range are more effective than the others.

For phototherapy to be effective, bilirubin needs to be present in skin so there is no role for prophylactic phototherapy. Phototherapy acts by several ways:

- *Configurational isomerization:* Here the Z-isomers of bilirubin are converted into E-isomers. The reaction is instantaneous upon exposure to light but reversible as bilirubin reaches into the bile duct. After exposure of 8–12 hr of phototherapy, this constitutes about 25% of TSB, which is nontoxic. Since this is excreted slowly from body this is not a major mechanism for decrease in TSB.
- *Structural isomerization:* This is an irreversible reaction where the bilirubin is converted into lumirubin. The reaction is directly proportional to dose of phototherapy. This product forms 2–6% of TSB which is rapidly excreted from body thus is mainly responsible for phototherapy induced decline in TSB.
- *Photo oxidation:* This is a minor reaction, where photo-products are excreted in urine.

Types of phototherapy lights. The phototherapy units available in the market have a variety of light sources that include florescent lamps of different colors (cool white, blue, green, blue-green or turquoise) and shapes (straight or U-shaped commonly referred as compact florescent lamps, i.e. CFL), halogen bulbs, high intensity light emitting diodes (LED) and fibro-optic light sources.

With the easy availability and low cost in India, CFL phototherapy is being most commonly used device. Often, CFL devices have four blue and two white (for examination purpose) CFLs but this combination can be replaced with 6 blue CFLs in order to increase the irradiance output.

In last couple of years, blue LED is making inroads in neonatal practice and has been found to at least equally effective. LED has advantage of long life (up to 50,000 hr) and is capable of delivering higher irradiance than CFL lamps.

Maximizing the efficacy of phototherapy. The irradiance of phototherapy lights should be periodically measured and a minimum level of 30 microW/cm^2/nm in the wavelength range of 460 to 490 nm must be ensured. The lamps should be changed if the lamps are flickering or ends are blackened, if irradiance falls below the specified level or as per the recommendation of manufacturers.

Expose maximal surface area of the baby (Fig. 8.53). Avoid blocking the lights by any equipment (e.g. radiant warmer), a large diaper or eye patch, a cap or hat, tape, dressing or electrode, etc. ensure good hydration and nutrition of the baby. Make sure that light falls on the baby perpendicularly if the baby is in incubator. Minimize interruption of phototherapy during feeding sessions or procedures.

Administering phototherapy. Make sure that ambient room temperature is optimum 25° to 28°C to prevent hypothermia or hyperthermia in the baby. Remove all clothes of the baby except the diaper. Cover the baby's eyes with an eye

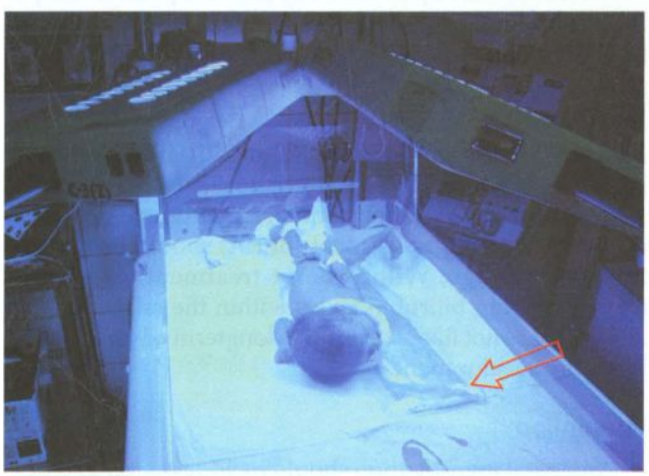


Fig. 8.53: A jaundiced baby receiving phototherapy with two overhead units and biliblanket pad (arrow)

patch, ensuring that it does not block baby's nostrils. Place the naked baby under the lights in a cot or bassinet if weight is more than 2 kg or in an incubator or radiant warmer if the baby is small (<2 kg). Keep the distance between baby and light 30 to 45 cm (or as per manufacturer recommendation).

Ensure optimum breastfeeding. Baby can be taken out for breastfeeding sessions and the eye patch can be removed for better mother-infant interaction. However, minimize interruption to enhance effectiveness of phototherapy. There is no need to supplement or replace breast milk with any other types of feed or fluid (e.g. breast milk substitute, water, sugar water, etc.).

Monitoring and stopping phototherapy. Monitor temperature of the baby every 2 to 4 hr. Measure TSB level every 12 to 24 hr.

Discontinue phototherapy once two TSB values 12 hr apart fall below current age specific cut offs. The infant should be monitored clinically for rebound bilirubin rise within 24 hr after stopping phototherapy for babies with hemolytic disorders.

Exchange Transfusion

Double volume exchange transfusion (DVET) should be performed if the TSB levels reach to age specific cut-off for exchange transfusion (Fig. 8.52 and Table 8.25) or the infant shows signs of bilirubin encephalopathy irrespective of TSB levels.

Indications for DVET at birth in infants with Rh isoimmunization include:

i. Cord bilirubin is 5 mg/dl or more
ii. Cord Hb is 10 g/dl or less

At birth, if a baby shows signs of hydrops or cardiac decompensation in presence of low PCV (<35%), partial exchange transfusion with 50 ml/kg of packed red blood cells should be done to quickly restore oxygen carrying capacity of blood.

The ET should be performed by pull and push technique using umbilical venous route. Umbilical catheter should be inserted just enough to get free flow of blood.

Followup

Babies with serum bilirubin ≥20 mg/dl and those who require exchange transfusion should be kept under followup in the high-risk clinic for neurodevelopmental outcome. Hearing assessment (BERA) should be done at 3 months of age. With prompt treatment, even very elevated serum bilirubin levels within the range of 25 to 29 mg/dl are not likely to result in longterm adverse effects on neurodevelopment.

Prevention

- Antenatal investigation should include maternal blood grouping. Rh positive baby born to a Rh negative mother is at higher risk for hyperbilirubinemia and requires greater monitoring. Anti D (RhoGam) injection after first obstetrical event ensures decreased risk of sensitization in future pregnancies.
- Ensuring adequate breastfeeding
- Parent education regarding danger signs should include yellowish discoloration below knees and elbows or persistent jaundice beyond 15 days as reason for immediate checkup by health personnel.
- High risk babies such as ones with large cephalohematoma or family history of jaundice should be followed up after 2–3 days of discharge.

CONGENITAL MALFORMATIONS

Tracheoesophageal Fistula (TEF)

Upper part of esophagus is developed from retropharyngeal segment and the lower part from pregastric segment of the first part of the primitive gut. At four weeks of gestation, the laryngotracheal groove is formed. Later, two longitudinal furrows develop to separate the respiratory primordium from the esophagus. Deviation or altered cellular growth in this septum results in formation of tracheoesophageal fistulae. Incidence is 1 in 4000 live births. In the most common variety (over 80% of cases), the upper part of the esophagus ends blindly and the lower part is connected to the trachea by a fistula.

Clinical Features

The presence of maternal polyhydramnois and single umbilical artery should alert the health provider to look for atresia of the upper digestive tract. Association of congenital anomalies of vertebrae, anorectal region, heart, kidneys or limbs should also arouse suspicion. The newborn baby has excessive drooling soon after birth with frothing. There is choking and cyanosis on feeding. Overflow of milk and saliva from esophagus and regurgitation of secretion through the fistulous tract (when present) into the lungs results in aspiration pneumonia.

Diagnosis

A stiff red rubber catheter cannot be passed into stomach as it gets arrested at a distance of 7–10 cm from the mouth (Fig. 8.54). A skiagram may be obtained after instilling 1–2 ml of air through the catheter. It is not advisable to use barium as a contrast material since it may be aspirated in lungs.

On X-ray, an air bubble is seen in the stomach if there is communication between the lower part of the esopagus and trachea, which occurs in the commonest variety of tracheoesophageal fistula. In other variety, wherein there is no communication of esophagus and trachea, there will be no gas in stomach.

Management

The baby should be nursed supine or in an upright position and esophageal pouch should be gently sucked

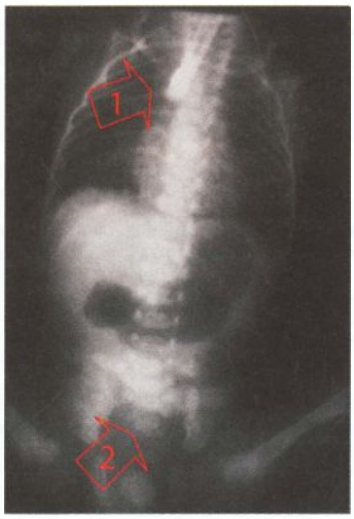


Fig. 8.54: Esophageal atresia with tracheoesophageal fistula. Note the red rubber catheter stopping at T4 level (arrow 1). There is a double gas bubble sign indicating presence of concomitant duodenal atresia (arrow 2)

every five minutes, or continuously using a slow suction device. Intravenous fluids should be administered and infection, if any should be treated. Surgical repair should be undertaken as early as possible.

Anorectal Malformation

A variety of anorectal anomalies have been described. These may be anatomically classified as high, intermediate or low. The position is determined by the relation of terminal part of bowel to the puborectalis sling. High or intermediate lesions are more common in males. Anal stenosis or covered anus, anocutaneous fistulae are common in both sexes. Anovestibularfistula (low lesion) in females and anorectal agenesis with rectoprostatic urethral fistula (high lesion) are common in male infants.

Among the males with high or intermediate lesions, 80% are rectovesical fistulae, but among the females with high defect, 80% have a rectovaginal fistula. There are significant chances of associated anomalies in case of higher anorectal anomalies.

An X-ray film of the abdomen is obtained 12–24 hr after birth, with the baby being kept in an inverted position. A lateral picture of the pelvis should be obtained to define whether the rectal pouch is above or below a line drawn from the pubis to the coccyx.

Treatment is surgical. Prognosis is better with low defects. About 80 to 90% of patients become continents after surgery for low defects. More than two-thirds of patients are incontinent after surgery of high defects.

Neural Tube Defects

Anencephaly. Anencephaly is due to a defect in the development of neural axis and is not compatible with life.

Encephalocele. In encephalocele, the brain and/or its coverings herniate through a defect in the skull.

Congenital hydrocephalus. Congenital hydropcephalus results from impaired CSF circulation or absorption in basal cisterns. This usually follows intrauterine infections such as toxoplasmosis, rubella, cytomegalovirus and syphilis, but may also be the result of a congenital malformation of the aqueduct, Dandy-Walker syndrome (posterior fossa cyst and a defect of cerebellar vermis), Arnold-Chiari malformation (displacement of brainstem and cerebellum in the spinal canal) or multiple congenital malformations of the nervous system.

Diagnosis should be suspected if the head is too large or sutures and fontanels are wide open or if the head circumference increases rapidly (more than 1 cm in a fortnight during the first three months). CT or MRI scan should be done to confirm the diagnosis. The type of dilatation of ventricles indicates the site of obstruction. Isolated aqueductal stenosis has better prognosis.

Treatment should be directed at the specific cause if amenable to therapy and surgical intervention such as ventriculocaval or ventriculoperioneal shunt.

Myelomeningocele. It presents as membranous protrusion at the lumbosacral region and contains meninges, cerebrospinal fluid, nerve roots and a dysplastic spinal cord. The defect is open and not covered by skin. In contrast, meningocele is covered with skin. There may be no associated neurological deficit, but Arnold-Chiari malformation and congenital hydrocephalus are often associated. Severe motor and sensory deficit are common and urinary and fecal incontinence are usually present. Meningomyelocele is operated only if there is no paralysis of lower limbs and if there is no bladder/bowel involvement.

Folic acid 4 mg per day should be prescribed to the women in periconceptional period to prevent recurrence.

Cleft Lip and Cleft Palate

Cleft lip is recognized readily (Fig. 8.55), but a careful inspection of the oral cavity is necessary to identify cleft

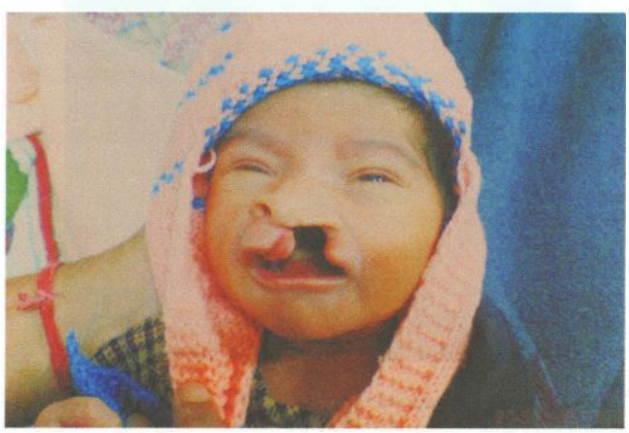


Fig. 8.55: Unilateral cleft lip and cleft palate

palate. A cleft of the soft palate can be easily missed unless the baby is examined carefully. Ventricular septal defect is a common associated anomaly with cleft palate.

In Pierré-Robin syndrome, cleft palate is associated with retracted jaw (micrognathia) and large tongue, with a tendency for glossoptosis. Feeding is difficult in cases of cleft palate. For the first few days, gavage feeding or spoon-feeding may be done. Bottle feeding may be tried with a soft nipple with rubber flange, which close the cleft and help the baby in sucking. If this is not successful, palatal prosthesis may be used.

Management. Management of cleft palate requires a team effort involving a pediatrician, a plastic surgeon, orthodontist, ENT specialist and speech therapist. Cleft lip is repaired in the neonatal period. Operation for cleft palate is generally deferred until the second year.

Diaphragmatic Hernia

Diaphragmatic hernia occurs because of failure of closure of the pleuroperitoneal membrane. This allows intestinal loops to ascend to the thorax that compress the developing lung and can result in pulmonary hypoplasia (Fig. 8.56). These babies can present at any time after birth. At birth, a baby may be suspected to have diaphragmatic hernia if there is respiratory distress and a scaphoid abdomen. Bag and mask ventilation should be avoided in these babies. Surgical repair after stabilization is the treatment of choice.

TRANSPORT OF NEONATES

Transport is an important component of sick newborn care. It requires careful attention to vital parameters, temperature and blood glucose levels as well as coordination with the receiving hospital (Fig. 8.57).

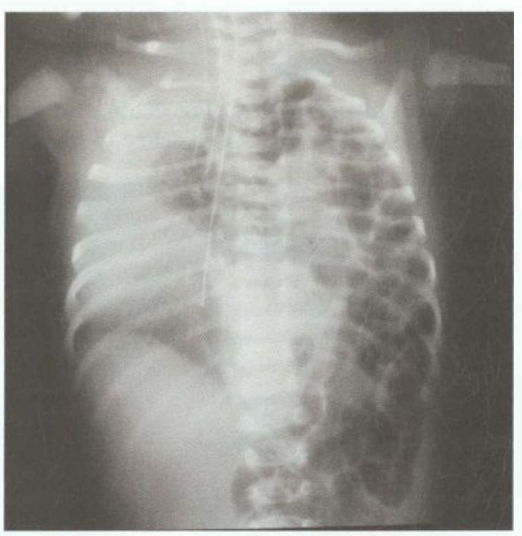
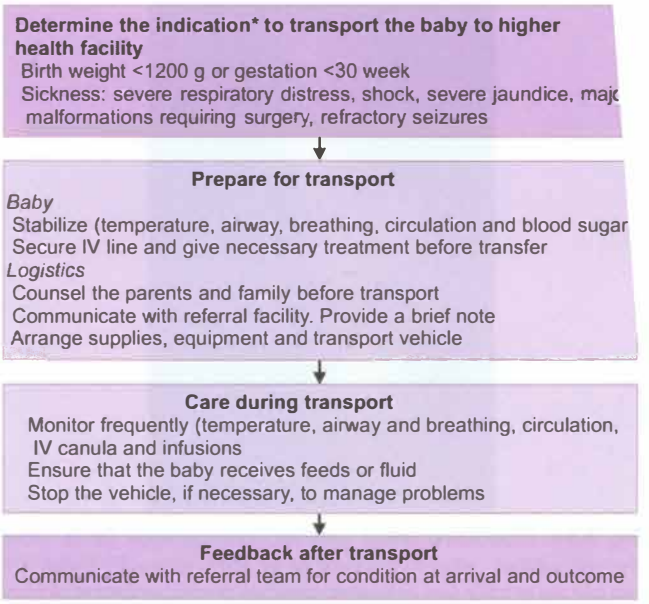


Fig. 8.56: Diaphragmatic hernia: Note multiple air filled cysts in left hemithorax, shift of mediastinum to the right and the absence of outline of the left diaphragm



* Indications may vary as per the facility

Fig 8.57: Transport of sick neonates

If the birth of an at-risk neonate is anticipated, the mother should be transported (*in utero* transport) to a facility with optimum maternal and neonatal care before delivery (*in utero* transfer). However, if referral of a neonate is unavoidable, efforts should be made to do the best possible job.

The principles of efficient transport are:

i. Make sure that there is a genuine indication for referral. One should explain the condition and reasons for transport to the family.
ii. Correct hypothermia before transporting, as it may worsen on the way. Stabilize the baby as much as possible.
iii. A precise note should be written providing details of the baby's condition, need for referral and treatment given to the baby.
iv. The mother should be encouraged to accompany the baby. In case she cannot accompany immediately, she should be encouraged to reach the facility at the earliest.
v. A doctor/nurse/dai/health worker should accompany the baby, if feasible, to provide care en route.
vi. Take the baby to the nearest referral facility (inform them in advance on phone or otherwise), by the shortest route, using the fastest possible and affordable mode of transport.

FOLLOWUP OF HIGH RISK NEONATES

Improved perinatal and neonatal care has resulted in improved survival of many sick and small neonates who are atrisk for longterm morbidities such as growth failure, developmental delay and visual/hearing problems. A proper and appropriate followup program would help in

prevention, early detection and appropriate management of these problems, thereby ensuring disability and morbidity free survival.

Who Needs Followup Care?

Table 8.26 lists the cohort of high risk infants who require followup services.

Table 8.26: Common newborn conditions requiring high risk followup care

Birth weight <1500 g and/or gestation <32 weeks
Perinatal asphyxia: Apgar score ≤3 at 5 min and/or hypoxic ischemic encephalopathy
Mechanical ventilation for >24 hr
Metabolic problems: Symptomatic hypoglycemia and hypocalcemia
Infections: Meningitis and/or culture positive sepsis
Hyperbilirubinemia >20 mg/dl or requirement of exchange transfusion

When to Followup?

The following should be the followup schedule:

- 2 weeks after discharge
- At 6, 10, 14 weeks of postnatal age
- At 3, 6, 9, 12 and 18 months of corrected age and then 6 monthly until at least 5 yr.

What should be Done at Followup?

i. *Assessment of feeding and dietary counseling:* Parents should be asked about the infants' diet and offered dietary counseling at each visit. Breastfeeding frequency and adequacy should be assessed. The amount, dilution and mode of feeding should be noted if supplemental feeding is given. It is also important to record the duration of exclusive breastfeeding. If a baby is not gaining adequate weight on exclusive breastfeeding, take care of any illness or maternal problems which may interfere with feeding and milk output. If poor weight gain persists despite all measures to improve breast milk output supplementation can be considered. Complementary feeding should be started at 6 months corrected age. Initially, semisolids should be advised in accordance with the local cultural practices.

ii. *Growth monitoring:* Growth (including weight, head circumference, mid-arm circumference and length) should be monitored and plotted on an appropriate growth chart at each visit.

iii. *Developmental assessment:* Assessment of developmental milestones should be done according to the corrected age. The milestones should be assessed in four domains — gross motor, fine motor, language and personal-social. Infants who lag behind in any domain should undergo a formal developmental evaluation by a clinical psychologist using tests such as Developmental Assessment of Indian Infant II (DASII II). Age appropriate stimulation should be provided to these babies.

iv. *Immunization:* Immunization should be ensured according to chronological age. Parents should be offered the option of using additional vaccines such as *Hemophilus influenzae* B, typhoid, MMR.

v. *Ongoing problems:* Ongoing morbidities such as diarrhea, pneumonia occur more frequently in these babies and should require appropriate treatment.

vi. *Neurological assessment:* Muscle tone should be assessed, any asymmetry between the extremities should also be recorded. Any history of seizures or involuntary movements should also be recorded.

vii. *Eye evaluation:* An ophthalmologist should evaluate the baby for vision, squint, cataract and optic atrophy. Subjective visual assessment can be made from clinical clues as inability to fixate eyes, roving eye movements and nystagmus. Objective visual assessment should be done with the Teller Acuity Card.

viii. *Hearing evaluation:* High risk infants have higher incidence of moderate to profound hearing loss (2.5–5% *versus* 1%). Since clinical screening is often unreliable, brainstem auditory evoked responses (BAER/BERA) should be performed between 40 weeks PMA and 3 months postnatal age.

METABOLIC DISORDERS

Hypoglycemia

Hypoglycemia is defined as a blood glucose value of less than 40 mg/dl (plasma glucose less than 45 mg/dl).

Screening for hypoglycemia is recommended in high risk situations (Table 8.27). These babies should be screened for hypoglycemia at 2, 6, 12, 24, 48 and 72 hr after birth with reagent strips (dextrostix). Babies showing blood sugar value of less than 40 mg/dl on reagent strip should be treated for hypoglycemia but should have confirmation of hypoglycemia by a lab test as reagent strips have high false positive rates. Appropriate for gestational age babies who are breastfeeding adequately do not require any screening for hypoglycemia.

Table 8.27: Common causes of hypoglycemia

Inadequate substrate: Small for gestational age (weight for gestation <3rd percentile), gestation <35 week, birth weight <2000 g
Relative hyperinsulinemia: Infants of diabetic mother, large for date baby (weight for gestation >97th percentile), Rh isoimmunization.
Sickness: hypothermia, sepsis, asphyxia

Clinical Features

Clinically the hypoglycemia may be asymptomatic or may manifest with a range of clinical features like stupor, tremors, apathy, cyanosis, convulsions, apneic spells,

tachypnea, weak and high pitched cry, lethargy, difficulty in feeding, eye rolling, episodes of sweating, sudden pallor, hypothermia and rarely, cardiac arrest.

Management of Hypoglycemia

Prevention of hypoglycemia. All high risk babies should receive proper breastfeeding counseling and support. Adequacy of breastfeeding should be assessed and small babies not able to suck effectively on the breast, should receive expressed breast milk by alternate methods.

Asymptomatic babies. If the blood sugar is more than 20 mg/dl in an asymptomatic baby, a trial of oral feeds is given and blood sugar be tested after 30–45 minutes. If repeat blood sugars values are above 40 mg/dl, frequent feeding is ensured with 6 hourly monitoring of blood sugar for 48 hr. However if blood sugar values persists below 40 mg/dl, baby should receive IV glucose infusion.

If the initial blood sugar value is less than 20 mg/dl, then intravenous glucose infusion is started.

Symptomatic babies: A bolus of 2 ml/kg of 10% dextrose should be given, followed immediately by glucose infusion at an initial rate of 6 mg/kg/min. Blood sugar is checked after 30–45 minutes and then 6 hourly. Repeat hypoglycemic episodes may be treated by increasing the glucose infusion rate by 2 mg/kg/min until a maximum of 12 mg/kg/min. If two or more consecutive values are >50 mg/dl after 24 hr of parenteral therapy, the infusion can be tapered off at the rate of 2 mg/kg/min every 6 hr, with glucose monitoring. Tapering has to be accompanied by concomitant increase in oral feeds.

Followup and Outcomes

Hypoglycemia has been linked to longterm adverse outcomes. These babies are followed up and assessed at one month corrected age for vision/eye evaluation and at 3, 6, 9, 12 and 18 months corrected age for growth, neurodevelopment and vision and hearing loss.

Hypocalcemia

Hypocalcemia is defined as total serum calcium level of <7 mg/dl or ionized calcium level of <4 mg/dl. Hypocalcemia may be of early onset (<72 hr) or rarely late onset (>72 hr).

Early onset neonatal hypocalcemia: Commonly seen in preterms less than 32 weeks, infants of diabetic mothers, perinatal asphyxia and maternal hyperparathyroidism. Such babies are at increased risk of hypocalcemia.

Late onset hypocalcemia: Neonates born to mothers with vitamin D deficiency, babies on anticonvulsant therapy or with malabsorption, those on cow milk feeding, or with hypoparathyroidism are at risk of late onset hypocalcemia.

Clinical Presentation

Early onset hypocalcemia is usually asymptomatic unlike the late onset hypocalcemia variety and is diagnosed on routine screening. The symptoms when present may be of neuromuscular irritability: myoclonic jerks, jitteriness, exaggerated startle and seizures. They may represent the cardiac involvement like tachycardia, heart failure, prolonged QT interval, decreased contractibility. Apnea, cyanosis, tachypnea, vomiting and laryngospasm are other rare symptoms.

Treatment

Prevention. They should receive 40 mg/kg/day of elemental calcium (4 ml/kg/day of 10% calcium gluconate). Infants tolerating oral feeds may receive this calcium orally q 6 hourly. Therapy should be continued for 3 days.

Asymptomatic hypocalcemia. They should receive 80 mg/kg/day elemental calcium for 48 hr. This may be tapered to 50% dose for another 24 hr and then discontinued.

Symptomatic hypocalcemia. They should receive a bolus dose of 2 ml/kg/dose. This should be followed by a continuous IV infusion of 80 mg/kg/day elemental calcium for 48 hr. Calcium infusion should be reduced to 50% of the original dose for the next 24 hr and then discontinued. The infusion may be replaced with oral calcium therapy on the last day.

Bradycardia and arrhythmia are known side effects of bolus IV calcium administration and bolus doses of calcium should be diluted 1:1 with 5% dextrose and given under cardiac monitoring. Skin and subcutaneous tissue necrosis may occur due to extravasation.

Drug Therapy and Breastfeeding

Though most drugs given to mother get transferred into human milk, the amount is not significant and does not pose any risk to the baby. The clinician should evaluate each medication carefully, examine published data on the drug and advise the mother carefully about the use of medications while breastfeeding. Table 8.28 enlists the maternal medications which may influence the baby.

Maternal Medications and Fetal Hazards

The risk by exogenous agents to the fetus is most pronounced during the period of embryogenesis and may result in abortion or congenital malformation (Fig. 8.58). In the late part of pregnancy, these agents only cause organ dysfunction or disturbances of enzyme systems. As a general principle, the use of drugs during pregnancy should be minimized. The benefits of medication to the mother must always be carefully weighed against the risk to the fetus.

Drugs listed in Table 8.29 are known to be or suspected to be teratogenic when given during the first trimester of pregnancy.

Table 8.28: Maternal medications that confer high risk to breastfed infants

Amiodarone	Accumulation in breast milk may cause thyroid suppression and cardiovascular toxicity
Anticancer agents	Some agents with short half-lives may permit breastfeeding with brief interruption
Doxepin	Sedation and respiratory arrest
Drugs of abuse (cocaine, amphetamines, phencyclidine, heroin)	Should be avoided
Ergotamine, cabergoline, bromocriptine	Ergotism has been reported
Sodium or potassium iodide; povidone-iodide solutions	Iodine concentration in milk may cause thyroid suppression in infants
Methotrexate	Immune suppression; concentration in gastrointestinal tract of infant
Lithium	Lithium concentrations in infant plasma may reach 33–40% of maternal levels
Radioisotopes	Brief interruptions advised; consult Nuclear Regulatory Commission recommendations
Tetracycline	Short-term use (up to 3-4 week) are not harmful

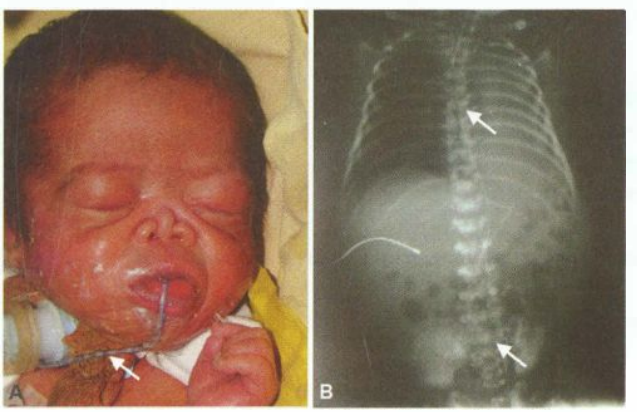


Fig 8.58: Warfarin embryopathy. Maternal warfarin intake during first trimester has resulted in (A) severe hypoplasia of nasal bones requiring tracheostomy for (B) maintenance of upper airways (solid arrow) and epiphyseal stippling (open arrow)

EFFECT OF MATERNAL CONDITIONS ON FETUS AND NEONATES

Diabetic Mellitus

Diabetes is one of the most common endocrine disorders affecting women during pregnancy. The following complications are likely to occur during pregnancy of a diabetic mother.

i. Fetus may die suddenly during the last trimester of pregnancy
ii. Macrosomia or large size of the body (Fig. 8.59) and its attending risks during delivery such as birth trauma, asphyxia and increased possibilities of cesarean section
iii. Neonatal respiratory distress
iv. Metabolic problems such as hypoglycemia and hypocalcemia
v. Polycythemia, increased viscosity of blood and hyperbilirubinemia
vi. Higher risk of congenital anomalies. (Infants of mothers with diabetes are 20 times more at risk to develop cardiovascular defects)

Pathogenesis

Maternal hyperglycemia leads to fetal hyperglycemia and that in turn leads to fetal hyperinsulinemia (Pederson hypothesis). Insulin is an anabolic hormone and promotes growth. Excess maternal glucose and amino acids provide the substrate for increased synthesis of protein, lipids and glycogen in the fetus. Large fetal size is mostly due to the accumulation of fat.

Hyperinsulinemia in the neonate causes hypoglycemia. The cause of hypocalcemia is not clear but is probably due to diminished production of parathormone. Hyperbilirubinemia may be due to the increased red cell mass. Since insulin blocks induction of enzyme system, this may explain lower production of surfactant. Reduced surfactant pool and the higher risk of preterm deliveries explains higher risk of respiratory distress syndrome in these babies.

Management

The infant should be screened for malformations and injuries. Frequent breastfeeding should be encouraged. The neonate should be monitored for blood glucose levels during first three days of life. The other morbidities such as respiratory distress, hyerbilirubinemia should treated appropriately.

Hypothyroidism

Hypothyroidism during pregnancy if treated adequately does not affect pregnancy outcomes; however, inadequate treatment of the mother predisposes the fetus to adverse neurodevelopment. Neonate should be screened for hypothyroidism using either cord blood or on blood sample taken after 72 hr of birth.

Table 8.29: Common teratogenic drugs

Drugs or chemical	*Teratogenic effect*
Alcohol	Growth retardation; cardiac, limb and facial anomalies
Amphetamines	Learning disability, motor incoordination, hepatic calcification
Androgens	Cleft lip and palate, tracheoesophageal fistula, congenital heart disease, masculinization
Barbiturates	Cleft lip and palate, congenital heart disease, induction of hepatic microsomal enzymes, respiratory depression, withdrawal symptoms
Chloroquine	Deafness after prolonged use, hemolysis in susceptible individuals
Diazepam	Cleft lip and palate, apnea, hypothermia
Dicumarol	Bleeding, fetal death, depressed nasal bridge, stippling of phalanges, choanal atresia, cardiac, renal and ophthalmic defects
Diphenylhydantoin	Facial, cardiac and limb anomalies
Excessive smoking	Growth retardation
Gentamicin	Eighth nerve damage
Heroin	Intrauterine death, low birth weight, sudden infant death
Indomethacin	Low birth weight, platelet dysfunction
Iodides	Hypothyroidism, goiter
Lithium carbonate	Congenital heart disease, goiter
Propylthiouracil	Hypothyroidism
Methotrexate	Congenital malformation, fetal death
Oral contraceptives	Cardiac, limb and visceral anomalies
Progestins	Masculinization, advanced bone age
Quinine	Deafness, neurologic anomalies, thrombocytopenia
Radiation	Microcephaly, mental retardation
Tetracycline	Staining of teeth, enamel hypoplasia, inhibition of bone growth, congenital cataracts
Tolbutamide	Fetal death, thrombocytopenia
Vitamin D (heavy dose)	Mental retardation, supravalvular aortic stenosis, ventricular opacities, elfin facies

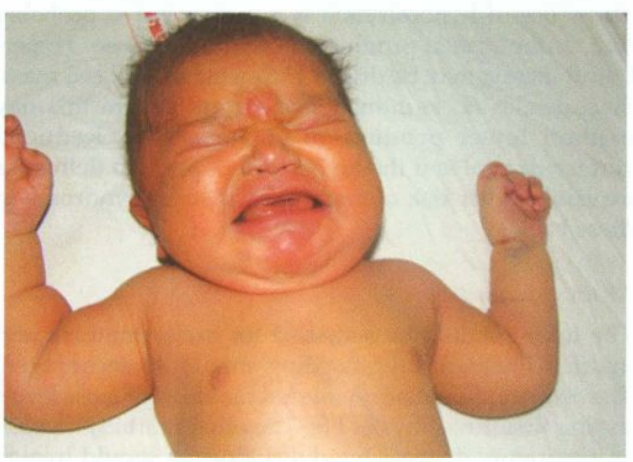


Fig. 8.59: Infant of diabetic mother. Note the large size of the baby with broad shoulders and torso and a relatively smaller head

Tuberculosis

If the mother has active pulmonary tuberculosis that has been treated for less than 2 months before birth or the diagnosis of tuberculosis was made after birth, the baby is at risk to acquire infection from the mother. Such babies should not be separated from the mother. Exclusive breastfeeding is encouraged. The infant should be given isoniazid prophylaxis (5 mg/kg/day) and is evaluated at 6 weeks of age. If there is any evidence of tubercular infection in the baby (clinically or radiologically), the infant should be started on antitubercular therapy. If the infant does not have any evidence of tuberculosis at 6 weeks, the isoniazid therapy continued for 6 months and the infant given BCG vaccine after 2 weeks of cessation of therapy.

Syphilis

Syphilis infection can be transmitted to the infant who have significant disease and its sequelae. If the mother was diagnosed to have syphilis and she received adequate treatment at least one month before delivery, the infant does not require any treatment.

If the mother did not receive any treatment or inadequate treatment or her treatment status is not known and the neonate does not have any signs of congenital syphilis, the infant should be treated with procaine or benzathine penicillin. Along with the baby, the mother and her partner should also be treated.

If the infant shows signs of congenital syphilis, he should be treated with crystalline penicillin for 10 days.

The infant should be followed up in four weeks to examine the baby for growth and signs of congenital syphilis.

Hepatitis B Infection

The women who have hepatitis B infection (active or carrier stage) can transmit the infection to their babies. Such babies should receive hepatitis B vaccine within 12 hr of birth, which can prevent perinatal transmission of hepatitis B virus significantly. Hepatitis B immunoglobulins (HBIG; 200 IU, IM) can be given to enhance the protection but it is costly and there are availability issues.

HIV infection

Most children living with HIV acquire the infection through mother-to-child transmission (MTCT). HIV infection can be transmitted from an infected mother to her fetus during pregnancy, delivery, or by breastfeeding.

Prevention

In the absence of any intervention, the risk of perinatal transmission is 15–30% in non-breastfeeding populations. Breastfeeding by an infected mother increases the risk by 5–20% to a total of 20-45%.

The risk of MTCT can be reduced to under 2% by interventions that include antiretroviral (ARV) prophylaxis given to women during pregnancy and labor and to the infant in the first 6 week of life, obstetrical interventions including elective cesarean delivery (prior to the onset of labor and rupture of membranes) and complete avoidance of breastfeeding.

Approach to a women with HIV infection and her infant is summarized in Fig. 8.60.

Breastfeeding

Mothers known to be HIV-infected should only give commercial infant formula milk as *replacement* feeding when specific conditions are met (referred to earlier as AFASS –Affordable, Feasible, Acceptable, Sustainable and Safe in the 2006 WHO recommendations on HIV and Infant Feeding)

If replacement feeding is not feasible, mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter and continue breastfeeding for the first 12 months of life. Breastfeeding should then stop once a nutritionally adequate and safe diet without breast milk can be provided.

Immunization

HIV exposed or infected but asymptomatic children should receive all standard vaccines as per national schedule. HIV infected children with immune suppression or symptoms should receive all standard vaccines except BCG, OPV and varicella vaccines. Consider HiB and pneumococcal vaccines in all HIV exposed children (irrespective of symptoms or CD4 count).

Suggested Reading

Rapid Advice: Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. World Health Organization,WHO Press, Geneva, 2009; available at www.who.int/iris/bitstream/10665/44249/1/9789241598934_eng.pdf

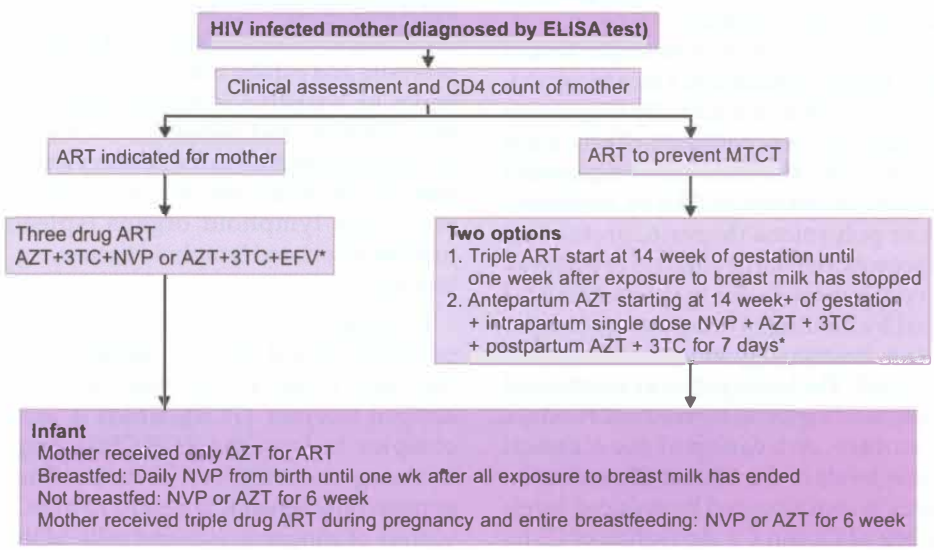


Fig. 8.60: Approach to an infant born to HIV-infected mother. * Efavirenz (EFV) based regimens should not be newly-initiated during the first trimester of pregnancy# single dose nevirapine (Sd-NVP) and zidovudine (AZT) with lamivudine (3TC) intra- and postpartum can be omitted if mother receives more than 4 weeks of AZT during pregnancy. ART antiretroviral therapy; AZT (4 mg/kg PO per dose twice a day for infant); Sd NVP (10 mg/day for infants <2.5 kg, 15 mg/day for infants 2.5 kg or more)

9 Immunization and Immunodeficiency

Aditi Sinha, Surjit Singh

IMMUNITY

The immune system recognizes microorganisms and other foreign material, discriminates it from self and mounts an appropriate response to eliminate it. There are two major components of immunity: the innate immune system and the adaptive immune response. Innate immunity is primitive, nonspecific, has no memory and provides the first line of defense against infections, while the adaptive immune system is highly evolved, specific and has memory, characterized by a rapid rise in immune response when exposed again to the microorganism.

Innate Immune System

The skin and mucous membranes provide an important mechanical barrier to infection. Gastric acidity is an effective physiologic barrier as very few microorganisms can survive the low acidic pH in stomach.

The complement system consists of multiple serum proteins circulating as inactive precursors. Once triggered, these proteins activate each other sequentially to generate active components. There are three pathways of activation of the complement cascade. The classical complement pathway is triggered by activation of C1q by antibody-antigen complexes or polyanions (heparin, protamine, nucleic acids from apoptotic cells). The alternative pathway is continuously active at low levels due to spontaneous C3 lysis, and is amplified by binding of complement components to pathogen (e.g. bacterial lipopolysaccharides or endotoxin, yeast cell wall). The lectin pathway is activated by binding of mannose binding lectin to mannose residues on pathogen cell surface. Activation of the classical pathway results in low levels of C4, C2 and C3; activation of alternative pathway is characterized by reduced levels of C3 and normal levels of C4 and C2. Activation of C3 by either pathway results in formation of the membrane attack complex, which binds to the surface of bacteria, fungi and viruses leading to their lysis. C3b component can opsonize immune complexes or foreign cell surface anaphylatoxin, including C3a, C4a and C5a, bind to receptors on mast cells and basophils, resulting in their degranulation and release of histamine and intracellular enzymes. C3a and C5a induce the adherence of monocytes, macrophage and neutrophils to vascular endothelial cells causing extravasation and chemotaxis at the site of inflammation.

Cellular components of innate immunity comprises polymorphonuclear leukocytes, macrophages and natural killer (NK) cells. These ingest extracellular material by phagocytosis. The activation of myeloperoxidase in phagolysosomes results in production of superoxide that oxidizes and inactivates microbial proteins.

Adaptive Immune System

Adaptive immune responses develop through cooperation between lymphocytes and antigen presenting cells following specific antigenic challenge, show tremendous diversity and exhibit immunological memory. The components of adaptive immune system are lymphocytes, macrophages and antigen presenting cells. These cells develop and mature in the primary lymphoid organs (bone marrow, thymus) and interact with foreign antigens in secondary lymphoid organs (spleen, lymph nodes, mucosa associated lymphoid tissues, e.g. tonsils and Peyer patches).

Lymphocytes constitute 20-40% of white cells in the peripheral blood and are classified as B cells, T cells and NK cells. T cells are identified by the presence of T cell antigen receptor (TCR), which is associated with CD3 complex to form the TCR-CD3 complex that remains unchanged during cell division. The TCR recognizes antigen only when it is bound to MHC molecules on the surface of antigen presenting cells. Mature T lymphocytes are distinguished into CD4+ cells and CD8+ cells based on the presence of membrane glycoprotein molecules. The normal ratio of the number of CD4+ and CD8+ cells in

peripheral blood is 2:1; this is altered in immunodeficiency and autoimmune diseases. CD4+ cells or T helper (Th) cells can recognize antigen only if bound to class II MHC molecules, whereas CD8+ cells or T cytotoxic (Tc) cells recognize antigen bound to class I MHC molecules. Th cells differentiate into Th1 and Th2 cells under the influence of cytokines. Th1 immune response supports inflammation and activates Tc cells and macrophages (e.g. in tuberculoid leprosy, rheumatoid arthritis) whereas Th2 responses induce antibody mediated immunity (e.g. lepromatous leprosy, allergic disorders). Tc cells are important in eliminating intracellular pathogens like viruses, and in organ transplant rejection.

About 5–15% of the circulating lymphocytes are B cells, characterized by surface expression of immunoglobulin isotypes. The majority express IgM and IgD isotypes and less than 10% express IgG, IgA or IgE isotypes. NK cells constitute 15% of circulating lymphocytes and are also present in lymphoid tissues, particularly spleen. They do not carry markers of T or B cells but have IgG Fc surface receptors. NK cells show nonspecific cytotoxicity and enable immune surveillance against viruses and tumors.

PRIMARY IMMUNODEFICIENCY DISORDERS

A small but significant proportion of children evaluated for frequent infections have immunodeficiency. Immunodeficiency disorders can be secondary or primary, the former being far more common. Infection with the human immunodeficiency virus (HIV) is the commonest cause of secondary immunodeficiency (Chapter 10). Table 9.1 lists clinically important causes of secondary immunodeficiency.

Primary immunodeficiency disorders can affect any of the major components of the immune system, including T and/or B lymphocytes, antibody production, phagocyte number or function and complement components. The condition should be suspected in patients presenting with ≥2 of the following ten warning signs: (i) ≥4 new infections in a year; (ii) ≥2 serious sinus infections in a year; (iii) ≥2 cases of pneumonia in a year; (iv) ≥2 month of antibiotics without effect; (v) failure of an infant to gain weight or grow normally; (vi) recurrent deep skin infections or organ abscesses; (vii) persistent oral thrush, or candidiasis elsewhere beyond infancy; (viii) need for intravenous antibiotics to clear infections; (ix) ≥2 deep seated infections (e.g. meningitis, cellulitis); and (x) family history of immunodeficiency (based on recommendations of the Jeffrey Modell Foundation). Table 9.2 outlines the investigative workup required in such patients. Conditions that mimic immunodeficiency (gastroesophageal reflux, Kartagener syndrome) should be excluded.

Table 9.1: Common secondary causes of immunodeficiency

Human immunodeficiency virus infection
Following measles
Severe malnutrition
Nephrotic syndrome
Lymphoreticular malignancies
Severe burns
Immunosuppressive drugs (e.g. glucocorticoids, cyclophosphamide, azathioprine) phenytoin
Severe or chronic infections

Disorders of Specific Immunity

Cellular and/or Combined Immunodeficiency

Severe combined immunodeficiency (SCID) Children with the SCID syndrome usually present in early infancy with severe infections due to viruses, fungi (e.g. *Pneumocystis jiroveci*) and intracellular pathogens (e.g. *Mycobacteria*). Tonsillar tissue is usually absent and lymph nodes are not palpable. Left untreated, such babies do not live for more than a few months. The most common form of SCID is X-linked and caused by mutations in the common gamma chain (IL2 receptor γ); approximately one-fourth cases have adenosine deaminase deficiency. SCID due to purine nucleoside phosphorylase deficiency may present later in childhood with milder immunodeficiency. The phenotype in patients with SCID may be T– B+ NK– (X-linked SCID), T– B– NK– (adenosine deaminase deficiency), T–B– NK+ (mutations in recombination activating genes) or T– B+ NK+ (IL7Rα deficiency).

DiGeorge anomaly This disorder arises due to defects in embryogenesis of the third and fourth pharyngeal pouches. It is characterized clinically by an unusual facies (hypertelorism, antimongoloid slant, low set ears, micrognathia, short philtrum of upper lip, bifid uvula),

Table 9.2: Investigations for suspected immunodeficiency

Screening investigations
Total and differential leukocyte counts, leukocyte morphology
HIV serology
X-ray chest
Delayed skin tests (Candida, tetanus toxoid)
Specific investigations
Blood levels of immunoglobulins: IgG, IgA, IgM; IgG subclasses
Blood group isohemagglutinins (for functional IgM)
Anti-diphtheria and anti-tetanus antibodies (functional IgG)
Lymphocyte subsets: CD3, CD4, CD8, CD19, CD16
Mitogen stimulation tests (response to phytohemagglutinin)
Nitroblue tetrazolium (NBT) dye reduction test
CH50, complement component assays
Mannan binding lectin assay
Enzyme assays: adenosine deaminase, purine nucleoside phosphorylase
HLA typing
Bacterial killing
Chemiluminiscence studies

hypocalcemic tetany, aortic arch anomalies and an absent thymus. In addition, 20–30% patients show a variable T cell defect, ranging from a mildly increased susceptibility to infections to severe disease requiring hematopoietic stem cell transplantation.

Wiskott-Aldrich syndrome This X-linked recessive disorder is characterized by eczema, thrombocytopenia and recurrent serious bacterial infections. It is caused by mutations at Xp11.22–23, encoding WAS protein present in the cytoplasm of lymphocytes and platelets. The eczema begins in early infancy and may mimic atopic dermatitis with atypical features. Thrombocytopenia is associated with characteristic small sized platelets. Due to impaired responses to polysaccharide antigens, such patients are susceptible to infections with *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. The clinical phenotype varies; some children have a fulminant course with repeated severe infections causing death, while others survive childhood and may present predominantly with bleeding manifestations. The risk of lymphoreticular malignancies is increased. There is a profound IgM deficiency in addition to defective T cell signaling which is secondary to the deficient expression of CD43 in lymphocytes.

Ataxia-telangiectasia This is an autosomal recessive disorder characterized by progressive ataxia (often starting during infancy), telangiectasia (initially on bulbar conjunctiva), sinopulmonary infections, excessive chromosomal breakage and increased sensitivity to ionizing radiation. The gene is localized to chromosome 11q 22–23 and its product regulates the cell cycle. The degree of immunodeficiency is less profound than seen in Wiskott-Aldrich syndrome. Serum IgA, IgG2 subclass and IgE levels are usually reduced; lymphocyte proliferative responses are decreased and γδ-T cell numbers are increased.

Hyper IgM syndrome This T cell deficiency result is from a CD40 ligand defect. Affected children have a profound immunodeficiency characterized by low levels of IgG but normal or raised IgM. There is increased susceptibility to infections with *P. pneumocystis jiroveci*. Some patients may have associated autoimmune disorders.

9

Humoral Immunodeficiency

X-linked (Bruton) agammaglobulinemia This was the first primary immunodeficiency disorder to be described. The inheritance is X-linked recessive. Affected boys usually present in the second half of infancy with infections due to pyogenic bacteria. Presentation later in childhood has also been described. Tonsils and lymph nodes are usually atrophic. B cells (CD19+) are absent in peripheral blood but T cells (CD3+) are normal in number and function. The disease is secondary to a mutation in the gene for tyrosine kinase (Btk or Bruton tyrosine kinase).

Common variable immunodeficiency This term refers to a heterogeneous group of conditions characterized by hypogammaglobulinemia and variable defects in T cell number and function. Presentation is usually much later in childhood and, unlike X-linked agammaglobulinemia, affected children may have significant lymphadenopathy and hepatosplenomegaly. Unlike X linked agammaglobulinemia, the B cell number is usually normal. Low levels of lymphocyte proliferation following mitogen stimulation may be demonstrated. Mutations in any of the following genes may cause this disorder: inducible costimulator (ICOS), SLAM associated protein (SH2DIA); CD19; CD20; CD81, B cell-activating factor of the tumor necrosis factor family receptor (BAFF-R), tumor necrosis factor receptor superfamily member 13B or transmembrane activator (TNFRSF13B or TAC1) or TNFRSF13C. Autoimmune disorders (leukopenia, hemolytic anemia, arthritis) are commonly associated. Patients require close monitoring for development of lymphoreticular malignancies.

IgA deficiency This is one of the commonest causes of primary immunodeficiency. Affected individuals usually do not have a clinically significant immunodeficiency. They may remain entirely asymptomatic throughout life or have recurrent mild respiratory infections, especially if IgG subclass deficiency is also present.

IgG subclass deficiency Of the four IgG subclasses, IgG1 provides protection against bacterial pathogens (e.g. diphtheria, tetanus), IgG2 protects against capsular polysaccharide antigens (e.g. pneumococcus, *Haemophilus influenzae*), IgG3 has antiviral properties while IgG4 has antiparasitic activity. Children with deficiency of one of the IgG subclasses may have normal, or sometimes even elevated, total IgG levels. This is ascribed to a compensatory overproduction of IgG of other subclasses.

Transient hypogammaglobulinemia of infancy All infants go through a period of physiological hypogammaglobulinemia between 3–6 months of age, when the transplacentally acquired maternal IgG has been catabolized and the child's own immunoglobulin production has not begun. In some infants, this period of physiological hypogammaglobulinemia is prolonged to 18–24 months, resulting in the development of transient hypogammaglobulinemia of infancy. Unlike X-linked agammaglobulinemia, the B cell (CD19) numbers are normal. These children recover over time and the longterm prognosis is excellent. The condition must be considered in the differential diagnosis of young children with hypogammaglobulinemia. Serum IgG levels in infancy and early childhood should only be interpreted in the context of age related nomograms.

Disorders of Nonspecific Immunity

Cellular Immunodeficiency

A number of cellular defects have been recognized in the nonspecific arm of the body's immune system. These may

be quantitative (e.g. congenital neutropenia, cyclic neutropenia) or qualitative (e.g. chronic granulomatous disease, Chediak-Higashi syndrome). *Chronic granulomatous disease* refers to a group of disorders with reduced activity of NADPH oxidase leading to impaired generation of superoxide radical. The disease is X-linked in more than 50% patients secondary to mutations in the gene encoding gp9-PHOX, while others have autosomal recessive inheritance with mutations in the gene encoding p47-PHOX on chromosome 7. Children present with recurrent life-threatening infections, often starting in early infancy. These infections are typically caused by catalase-positive bacteria (e.g. *Staphylococcus aureus, Serratia* spp.). Fungal infections are also common, especially *Aspergillus*. Typical findings include persistent pneumonia, prominent lymphadenitis, multiple liver abscesses and osteomyelitis of the small bones of hands and feet. The diagnosis is suggested by screening on nitroblue tetrazolium dye reduction test (NBT), and confirmed by flow cytometric evaluation.

Humoral Immunodeficiency

Individuals with deficiencies of the early complement components (C2–C4) may present with recurrent bacterial infections, while those with deficiency of the later components (C5–C9) have predilection for *Neisseria* infections. Systemic lupus erythematosus may occur in individuals with C2/C4 deficiency. A deficiency of the C1 esterase inhibitor is associated with hereditary angioneurotic edema, characterized by sudden appearance of recurrent nonitchy swellings in the body.

Miscellaneous

Hyper IgE syndrome This is characterized by recurrent 'cold' staphylococcal abscesses involving the skin, joints and lungs, and markedly elevated serum IgE concentrations (usually >2000 IU/ml). Inheritance is variable.

Mannan binding lectin deficiency This is a dominantly inherited, relatively common disorder characterized by recurrent respiratory infections in early childhood. The degree of immunodeficiency is never profound; most patients remain asymptomatic throughout life.

Table 9.3 summarizes the findings in various forms of primary immunodeficiency.

Treatment of Primary Immunodeficiency Disorders

Hematopoietic stem cell transplantation is the treatment of choice for most forms of significant cellular immunodeficiency (e.g. SCID, Wiskott-Aldrich syndrome, hyper IgM syndrome). For it to succeed, the procedure should be done in early infancy. However, it cannot be carried out for children with ataxia-telangiectasia.

Children with X-linked agammaglobulinemia and common variable immunodeficiency need to be administered 3–4 weekly injections of IV immunoglobulin (IVIG). While expensive, therapy can result in an almost normal lifespan. While children with IgA deficiency usually do not require any specific therapy, those with IgG2 subclass deficiency may require monthly replacement IVIG therapy. Prophylactic therapy with antimicrobials (usually cotrimoxazole) is required for some children with IgG1 and IgG3 deficiency.

Table 9.3: Clinical clues to the diagnosis of primary immunodeficiency

Type of infection	*Age at presentation*	*Associated findings*	*Likely etiology*
Pneumonia or diarrhea; cryptosporidiosis; disseminated BCG infection	First few months of life	Failure to thrive; rash; atrophic tonsils and lymph nodes	Severe combined immunodeficiency
Pneumonia; pyogenic infections (*S. pneumoniae, H. influenzae)*	4–6 mo	Only boys affected; failure to thrive	X-linked agammaglobulinemia
Diarrhea, sinopulmonary infections; often pyogenic (*S. pneumoniae, H. influenzae)*	Later childhood (>5–10 yr)	Hepatosplenomegaly; lymphadenopathy	Common variable immunodeficiency
Recurrent staphylococcal cold abscesses, pneumonia (often with pneumatocele	Any age	Coarse facial features, eczematous rash	Hyper IgE syndrome
Recurrent or persistent giardiasis	Any age	Autoimmune diseases	IgA deficiency
Recurrent staphylococcal infections of lungs, skin or bone; persistent fungal (*Aspergillus*) pneumonia; liver abscess	Usually early childhood	Lymphadenopathy; draining nodes; hepatosplenomegaly	Chronic granulomatous disease
Pyogenic bacteria (*S. pneumoniae, H. influenzae*)	4–6 mo		Deficiency in early complement components
Recurrent *Neisseria* infections, e.g. meningitis			Deficiency in late complement (C5–9) components
Recurrent infections	Early infancy	Boys; atypical eczema; thrombocytopenia	Wiskott-Aldrich syndrome
Recurrent bacterial infections, e.g. pneumonia		Progressive ataxia; precedes telangiectasia	Ataxia-telangiectasia

Longterm cotrimoxazole and itraconazole prophylaxis has greatly improved the management of chronic granulomatous disease. Interferon-γ, although expensive, has been used for the treatment of life-threatening infections as well as for prophylaxis in difficult cases. Some children with CGD may require bone marrow transplantation.

While there is no specific therapy for complement deficiencies, plasma infusions may be useful in life-threatening situations. For C1 esterase inhibitor deficiency, prophylactic danazol or stanozolol therapy results in significant improvement. Injections of synthetic C1 esterase inhibitor is required if there is laryngeal involvement with airway compromise. Therapy with adrenaline and hydrocortisone is usually of no benefit.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is pooled normal intact polyspecific IgG derived from the plasma of healthy donors who have been subjected to strict screening procedures. Each batch of IVIG represents a donor pool of 4000–8000 individuals such that the repertoire of antibodies is representative of the population at large. Most IVIG preparations contain 90% monomeric IgG with only small amounts of IgA and IgM. Ideally, the IgG subclass distribution of IVIG should be the same as in normal plasma, but this depends on the manufacturing process. For instance, some IVIG preparations do not contain adequate quantities of IgG3.

IVIG is the treatment of choice for Kawasaki disease, autoimmune demyelinating polyradiculoneuropathy and idiopathic thrombocytopenic purpura. The dose is 2g/kg given as a single infusion. However, lower doses are equally effective in idiopathic thrombocytopenic purpura.

IVIG is also used as replacement therapy in various forms of hypogammaglobulinemia. The recommended dose is 0.4–0.6 g/kg every 3-4 weeks. Its use may also be considered in selected cases of severe myasthenia gravis, autoimmune neutropenia, neonatal alloimmune and autoimmune thrombocytopenia, lupus crisis, dermatomyositis not responding to conventional steroid therapy and certain vasculitides. IVIG has been used for prophylaxis and treatment of neonatal sepsis in low birthweight babies but the results are equivocal. Use of IVIG for treatment of sepsis in older children is controversial.

Administration of IVIG is commonly associated with adverse effects. The infusion must be started very slowly (initially a drop per minute) and the child monitored for allergic reactions, including anaphylaxis. The infusion rate should be slowed or discontinued if the child develops chills or rigors. Longterm risks include transmission of hepatitis C infection. The risk of acute renal failure is negligible with current iso-osmolar preparations.

Suggested Reading

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IMMUNIZATION

Immunization is the administration of all or part of a pathogen or preformed antibodies to elicit an immunological response that protects from disease. Considered one of the most cost effective health interventions of all times, immunization programs have enabled the eradication of small pox, elimination of poliomyelitis from several countries and a significant decline in incidences of measles, tetanus and diphtheria. Advances in vaccine technology have led to the introduction of potent vaccines against a wide spectrum of infections.

Terminology

Active immunity is the protective response mounted by the immune system following exposure to an infectious organism (as clinical or subclinical infection) or after vaccination with live or killed organism, a toxoid or subunit. Active immunity comprises humoral (antibody-mediated) and/or cellular (cell-mediated) immune responses. Following first exposure, the *primary* immune response is slow to develop (over 3–14 days or longer) and may or may not be sufficient to counteract the infection. The humoral response involves formation of IgM followed by IgG antibodies. Host response to re-exposure to the infectious agent (or its component), termed *secondary* response, is fairly rapid, involves induction of high titers of IgG antibodies, is usually sufficient to prevent disease and provides protection for several years.

Passive immunity refers to protection from disease provided by introduction of preformed animal or human antibodies into the body. Examples include the passage of IgG from the mother across the placenta to the fetus, transmission of secretory IgA in breast milk, and administration of immunoglobulin or antisera to prevent disease (*see* section on 'Passive Immunization'). While these antibodies provide immediate protection by neutralizing pathogenic toxins or restricting viral multiplication, the effect is not sustained.

A vaccine is composed of one or more antigens of a pathogenic agent which, when administered to a previously unexposed individual, will elicit an immune response but not cause disease. The secondary immune response, elicited when the host encounters the pathogen itself, is rapid and protects from disease.

Immunization is the process of inducing acquired immunity, by administering (i) live killed or attenuated organisms or specific antigens (active immunization), usually prior to natural exposure to infectious agent; or (ii) preformed exogenous antibodies, given soon after or prior to exposure, in order to suppress disease (passive immunization).

Vaccination is to the process of administration of a vaccine. Vaccination may elicit predominantly humoral immune response (e.g. *Haemophilus influenza* b vaccine), cellular immunity (e.g. BCG), or both responses (e.g. most vaccines).

Seroconversion refers to the change from antibody negative to antibody positive state, due to induction of antibodies in response to infection or vaccination.

Seroprotection refers to the state of protection from disease, due to the presence of detectable serum levels of antibody.

Immunogenicity is the ability of a vaccine to elicit an immune response, whether cellular, humoral or both.

Adjuvants are substances unrelated to the organism that, when added to a vaccine, enhance its immunogenicity. The action results from nonspecific stimulation of lymphocytes or by enabling slow release of the antigen. Examples include aluminum hydroxide and lipids.

Protective efficacy is the vaccine's actual ability to protect against disease. Live viral vaccines and toxoids have good protective efficacy, while BCG and killed bacterial vaccines may not protect from disease. It is assessed in prospective or retrospective epidemiological studies as follows:

Efficacy= (rate of disease in unvaccinated persons–rate of disease in the vaccinated) × 100/rate of disease in unvaccinated persons

Vaccine effectiveness is the ability of a vaccine to protect the population from disease, when administered in an immunization program. Vaccine effectiveness depends on vaccine efficacy, program implementation and herd effect (*see* below).

Vaccine failure is the occurrence of disease in an individual despite vaccination. *Primary* vaccine failure is the inability of the recommended vaccine dose(s) to induce an immune response, while *secondary* failure refers to the occurrence of disease despite an immune response. Vaccine failure is rare with measles, diphtheria and tetanus vaccines. Primary vaccine failure may occur despite 3 doses of oral poliovirus vaccine (OPV) and secondary failure may be seen after BCG, pertussis and typhoid vaccines.

Herd effect. If a large proportion of susceptible individuals are protected from infection with an organism by simultaneous vaccination, the transmission chain of the infectious agent can be broken by reducing carriage of the causative microorganism by vaccinated individuals, thus decreasing the risk of disease even among the unimmunized individuals. This phenomenon, termed the *herd effect*, is less pronounced for vaccines that protect only against disease (e.g. diphtheria) than those that prevent infection (e.g. measles, OPV). Vaccines with low protective efficacy (e.g. pertussis and typhoid) have insignificant herd effect. There is no herd effect for vaccines against diseases where humans are not the chief reservoir (e.g. tetanus). Herd effect is utilized as one of the strategies for eradication of poliovirus, and potentially, during measles epidemics. *Herd immunity* refers to the proportion of immune individuals in a population.

Types of Vaccines

A good vaccine is one that is easy to administer, induces permanent immunity, is free of toxic substances, has minimal side effects and is relatively stable for prolonged time. The timing of administration depends on the age at which the disease is anticipated, the ability to mount immune response to administered antigen(s) and feasibility. Vaccines may consist of live attenuated, killed or inactivated organisms, modified toxins (toxoids), or subunits. Some examples are listed in Table 9.4.

Live Vaccines

Live vaccines replicate in the host to produce an immune response mimicking natural infection. Therefore, these vaccines actually infect the recipient but do not cause disease because the potency of the organism has been attenuated. However, the vaccine may cause disease in immunocompromised hosts. Rarely, an attenuated viral vaccine may revert to its virulent form causing disease.

Table 9.4: Types of vaccines

Description		*Example*
Live attenuated organism	Bacterial	BCG, oral typhoid (*S. typhi* Ty21a)
	Viral	OPV, measles, MMR, varicella, rotavirus, yellow fever
Killed or inactivated organism	Bacterial	DTwP, whole cell killed typhoid
	Viral	IPV, rabies, hepatitis A, influenza (whole virion)
Modified bacterial toxins or toxoids		Diphtheria toxoid, tetanus toxoid
Bacterial capsular polysaccharide		*Salmonella typhi* (Vi), Hib, meningococcal, pneumococcal
Subunit	Bacterial	Acellular pertussis
	Viral	Recombinant hepatitis B, influenza (split subunit)

BCG Bacillus Calmette Guerin vaccine; DTwP diphtheria toxoid, tetanus toxoid, whole cell killed pertussis vaccine; Hib *Haemophilus influenza* type b; IPV inactivated poliovirus vaccine; MMR measles mumps and rubella vaccine; OPV oral poliovirus vaccine

Storage and transportation conditions are critical to maintaining the potency of live vaccines.

Usually a single dose of live vaccines is sufficient to induce immunity; OPV is an exception where multiple doses may be required to infect the intestinal mucosa. Residual maternal antibody in the infant's serum may neutralize the organism before infection occurs, thus interrupting the 'take' of a vaccine; hence, vaccines like measles and measles, mumps, rubella (MMR) are administered beyond 9 months of age. BCG and OPV are exceptions where maternally derived antibodies do not interfere with vaccine 'take'. This is because BCG induces cell mediated immunity that is not transferred from mother to fetus, and OPV infects the gut mucosa which is not interrupted by residual maternal antibody.

Killed Vaccines

Killed vaccines, prepared by growing bacteria or viruses in media followed by heat or chemical (e.g. formalin) inactivation, do not cause infection but elicit protective immune response. Interference by maternal antibodies is less significant. However, multiple doses are required since the organism cannot replicate in the vaccinee. The immunity is not permanent; booster doses are necessary to ensure prolonged protection. Most killed bacterial and some killed viral vaccines (e.g. influenza) are associated with significant local and systemic reactions. These vaccines are relatively heat stable.

Toxoids

Toxoids are modified toxins that, if well purified, are not injurious to the recipient. Primary immunization is in form of multiple divided doses in order to decrease the adverse effects at each administration and to elicit high antibody titres with repeated exposure to the same antigen. Booster doses are required to sustain the protection.

Subunit Vaccines

Other nonreplicating antigens include capsular polysaccharide and viral or bacterial subunits. Capsular polysaccharides are carbohydrate antigens that elicit humoral response by stimulating B cells directly, without modulation by helper T cells. Hence, there is no immunological memory and the antibodies produced are of the IgM class alone, rather than an IgG response.

Principles of Immunization

While immunizing children, certain guidelines are useful in order to maximize the benefit from vaccination. Important considerations during immunization are as follows:

i. Compliance with the recommended dose and route of vaccination limits adverse events and loss of efficacy.
ii. A minimum interval of 4 weeks is recommended between the administrations of two live vaccines, if not administered simultaneously. Exceptions are OPV and MMR and OPV and oral typhoid (Ty21a), where administration of one before or after another is permitted if necessary.
iii. Killed antigens may be administered simultaneously or at any interval between the doses. However, a minimum interval of 4 weeks between doses of DPT enhances immune responses. A gap of 3–4 weeks is recommended between two doses of cholera or yellow fever vaccine.
iv. There is no minimum recommended time interval between two types of vaccines. A live and an inactivated viral vaccine can be administered simultaneously at two different sites.
v. A delay or lapse in the administration of a vaccine does not require the whole schedule to be repeated; the missed dose can be administered to resume the course at the point it was interrupted.
vi. Mixing of vaccines in the same syringe is not recommended, unless approved by the manufacturer.
vii. The following are not contraindications to immunization: minor illnesses (e.g. upper respiratory tract infection and diarrhea, mild fever), prematurity, history of allergies, malnutrition, recent exposure to infection and current therapy with antibiotics.
viii. Live vaccines are contraindicated in children with inherited or acquired immunodeficiency and during therapy with immunosuppressive drugs. Live viral vaccines may be given after short courses (less than 2 weeks) of low dose steroids.
ix. Immunoglobulins interfere with the immune response to certain live vaccines like measles or MMR. If immunoglobulins are administered within 14 days of the vaccine, vaccination should be repeated after 3–6 months. Immunoglobulins do not interfere with the immune response to OPV, yellow fever or oral typhoid vaccines. Hepatitis B, tetanus and rabies vaccine or toxoid may be administered concurrently with their corresponding immunoglobulin.
x. Active immunization is recommended following exposure to rabies, measles, varicella, tetanus and hepatitis B.

COMMONLY USED VACCINES

The following section describes vaccines used commonly, either as a part of the National Immunization Program, or as recommended by the Indian Academy of Pediatrics Committee on Immunization (IAPCOI, 2012) for all children. Some vaccines are recommended for use only in certain high-risk categories of patients. Important instructions for vaccination are summarized in Boxes.

BCG Vaccine

The Bacillus Calmette Guérin (BCG) vaccine is a live attenuated vaccine that protects against tuberculosis. The

most common used strains of BCG bacteria are Copenhagen (Danish 1331), Pasteur and Glaxo. The Danish 1331 strain used in India was produced at Guindy, Tamil Nadu. The vaccine is available as a lyophilized (freeze dried) powder in a vacuum-sealed dark multidose vial that is reconstituted with sterile normal saline. Each dose contains 0.1–0.4 million live viable bacilli. Since the vaccine is extremely sensitive to heat, the cold chain should be maintained during transit. While the lyophilized form is stable for one year at 2–8°C, the potency drops rapidly upon reconstitution.

BCG vaccine primarily induces cell mediated immunity. The protective efficacy of BCG vaccine against severe forms of tuberculosis (e.g. miliary tuberculosis, tubercular meningitis) is about 80%, and the risk of death from tuberculosis is reduced significantly. However, primary infection is not prevented and protection from pulmonary tuberculosis is only 50%. Since childhood tuberculosis accounts for 15–20% of cases, vaccine administration in infancy is useful in preventing serious morbidity. Due to lack of interference in cellular immune response by maternal antibody, administration at birth provides early protection, ensures compliance and is convenient to implement.

Conventionally, the BCG vaccine is administered on the left shoulder at insertion of the deltoid to allow easy identification of the BCG scar (Box 9.1). Intradermal injection using a 26G needle raises a wheal of about 5 mm. Bacilli multiply to form a small papule by 2–3 weeks that enlarges to 4–8 mm in size at 5–6 weeks. The papule ulcerates and heals by scarring at 6–12 weeks. Most children show a positive tuberculin test if tested 4–12 weeks after immunization. Adverse effects including persistent ulceration and ipsilateral axillary or cervical lymphadenopathy are more likely with subcutaneous injection. Children with severe cellular or combined immunodeficiency may develop disseminated BCG disease. Children who are tuberculin positive have an accelerated and enhanced response to BCG administration. This BCG test was previously used as a diagnostic test for tuberculosis. Although considered more sensitive than tuberculin test, the BCG test carries risk of severe ulceration, and is used rarely.

Box 9.1: Bacillus Calmette Guérin (BCG) vaccine

Dose, route	0.1 ml; intradermal
Site	Left upper arm at insertion of deltoid
Schedule	
National Program	At birth; up to 1 yr if missed (catch up)
IAP 2012	As above; catch up till 5 yr
Adverse reactions	Local ulceration or discharging sinus; axillary lymphadenitis; disseminated infection, osteomyeltis or scrofuloderma (in immunodeficient recipient)
Contraindication	Cellular immunodeficiency; symptomatic HIV
Storage	2–8°C; sensitive to heat and light; discard unused vaccine after 4 hr

Poliomyelitis Vaccines

Vaccination is an important strategy for preventing paralytic poliomyelitis, caused by poliovirus serotypes 1–3, chiefly in young children. Two types of vaccines are available as trivalent preparations, the live attenuated oral poliovirus vaccine (OPV) developed by Sabin, and the inactivated poliovirus vaccine (IPV), developed by Salk.

Oral Polio Vaccine (OPV)

The OPV contains live polioviruses attenuated by repeated passage and multiplication during culture in Vero cells. Each dose (two drops) contains 10^5–10^6 median cell culture infectious doses of each serotype 1, 2 and 3. When administered orally, the vaccine viruses infect the intestinal mucosa and multiply in the mucosal cells, termed as 'take' of the vaccine. Mucosal immunity in response to this 'infection' protects from paralytic poliomyeltis by reducing the chances of infection when wild-type poliovirus is encountered: the wild virus is excreted for shorter periods and in lower numbers, thus reducing feco-oral transmission and interrupting wild virus circulation.

OPV contains magnesium chloride as a stabilizing agent. The vaccine is stable at 4–8°C for 3–4 months and at –20°C for a year, but its potency drops rapidly with temperature fluctuations. Potency is monitored using the vaccine vial monitor (VVM), a heat sensitive patch displayed on the label of the vial. The vaccine should be discarded if the color of the inner square in the VVM is as dark as, or darker than, the color of the outer circle.

Multiple doses of OPV are essential to ensure take, which may be affected by competition for mucosal infection by other enteroviruses, concomitant diarrhea (rapid intestinal transit reduces the time available for mucosal infection) and interruption in the vaccine cold chain. For these reasons, vaccine take and seroconversion rates are lower in developing countries as compared to developed countries. To decrease the chances of vaccine failure, at least 3 doses should be administered 4–8 weeks apart. For convenience, OPV vaccine is given simultaneous with DTP vaccination at 6, 10 and 14 weeks (Box 9.2). Seroconversion rates after 3 doses of OPV are highest for serotype 2 (90%) and lowest for serotype 3 (70%). The administration of a 'zero' dose at birth enhances the rates of seroconversion. Two booster doses are given along with DTP boosters at 15–18 months and at 5 yr.

Breastfeeding and mild diarrhea are not contraindication for the administration of OPV. However, children with inherited or acquired immunodeficiency and pregnant women should not receive OPV. OPV should be avoided in household contacts of immunodeficient patients, due to the risk of feco-oral transmission of OPV strain.

Children below 5 yr should receive additional doses of OPV during pulse polio immunization (PPI) campaigns on every National Immunization Day (NID) and sub-National Immunization Day (sNID). In communities

Box 9.2: Oral poliovirus (OPV) vaccine

Dose, route	Two drops; oral
Schedule	
National Program	Administer one dose at birth or within 15 days (zero dose); three doses at 6, 10 and 14 weeks (primary) and two doses at 15–18 mo and 5 yr (boosters); give additional doses on NIDs and SIAs; catch up till 5 yr
IAP 2012	*In sequential IPV-OPV schedule:* OPV given at birth, 6 mo, 9 mo and 5 yr *If IPV not available or not afforded:* Give OPV as in National Program
Adverse reactions	Vaccine derived poliovirus; vaccine associated paralytic poliomyeltis
Contraindications	Inherited or acquired immunodeficiency; symptomatic HIV
Storage	2–8°C; sensitive to heat; use vaccine vial monitor

where poliovirus circulation continues, most adults are immune and only young children are susceptible. Simultaneous administration of OPV to all infants and young children in the community interferes with feco-oral transmission of the circulating wild poliovirus. These interruptions in the circulation of the wild virus are expected to eventually eradicate the wild poliovirus.

OPV is the vaccine of choice for the eradication of poliovirus in countries where wild poliovirus circulation is continued. However, OPV, particularly the serotype 2, is associated with a risk of the virus regaining its neurovirulence to cause vaccine associated paralytic poliomyelitis (VAPP) in 1 of 1.5 million OPV recipients. Another relatively recent phenomenon has been the occurrence of outbreaks of paralytic poliomyelitis by a virulent strain of poliovirus formed by mutation of OPV, called the circulating vaccine derived poliovirus (cVDPV). The epidemiological and biological characteristics of cVDPV are similar to the wild virus. Hence, cVDPV spreads through the community rapidly to cause outbreaks, particularly in areas with low or declining rated of OPV coverage. At least 13 cases of VPDV have been reported from India since 2009.

The activities in the PPI program since 1995–96, and the National Polio Surveillance Project since 1997, have been successful in reducing wild poliovirus circulation in India. Some of these measures included the use of monovalent OPV (mOPV, serotypes 1 and 3) and bivalent OPV (bOPV, lacking serotype 2) during supplementary NIDs and mop-up activities, targeting migrant populations and high-risk areas through supplementary immunization activities (SIAs), environmental surveillance through sewage sampling, and statewise implementation of the Emergency Preparedness and Response Plan. The last wild polio case (serotype 1) was reported from Howrah in January 2011, and India is no longer considered a polio endemic country. The following strategies are proposed by the India Expert Advisory Group on Poliomyelitis to ensure sustained poliovirus eradication from India and to prevent the emergence of cVPDV: (i) sustain standard AFP surveillance; (ii) ensure high rates of routine immunization coverage; (iii) switch from trivalent OPV to bOPV (lacking serotype 2) in 2014; (iv) introduce IPV (booster dose to entire population) in 2013 prior to switch to bOPV to minimize risk of emergence of cVPDV type 2; and (v) conduct two rounds of NIDs using trivalent OPV in 2013 and 2014.

Inactivated Polio Vaccine (IPV)

IPV is a suspension of formaldehyde killed poliovirus grown in monkey kidney, human diploid or Vero cell culture. The vaccine primarily induces humoral immune response, but pharyngeal and possibly, intestinal mucosal antibodies are also induced. Vaccine potency is measured by its 'D' antigen content. Each dose of currently used enhanced potency IPV (eIPV) vaccines contain 40D, 8D and 32D units of the types 1, 2 and 3 polioviruses, respectively. IPV is highly immunogenic, with seroconversion noted in 90–95% infants administered two doses of IPV 2 months apart beyond 8 weeks of age and in 99% of those given 3 doses 4 weeks apart. Hence, vaccination with 2–3 doses of IPV may be combined with DTP beginning at 6–10 weeks (Box 9.3).

While the titers of secretory IgA antibodies and extent of herd immunity induced by IPV are lower than with OPV, the efficacy of IPV in preventing poliomyelitis is excellent. IPV administration has the advantage of not causing VAPP. Hence, most countries with sustained eradication of circulating wild poliovirus have switched to exclusive use of IPV, following a phase of sequential or combined OPV-IPV usage. The Indian Academy of Pediatrics (IAP) recommends the use of a 'sequential IPV-OPV schedule' (Box 9.3) which shall enable the implementation of an exclusive IPV schedule in the future. The administration of two doses each of IPV and OPV is seroprotective for over 90% of vaccines. The advantage of administering IPV and OPV in sequence is that the risk of

Box 9.3: Inactivated poliovirus (IPV) vaccine

Dose, route	0.5 ml; intramuscular or subcutaneous
Schedule	
National Program	Not recommended
IAP 2012	*Sequential IPV-OPV schedule*: Administer 3 doses of IPV at 6, 10 and 14 weeks or 2 doses at 8 and 16 weeks (primary) and one dose at 15–18 mo (booster); also give OPV at birth, 6 mo, 9 mo and 5 yr, and on NIDs and SIAs
Catch up	Up to 5 yr; 3 doses at 0, 2 and 6 mo
Adverse reactions	Local pain, swelling
Contraindication	Known allergy
Storage	2–8°C; sensitive to light

OPV induced VAPP is minimized by prior administration of IPV, while ensuring that adequate mucosal immunity interrupts wild poliovirus circulation. Thus, the sequential schedule maintains high rates of mucosal immunity while preventing VAPP. An 'all IPV' schedule would keep the child at a small risk for VAPP through exposure to the OPV virus through contacts or environment before seroprotective titres are reached by IPV, and is not recommended at present. The IAP schedule retains the birth dose of OPV; this neonatal dose is considered necessary in areas with continued risk of wild poliovirus transmission, and is unlikely to cause VAPP in presence of maternally transmitted antibodies. The IAP recommends the administration of OPV on all NIDs and during SIAs.

A child less than 5-yr-old who has completed primary immunization with OPV may be offered IPV as catch up vaccination in three doses (Box 9.3). IPV is the vaccine of choice in patients with immunodeficiency including symptomatic HIV, and in siblings and close contacts of such patients. These children should not receive OPV, and should receive an additional booster dose of IPV at 5 yr.

Diphtheria Vaccine

Diphtheria continues to be a significant cause of childhood morbidity in countries with poor immunization coverage. Natural immunity to diphtheria is acquired through apparent or inapparent infections (*see* Chapter 10). In developed countries where EPI coverage is high and natural boosting is low, a large proportion of adults are susceptible to diphtheria as a result of waning immunity.

Diphtheria vaccine is a toxoid (DT), containing diphtheria toxin inactivated by formalin and adsorbed on aluminum hydroxide that acts as an adjuvant. The quantity of toxoid contained in a vaccine is expressed as its limit of flocculation (Lf) content. The most commonly used vaccine containing DT is DTwP, a combination vaccine containing 20–30 Lf of DT, 5–25 Lf of tetanus toxoid (TT) and >4 IU of whole cell killed pertussis. Common adverse effects, relating chiefly to the pertussis component, include fever, local pain and induration; rarely, incessant crying and encephalopathy are seen.

Maternal antibodies protect the infant against disease and interfere with immune responses to DTP vaccination, particularly against pertussis. To ensure protection against diphtheria, vaccination should begin within a few weeks after birth and requires multiple doses. Primary immunization with 3 doses given 4–8 weeks apart induces satisfactory antitoxin response to DT and TT in 95–100% infants. However, the protective efficacy against pertussis is lower, at about 70–90%. Immunization does not eliminate *Corynebacterium diphtheriae* from the skin or nasopharynx. Booster doses of diphtheria toxoid are required to achieve a protective antibody titer of 0.1 IU/ml and protect against disease in the first decade of life. Hence, a minimum of 5 doses is recommended; three in infancy (primary immunization) and two booster doses. Box 9.4 indicates the schedule for administration of DTwP or DTaP, containing DT, TT and acellular pertussis.

Other vaccines containing diphtheria toxoid are diphtheria and tetanus toxoids (DT) and combinations with reduced toxoid content (Td, TdaP). If given beyond 7 yr of age, primary immunization or booster doses should be in the form of Td or TdaP, which contain smaller amounts of diphtheria toxoid (2 Lf) and acellular pertussis vaccine than DTP. This reduction of diphtheria toxoid potency minimizes reactogenicity at the injection site but is sufficient to provoke an antibody response in older children and adults. To promote immunity against diphtheria, Td, rather than tetanus toxoid alone, should be used when tetanus prophylaxis is needed following injuries. In nonendemic countries, revaccination against diphtheria every 10 yr may be necessary to sustain immunity among adults, particularly health-care workers.

Pertussis Vaccine

Pertussis (whooping cough) is an important global cause of infectious morbidity, with an estimated annual occurrence of 16 million cases, chiefly in developing countries. While the incidence of pertussis has declined dramatically following EPI coverage, the infection continues to be endemic even in countries with high vaccination rates. The disease usually affects infants and unimmunized adolescents; those <6-month-old have the highest case fatality rate. Natural infections and immunization induce immunity lasting 4–12 yr.

Pertussis vaccine has been traditionally available as DTwP as described above. Two types of pertussis vaccines are available: whole-cell (wP) vaccines based on killed *B.*

Box 9.4: Diphtheria toxoid, tetanus toxoid and killed whole-cell pertussis (DTwP) or acellular pertussis (DTaP) vaccine

Dose, route	0.5 ml; intramuscular
Site	Anterolateral aspect of mid-thigh (avoid gluteal region: risk of sciatic nerve injury; inadequate response)
Schedule	
National Program	DTwP at 6, 10 and 14 weeks (primary); at 15–18 mo and 5, 10, 16 yr (boosters)
IAP 2012	DTaP or DTwP; primary schedule as above; Tdap/Td at 10–12 yr; Td every 10 yr
Catch up ≤7 yr:	DTaP or DTwP at 0, 1 and 6 mo
Catch up >7 yr:	Tdap at 0 mo; Td at 1 and 6 mo
Adverse reactions	Local pain, swelling, fever (DTwP>DTaP)
Contraindications: (i) Progressive neurological disease (administer DT or dT instead); (ii) anaphylaxis after previous dose; (iii) encephalopathy within 7 days of previous dose	
Precautions: Previous dose associated with (i) fever >40.5°C within 48 hr; (ii) collapse (hypotonic-hyporesponsive episode) within 48 hr; (iii) persistent inconsolable crying for >3 hr within 48 hr; (iv) seizures within 72 hr	
Storage	2–8°C; sensitive to light

pertussis organisms, and acellular (aP) vaccines based on highly purified, selected components of the agent. The protective efficacy of primary immunization with 3 doses of pertussis vaccine is only 70–90% and wanes over 6–12 yr, making booster doses essential for continued protection. The administration of DTwP vaccine is commonly associated with local (pain and redness) and systemic (fever) reactions that are chiefly attributed to the pertussis component (Box 9.4). The incidence of these adverse effects increases with the number of doses administered; hence the vaccine is not used beyond 5 doses or beyond 7 yr of age. DTP is also incriminated in the rare induction of serious neurological complications, though conclusive evidence is lacking. Hence, the vaccine is relatively contraindicated in children with progressive neurological disease, but children with stable neurological diseases (e.g. developmental delay, cerebral palsy and idiopathic epilepsy) may be vaccinated. Absolute contraindications to the administration of the vaccine and additional adverse events that require precaution are listed in Box 9.4. Parents should be cautioned about the risk of recurrence of events listed in 'precautions' with further doses of the vaccine; if such an event recurs with a subsequent dose, further doses are contraindicated. Individuals in which DTP is contraindicated should complete the immunization schedule with DT, that contains the same doses of DT and TT as DTP, but is devoid of the pertussis component. DT is recommended for use up to the age of 7 yr, beyond which Td must be used.

Acellular Pertussis Vaccine (DTaP)

The suspicion that the active pertussis toxin and endotoxin are responsible for the high incidence of adverse events associated with DTwP administration led to the development of various types of purified acellular pertusssis vaccines, or DTaP. The available DTaP vaccines contain inactivated pertussis toxin (PT) and one or more additional pertussis antigens, like filamentous hemagglutinin (FHA), pertactin, fimbrial protein and a nonfimbrial protein. Trials have demonstrated that the efficacy of these vaccines is similar to DTwP, but the risk of systemic and local side effects is reduced significantly. Each dose of the vaccine contains at least 4 IU (10–25 mg) of PT component and 6.7–25 Lf of DT.

The DTaP vaccine is not recommended as part of the National Program in India due to its cost. However, the IAP recommends that the vaccine be offered to children when parents opt for it in view of the advantage of fewer side effects, or are reluctant to the administration of further doses of DTwP after an adverse effect with a previous dose, while endorsing the continued use of the DTwP in the National Program. It must be noted that the contraindication for DTaP are the same as for DTwP; and the vaccine should not be administered if a previous dose of DTwP or DTaP was associated with immediate anaphylaxis, or the development of encephalopathy within 7 days of vaccination. These children should complete immunization with DT instead of DTwP or DTaP.

Reduced Antigen Acellular Pertussis Vaccine (Tdap) and Reduced Antigen Diphtheria Toxoid Vaccine (Td)

Immunity against pertussis induced by natural infection or through immunization in infancy wanes by adolescence, resulting in a second peak of the disease in adolescence. Pertussis control is unlikely to be achieved if adolescents and adults remain susceptible to the disease, because they act as a source of infection to susceptible individuals. Immunity against diphtheria also wanes with time and the only effective way to control the disease is through immunization throughout life to provide constant protective antitoxin levels.

The availability of Tdap offers the prospect of reducing pertussis incidence in the community. The rationale for its use is that the reduced antigen content causes less severe adverse effects while being sufficient to induce protective response in a previously immunized individual (booster effect). The available Tdap vaccines in India contain 5 Lf of tetanus toxoid, 2 Lf of diphtheria toxoid and three acellular pertussis components namely, pertussis toxoid 8 µg, filamentous hemagglutinin 8 µg and pertactin 2.5 µg. Contraindications to Tdap are the same as those listed for DTaP or DTwP. Unimmunized individuals should receive one dose of Tdap if older than 7 years; this is followed by two doses of Td vaccine at 1 and 6 months. In some countries, a single dose of Tdap is administered to all children at 10-12 years, followed by Td boosters every 10 yr. There is no data at present to support repeat doses of Tdap. Tdap may also be used as replacement for Td/tetanus toxoid (TT) booster in children above 10 yr and adults of any age if they have not received Tdap in the past and 5 yr have elapsed since the receipt of previous TT/Td vaccine. If less than 5 yr have elapsed since Tdap administration, TT is not required for wound prophylaxis. The IAPCOI recommends the use of Tdap or DTwP and not Tdap, as second booster in children below 7 yr of age.

While standard dose DT is recommended for primary immunization against diphtheria because of its superior immunogenicity and minimal reactogenicity, the reactogenicity of the vaccine increases with age. Since the adult preparation Td, containing 5 Lf of tetanus toxoid and 2 Lf of diphtheria toxoid, is adequately immunogenic in adults, it is recommended for booster doses administered to individuals 7 yr of age or older. The vaccine may be used whenever TT is indicated in children above 7 yr of age.

Tetanus Vaccine

Extensive routine immunization of pregnant women with two doses of TT has led to a decline in the incidence of neonatal tetanus, previously an important cause of neonatal mortality. Immunizing pregnant women with two doses, with the second dose administered at least 2

weeks prior to delivery, provides passive immunity to the baby due to the transplacental passage of IgG antibodies.

Tetanus toxin is inactivated by formalin to make tetanus toxoid (TT) and adsorbed onto aluminum salts to enhance its immunogenicity. Each dose of TT vaccine contains 5 Lf of the toxoid. The vaccine is heat stable and remains potent for a few weeks even at 37°C. The efficacy of TT vaccine varies between 80–100%. An antitoxin level of 0.01 IU/ml is considered protective; however, the level of protection available also depends on the toxin load.

Since tetanus may occur at any age, primary immunization should begin in early infancy. Tetanus toxoid is administered with DT and pertussis (killed or acellular) vaccine in DTP, with 3 doses of the vaccine given 4 weeks apart, followed by boosters at 18 months and 5 yr. DT Td and TT are also available for use in booster immunization at 10 and 16 yr of age and for wound prophylaxis. Previously unimmunized school children should receive 2 doses of TT 1 month apart. Recommendations for routine tetanus prophylaxis in wound management and indications of tetanus immunoglobulin (TIG) are listed in Table 9.5. TT should not be administered after every injury if immunization is complete and last dose was received within last 10 yr.

Table 9.5: Tetanus prophylaxis following wound

Past doses of TT	*Clean minor wound*		*All other wounds*	
	TT	TIG*	TT	TIG*
Unknown or <3 doses	Yes	No	Yes	Yes
≥3 doses	No**	No	No***	No

Use DTwP or DTaP if <7-yr-old and Td or TT in an older child

* TIG: Tetanus immunoglobulin (250 IU intramuscular)

** Yes if >10 yr since last dose

*** Yes if 5 yr since last dose

Measles Vaccine

Measles vaccine is a live attenuated vaccine. The strain used in India is derived from the Edmonston Zagreb strain of vaccine virus grown in human diploid cell culture. Measles vaccine has a shelf life of 1 yr at 4–8°C, and loses potency rapidly after reconstitution. The vaccine should be reconstituted using sterile precautions and any unused vaccine should be discarded after 4–6 hr since bacterial contamination may lead to staphylococcal sepsis and toxic shock syndrome. Box 9.5 lists standard instructions for its administration.

Maternal immunity may interfere with the immune response to the vaccine during infancy. Administration of the vaccine at 9 months in endemic countries like India balances the need of early protection with the ability to ensure seroconversion. Adequate titers of antibody are generated in 85–90% at 9 months age. In case of an outbreak, vaccine administration as early as 6 months of age may be carried out, with a repeat dose at 12–15 months as part of measles or MMR vaccine.

Box 9.5: Measles Vaccine

Dose, route	0.5 ml; subcutaneous
Site	Right upper arm (at insertion of deltoid) or anterolateral thigh
Schedule	
National Program	At 9 mo (≥6 mo during outbreaks; revaccinate ≥4 weeks later, preferably at 12–15 mo as MMR)
IAP 2012	At 9 mo; administer at least 2 doses of measles containing vaccine ≥4 weeks apart; preferably as MMR at 12–15 mo and 4–6 yr
Catch up <12 mo:	Administer measles vaccine
Catch up ≥12 mo:	Administer MMR vaccine
Adverse reactions	Fever, transient macular rash ('measles like' illness) 5–10 days later
Contraindications	(i) Immunosuppressive therapy (e.g. alkylating agents, high dose corticosteroids); (ii) malignancy; (iii) severe immunodeficiency (e.g. advanced HIV); (iv) untreated tuberculosis
Storage	2–8°C; sensitive to heat and light; use within 4–6 hrs of reconstitution

Post exposure prophylaxis with immunoglobulin is indicated for all immunocompromised contacts irrespective of immunization status, and exposed infants aged 6–12 months (*see* section on Passive Immunization). Unimmunized immunocompetent contacts older than 12 months should receive measles or MMR vaccine within 72 hr of exposure.

Measles Mumps Rubella Vaccine

Most developed countries use a combination of measles, mumps and rubella vaccines rather than measles vaccine alone for primary immunization. Since the occurrence of mumps in adulthood is associated with the risk of oophoritis, some programs recommend the administration of mumps vaccine to all young adults who have not had the disease. Rubella vaccination is mainly directed at prevention of the congenital rubella syndrome and not prevention of primary rubella infection, which is a benign illness.

The mumps component of MMR vaccine has live attenuated mumps virus derived from the Jeryl Lynn strain grown in chick embryo or human diploid cell cultures. Clinical efficacy is 75-90%. The vaccine is safe; there is no association of the vaccine with autism or Crohn disease unlike postulated previously. Aseptic meningitis may occur in 1 in 10^4 to 10^5 doses, but is mild and often subclinical. Monovalent mumps vaccine is currently not available in India. Available rubella vaccines are derived from the RA 27/3 strain of the virus grown in human diploid or chick embryo cell culture. The vaccine has a seroconversion rate of over 95% and long lasting immunity, possibly lifelong.

Adverse effects following immunization are mild (Box 9.6). The vaccine is contraindicated in pregnant women and in immunocompromised persons. However, MMR vaccine is recommended for asymptomatic and symptomatic individuals with HIV if not severely immunocompromised.

Each 0.5 ml dose of the vaccine contains 1000, 5000 and 1000 TCID50 of measles, mumps and rubella, respectively. The vaccine is dispensed as a lyophilized preparation in single and multiple dose. The vaccine should be used within 4 hr of reconstitution to prevent loss of potency. Box 9.6 summarises instructions for its administration. The vaccine is recommended for use beyond 12–15 months of age because maternal antibodies interfere with response to the vaccine if given earlier. IAP recommends two doses of MMR vaccine, to decrease the risk of primary vaccine failure to the mumps and rubella components.

Haphazard use of rubella or MMR vaccine in children without ensuring optimal immunization coverage may result in an epidemiological shift of disease with more clinical cases in adulthood and a paradoxical increase in congenital rubella syndrome. Hence, the vaccine should be introduced in the National Program only after ensuring that the routine immunization coverage is at least 80%.

Hepatitis B Vaccine

India has intermediate endemicity for hepatitis B virus (HBV), with about 4% individuals being chronic carriers of the virus. HBV is the leading known cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Infection with HBV may be acquired by the perinatal route (vertical transmission), during childhood through close contact with infected family members (horizontal transmission), through transfusions or use of infected needles and by sexual contact. Infection at younger age is associated with higher risk of chronic carriage and chronic liver disease. In regions of high and intermediate endemicity, vertical and horizontal transmissions are major modes of infection. Hence the WHO recommends universal hepatitis B vaccination in these regions. The Government of India has initiated the incorporation of the vaccine in the National Immunization Schedule in a phased manner.

The current hepatitis B vaccine is a highly purified vaccine produced by recombinant DNA techniques in yeast species and contains aluminium salts as adjuvant. Each pediatric dose of 0.5 ml contains 10 μg of antigenic component. It is recommended that the dose be doubled in adults, patients on hemodialysis, immunocompromised individuals and those with malignancies. Seroconversion rates are > 95% after three doses. An antibody titre of >10 mIU/ml is considered protective. Box 9.7 summarizes recommendations for administration of hepatitis B vaccine. Since immunization at birth prevents horizontal transmission, vaccination should begin at birth if the mother's HBsAg status is not known. Immunization at birth, 1 and 6 months is considered ideal in terms of its proven immunological efficacy. Attempts at integrating the vaccination into the National Schedule without increasing number of contacts have led to trials of other schedules which have been found to provide good efficacy. Where birth dose has been missed, it may be given at 6, 10 and 14 weeks of age. Currently, there is no evidence to suggest that booster doses are required.

Hepatitis B surface antigen (HBsAg) screening should be offered to all pregnant women. If the mother is known to be HBsAg negative, vaccination of the child may begin at 6 weeks. Where the mother's status is not known, it is safer to vaccinate the newborn within a few hours of birth. If the mother is known to be HBsAg positive, the child

Box 9.6: Measles, mumps, rubella (MMR) vaccine

Dose, route	0.5 ml; subcutaneous
Site	Right upper arm (at insertion of deltoid) or anterolateral thigh
Schedule	
National Program	At 15–18 mo (only in some states)
IAP 2012	Two doses at 15 (12–18) mo and 4–6 yr; minimum age 12 mo; second dose may be given at <4 yr but ≥4 weeks after the first dose
Catch up ≥12 mo:	Administer 2 doses ≥4 weeks apart; one dose if received MMR vaccine previously
Adverse reactions	Fever, transient rash, arthralgia, aseptic meningitis, lymphadenopathy
Contraindications	(i) Immunosuppressive therapy (e.g. alkylating agents, high dose corticosteroids); (ii) malignancy; (iii) severe immunodeficiency (e.g. advanced HIV); (iv) untreated tuberculosis
Storage	2–8°C; sensitive to heat and light; use within 4–6 hr of reconstitution

Box 9.7: Hepatitis B vaccine

Dose, route	0.5 ml (1 ml in adults and in children receiving hemodialysis); intramuscular
Site	Anterolateral thigh (deltoid in adults); avoid gluteal region
Schedule	
National Program	At birth (<12-hr-old), 6 weeks, 14 weeks
IAP 2012	At birth, 6 weeks and 6 mo; may give 3–4 doses in an alternative schedule* while ensuring that (i) doses 1 and 2 are ≥4 weeks apart; (ii) doses 2 and 3 are ≥8 weeks apart; (iii) final dose is at ≥6 mo of age and ≥16 weeks beyond first dose
Catch up	Complete 3 doses series; second dose is given ≥4 weeks and third dose ≥8 weeks after previous dose
Adverse reactions	Local soreness; fever; fatigue
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; do not freeze

*Alternative schedules: (i) birth, 1 and 6 mo; (ii) birth, 6 and 14 weeks; (iii) birth, 6, 10 and 14 weeks; (iv) 6, 10 and 14 weeks

must receive the vaccine within a few hours of birth, along with hepatitis B immunoglobulin (HBIG) within 24 hr of birth at a separate site (*see* section on Passive Immunization) If HBIG has been administered, any of the schedules incorporating a birth dose of the vaccine can be used. If HBIG is not administered, the baby should be immunized in an accelerated schedule at 0, 1 and 2 months, along with an additional dose at 9–12 months.

HBIG provides immediate passive immunity and is used in circumstances where an acute exposure to HBsAg positive biological material has occurred. Combined passive and active immunization with concurrent use of HBIG and HB vaccination results in 90% decrease in risk of HBV transmission in circumstances such as needle stick injuries, sexual exposure or use of blood product not screened for HBV (*see* section on Passive Immunization).

Varicella Vaccine

Chickenpox (varicella) chiefly affects children and young adults in whom it is usually a benign and self limiting infection. The disease may be associated with complications when occurring in adults, pregnant women and immunocompromised individuals. The available vaccines are live attenuated vaccines derived from the Oka strain of the virus grown in human diploid cell culture. Each dose of the lyophilized vaccine contains at least 1000 plaque forming units of the attenuated virus. The vaccine elicits both cellular and humoral immune responses and has high (95–99%) protective efficacy. In children above 12 yr, seroconversion rates are 80% with one dose and 90% after two doses. While one dose of the vaccine is sufficient to seroconvert 95% of younger children, two doses are recommended to reduce the risk of breakthrough infections due to waning immunity.

Varicella vaccine is not included in the National Immunization Program since varicella has less public health relevance than other vaccine preventable diseases, the vaccine is expensive, and ensuring high rates of immunization coverage would be essential to ensure that the disease epidemiology does not shift to affect older individuals, causing severe disease. The IAP recommends the use of varicella vaccine in all children where it is afforded (Box 9.8). It is particularly important to vaccinate children with chronic cardiac or pulmonary disease, HIV infection (while CD4 count is >15% for age), leukemia (during disease is remission with chemotherapy discontinued for >3 months) and conditions like nephrotic syndrome where prolonged immunosuppression is anticipated. The vaccine should also be considered in household contacts of immunocompromised children, and in adolescents and adults without history of varicella in the past, particularly if staying or working in an institutional setting (e.g. school, hospital or military establishment). Unimmunized household contacts of patients with varicella should receive varicella vaccine within 72 hr but its protective efficacy is uncertain. Varicella zoster immunoglobulin (VZIG) provides passive immunity to nonimmune individuals who are exposed to varicella and are at significant risk of complications, such as pregnant women, neonates whose mothers have developed varicella 5 days before or 2 days after delivery, and immunocompromised children and adults. These individuals should receive postexposure prophylaxis with VZIG (5–25 units/kg of body weight or 12.5 units/kg body weight IV) within 96 hr of exposure.

Box 9.8: Varicella vaccine

Dose, route	0.5 ml subcutaneously
Site	Anterolateral thigh or upper arm
Schedule	
National Program	Not included
IAP 2012	Two doses at 15–18 mo (minimum age 12 mo)* and 4–6 yr; second dose may be given >3 mo after the first dose
Catch up	Complete two dose series with minimum interval of 3 mo between the doses (≥4 weeks if ≥12-yr-old)
Adverse reactions	Fever, rash, local pain or redness
Contraindications	Anaphylaxis after previous dose; lymphopenia; immunodeficiency; during immunosuppressive therapy
Storage	2–8°C; protect from light; use within 30 min of reconstitution

*Risk of breakthrough infections is lower if given at ≥15 mo

Typhoid Vaccine

Enteric fever is an important public health problem in India. Three types of typhoid vaccines have been developed, with efficacy varying between 50% and 70%.

The whole cell inactivated typhoid vaccines (TA/TAB) were inexpensive vaccines containing heat-killed phenol-preserved or acetone-inactivated whole cell *Salmonella typhi*, and *S. paratyphi A* and *B*. Two doses of the vaccine, administered subcutaneously 4 weeks apart in children >6-month-old, induced antibodies against the cell wall somatic (O) and flagellar (H) antigens. The vaccine had a protective efficacy of 50–70% but required revaccination every 2–3 yr. The serological response interfered with the interpretation of Widal test. Adverse effects were common, including fever, local pain and malaise. This vaccine is currently not available in India.

The Vi capsular polysaccharide vaccine contains the purified Vi antigen that prevents phagocytosis of *S. typhi* and inhibits serum bactericidal action. This unconjugated polysaccharide vaccine elicits anti-Vi antibodies in children above 2 yr and has protective efficacy of 50–75% after 2 weeks of administration. Each dose of the vaccine has 25 µg of the antigen. The IAPCOI recommends its use in all children every 3 yr beginning at 2 yr (Box 9.9). While a Vi polysaccharide conjugate vaccine has been developed,

Box 9.9: Typhoid Vi capsular polysaccharide vaccine	
Dose, route	0.5 ml, subcutaneous or intramuscular
Site	Anterolateral thigh (deltoid in adults)
Schedule	
National Program	Not included
IAP 2012	One dose at 2 yr; repeat every 3 yr
Catch up	One dose beyond 2 yr
Adverse reactions	Local pain, swelling, redness; fever
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; do not freeze

current data on immunogenicity and safety is insufficient to recommend its use.

An oral vaccine has been developed that contains live attenuated bacteria of the Ty21a strain of *S. typhi*. A genetically stable mutation makes it unlikely for the bacteria to revert to a virulent form. The vaccine is available as an enteric capsule containing 2–6 million live lyophilized bacteria that induce intestinal mucosal immunity. Primary immunization, consisting of 3 doses given on alternate days on an empty stomach, has an efficacy of 50–60% within 7 days of completion of the schedule. Since the bacteria are inactivated by gastric acidity, capsules must be swallowed intact. Hence, the vaccine is unsuitable for children younger than 6 yr. Antibiotics should not be given between 3 days before to 7 days after the vaccine administration to avoid interference with vaccine 'take'. The vaccine is contraindicated in children with significant immunodeficiency. Mild adverse effects include abdominal discomfort and fever. Vaccination has to be repeated every 3 yr. The vaccine is not available in India.

Hepatitis A Vaccine

Infection with hepatitis A virus is endemic in India and is usually benign in children below 5 yr of age, with the majority (50–85%) presenting with minor manifestations like any viral illness. Disease severity, complications and mortality are higher in those with underlying chronic liver disease, adolescents and adults.

The available vaccine contains formalin inactivated viruses grown on human diploid cell lines. Each pediatric dose of the vaccine has an antigen content of 720 ELISA units and aluminium hydroxide as an adjuvant. The vaccine has protective efficacy of 95–100%. Since maternal antibody may interfere with immune response to the vaccine, the vaccine is avoided in infancy (Box 9.10). A combined vaccine containing hepatitis A and B vaccines may be used in a three dose schedule.

The hepatitis A vaccine is not recommended for universal immunization since the diseases prevented is usually benign and of less public health relevance. However, with improvement in hygiene, the infection is increasingly acquired at later age and may be symptomatic, sometimes with fulminant hepatic failure. Hence, IAP receommeds its administration to all children. The vaccine should

Box 9.10: Hepatitis A vaccine	
Dose, route	0.5 ml, intramuscular
Site	Deltoid
Schedule	
National Program	Not included
IAP 2012	Two doses beyond 1 yr of age, given 6 mo apart
Catch up	Complete two dose series with interval of ≥6 mo; if ≥10-yr-old, screen for HAV antibody first, administer vaccine only if seronegative; use adult vaccine (1440 units) if ≥13-yr-old
Adverse reactions	Local pain; nausea, anorexia, malaise
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; protect from light; use within 30 min of reconstitution

particularly be considered in children with chronic liver disease who are seronegative for HA virus, children attending crèches and day care facilities, travelers to endemic areas and in adolescents who are known to be seronegative for HA virus. The vaccine is effective if administered to unimmunized household contacts of patients symptomatic with HAV within the last 10 days.

A live attenuated vaccine has become available in India. Two doses of 1 ml each are administered subcutaneously with an interval of 6 months between the doses.

Rotavirus Vaccine

Rotavirus is a major cause of diarrhea related morbidity and mortality in children worldwide. Of the 7 known serogroups (A-G), group A rotaviruses cause most human disease. Epidemiologic studies indicate that rotavirus is responsible for 6–45% of diarrheal illnesses requiring hospital admission in Indian children. Rotavirus infections usually affect young infants, and natural infections do not protect against re-infection or severe disease. The first licensed rotavirus vaccine (Rotashield), a live oral tetravalent vaccine, was withdrawn soon after its introduction in 1998 due to occurrence of vaccine associated intussusception. Two live oral vaccines, namely Rotarix and RotaTeq, are currently marketed worldwide.

Rotarix is a monovalent (RV1) live attenuated vaccine containing the human rotavirus G1P (8) strain attenuated by culture in Vero cells. Each dose has at least 10^6 median cell culture infective dose (CCID50), and is given in orally in a 2 dose schedule (Box 9.11). RotaTeq is a pentavalent (RV5) vaccine consisting of strains reassorted between the bovine and human WC3 rotaviruses containing specific VP7, VP4 and/or G6 proteins, and attenuated by culture in Vero cells. Each dose of the vaccine contains a minimum titre of 2–2.8 × 10^6 infectious units per reassortant and not greater than 116 × 10^6 infectious units per aggregate dose, suspended in a solution of buffer and stabilizer. It is administered orally in a three dose schedule at 2, 4 and 6 months.

Box 9.11: Rotavirus vaccine

Dose, route	RV1: 1 ml (lyophilized) or 1.5 ml (liquid); RV5: 2 ml (liquid); oral
Schedule	
National Program	Not included
IAP 2012	RV1: 2 doses; RV5: 3 doses; at 6–14 weeks ≥4 weeks apart; maximum age <15 weeks for the first dose and <8 mo for the final dose; do not begin schedule at ≥15 weeks
Adverse reactions	Intussusception (rare)
Contraindication	Past history of intussusception; severe immunodeficiency
Precaution	Postpone vaccination during ongoing diarrhea or moderate illness
Storage	2–8°C; do not freeze; protect from light; use immediately after reconstitution or opening

In trials conducted elsewhere, both vaccines have shown 85–98% efficacy against severe rotavirus gastroenteritis and have been demonstrated to be safe with no increased risk of intussusception as compared to placebo. Simultaneous administration of rotavirus vaccines with OPV does not appear to affect adversely the efficacy of either vaccine. While efficacy trials in developing countries of Africa and Asia are ongoing, evidence suggests that the efficacy of the vaccine may be lower in countries with high rates of infection and competition for intestinal infection by other pathogens. However, the morbidity and mortality burden of rotavirus in countries like India is huge and routine immunization with current rotaviral vaccines, despite their lower efficacy in these settings, are expected to prevent significant morbidity and mortality. Hence the WHO and IAP endorse routine imminuzation with these vaccines while more efficacious and region specific vaccines are developed.

It is important to adhere to the vaccination schedule. Due to a small risk of intussusception, and the highest risk of rotaviral infections being in early infancy, it is recommended that immunization with current vaccines should be completed by the age of 8 months. Vaccination should be postponed in infants with acute gastroenteritis as it might compromise efficacy of the vaccine. Risks versus benefits of vaccination should be considered while considering vaccination for infants with theoretically increased risk of intussusception, such as chronic gastrointestinal disease and gut malformations.

Haemophilus influenza B Vaccine

Worldwide, *Haemophilus influenza* b (Hib) is an important cause of invasive infections like pneumonia, meningitis and bacteremia, especially in children below 2 yr of age. Effective vaccines are available and their incorporation into the immunization schedule of developed countries has resulted in a significant decline in morbidity and mortality attributable to invasive disease due to Hib.

The capsular polysaccharide is the moiety used as the antigen in the available vaccines. Since polysaccharide antigens are poorly immunogenic in children below 2 yr of age, it is conjugated to a protein antigen in order to enhance the immunogenicity. The PRP-T vaccine has the tetanus toxoid as the conjugate, the Hb-OC has the mutant CRM 197 diphtheria toxin, while PRP-OMP incorporates the outer membrane protein of meningococcus as conjugate. PRP-OMP is a more immunogenic vaccine than the other two. Conjugate vaccines for *haemophilus influenza* containing diphtheria toxoid do not contain enough toxoid to be a substitute for DTP or DT.

The IAP-COI recommends that Hib vaccine be administered to all children; however, given the epidemiological profile of infections with Hib, unimmunized children above 5 yr of age should not receive the vaccine. Vaccination is particularly recommended prior to splenectomy and in patients with sickle cell disease. Vaccination schedule depends on the age of the child at the time immunization is initiated (Box 9.12). The vaccine is safe and immunogenic and has a protective efficacy of over 95%. The vaccine has been recently introduced as a pentavalent vaccine in some states in India in the National Program.

Pneumococcal Vaccine

Worldwide, *S. pneumoniae* is responsible for 15–50% of all episodes of community acquired pneumonia, 30–50% of all cases of acute otitis media and 50% of deaths due to pneumonia every year. Among 90 known serotypes of *S. pneumoniae*, 20 serotypes are responsible for 80% of invasive pneumococcal disease in all ages, while only 13 serotypes account for 75% of disease burden in young children. In India, it has been demonstrated that serotypes 1, 4, 5, 6, 7, 14 and 19 are the most prevalent serotypes causing invasive pneumococcal disease in children. Children below the age of 2 yr are at greatest risk for invasive pneumococcal disease. The risk for pneumococcal disease is increased in children with congenital immunodeficiency, HIV, those on immunosuppressive therapy,

Box 9.12: *Haemophilus influenzae* b vaccine

Dose, route	0.5 ml intramuscular
Site	Anterolateral thigh
Schedule	
National Program	Introduced in some states as pentavalent vaccine with DPT and hepatitis B
IAP 2012	Three doses at ≥6 weeks given ≥4 weeks apart; one booster at 15–18 mo
Catch up	At 6–12 mo: Two doses ≥8 weeks apart with one booster at 15–18 mo; At 12–15 mo: one dose and one booster at 15–18 mo; 15–60 mo: one dose; not recommended >5-yr-old
Adverse reactions	Fever, rash, local pain or redness
Contraindication	Hypersensitivity to previous dose
Storage	2–8°C

organ transplant recipients, sickle cell disease, asplenia or hyposplenia, chronic cardiac, liver or pulmonary disease (excluding asthma unless on high dose oral steroids), chronic renal failure, nephrotic syndrome, diabetes mellitus and children with cerebrospinal fistula or cochlear implants. Currently, vaccines of two kinds are available, unconjugated polysaccharide vaccine and conjugated vaccines.

The unconjugated polysaccharide vaccine is a 23 valent vaccine (PPV23) containing 25 µg of polysaccharide of each of 23 serotypes contained in vaccine. Since capsular polysaccharides stimulate B cells directly independent of T cell stimulation, the vaccine is poorly immunogenic below 2 yr and immunological memory is low. The vaccine does not reduce nasopharyngeal carriage of *S. pneumoniae*; therefore, it does not provide herd immunity. Its efficacy in preventing invasive pneumococcal disease in the high-risk population is less than 70%. The vaccine is administered intramuscularly in a dose of 0.5 ml; more than two life time doses should not be given.

Pneumococcal conjugate vaccine (PCV) is available as a 13-valent polysachharide vaccine (PCV13) linked to a protein carrier and a 10-valent conjugate vaccine (PCV10) combined with non-typeable *Haemophilus influenzae* vaccine. The introduction of conjugated vaccines for routine immunization in developed nations was associated with a herd effect, resulting from reduction in nasopharyngeal carriage of *S. pneumoniae*, causing a significant decline in pneumococcal disease in unvaccinated contacts of the vaccines. The antigens in the 13-valent conjugate vaccine are from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F that account for the majority of invasive pneumococcal disease in children. The vaccine has a protective efficacy of 95–99% against invasive pneumococcal disease caused by these serotypes. The current vaccines replace the previously available PCV7 vaccine, which covered only 55% of pneumococcal serotypes prevalent in India. Conjugated vaccines with broader serotype vaccines should be available in future.

Since pneumococcus is a cause of significant morbidity and mortality in children (especially below 2-yr-old), the IAPCOI recommends the use of the currently available conjugate pneumococcal vaccine (PCV13 or PCV10) in healthy children aged <2 yr (Box 9.13). Revaccination or further doses after age appropriate primary series with PCV 13 is not currently recommended. Vaccination of healthy children >5 yr is likely to be associated with less benefits due to the low risk of invasive pneumococcal disease in these children and is not recommended.

All children at high-risk of acquiring the infection or at risk of complications should additionally receive the polysaccharide vaccine, because while PCV provides robust immune response and immune memory, PPV23 provides expanded serotype coverage. Where the cost of PCV is prohibitive, PPV23 alone is given to high-risk children >2 yr of age. If affordable, PCV should be given first, in the schedule described above; for children over 5 yr a single dose of PCV is recommended. In children aged >2 yr, PPV23 should is given as a single dose. Only one additional dose of PPV23 is recommended in high-risk children; this may be given after 3–5 yr if the child is less than 10 yr of age and after 5 yr if child is aged more than 10 yr.

Box 9.13: Pneumococcal conjugate vaccines

Dose, route	0.5 ml subcutaneous or intramuscular
Site	Anterolateral thigh
Schedule	
National Program	Not included
IAP 2012	Three doses at ≥6 weeks given ≥4 weeks apart and one booster at 15–18 mo[1,2]
Catch up	At 7–11 mo: Two doses ≥4 weeks apart and one booster at 15–18 mo; 12–23 mo: Two doses ≥8 weeks apart; 24–59 mo: one dose; >60 mo: one dose, only if in high-risk category
Adverse reactions	Fever, local pain, soreness, malaise
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; do not freeze

[1]If primary immunization was with the 7-valent vaccine, administer one dose of the 13-valent vaccine to (i) children 14–59-mo-old; (ii) children 60–71-mo-old and an underlying medical condition.

[2]Children in high-risk categories should additionally receive the polysaccharide vaccine ≥8 weeks after the last dose of PCV vaccine.at at 2 yr of age; revaccinate with polysaccharide after 3–5 yr if continue to be at high-risk of infections

Human Papillomavirus (HPV) Vaccine

Cervical cancer is the second most common cancer and the leading cause of cancer related deaths in women. The cancer is almost always caused by persistent infection with oncogenic human papillomavirus (HPV) belonging to 20 of 100 known serotypes of HPV. Serotypes 16 and 18 are associated with 70% cases of invasive cervical cancer. Oncogenic serotypes of HPV may also cause anal, vulvar, vaginal, penile and oropharyngeal cancers. Nononcogenic HPV serotypes 6 and 11 cause 90% of anogenital warts.

The available vaccines against HPV are self-assembling virus like particles (VLP) constituted of recombinant L1, the major capsid protein of HPV. Since these do not contain any nucleic acid, these empty capsids are noninfectious but capable of eliciting a host immune response. VLP based vaccines prevent more than 90% new infections with the serotypes included in the vaccines. The vaccines do not protect against serotypes with which infection has already occurred before vaccination.

Two vaccines are currently licensed. Gardasil (HPV4) is a quadrivalent vaccine active against HPV strains 6, 11, 16 and 18 and Cervarix (HPV2) is a bivalent vaccine targeting only HPV 16 and 18. Clinical trials with both vaccines have shown good efficacy against types 16, 18 related cervical *in situ* neoplasia grades 2 and 3 and

adenocarcinoma *in situ*. Gardasil is also effective in preventing vaccine type related genital warts, vaginal intraepithelial neoplasia and vulvar intraepithelial neoplasia. Both vaccines are highly immunogenic and persistent protection for up to 5 yr has been demonstrated. There are no serious adverse events associated with HPV immunization.

The vaccine is of public health importance in a country like India where compliance with routine screening for cervical cancer is low and several women are diagnosed with the cancer every year. However, the duration of protection provided and hence, the ideal age at vaccination and need of booster doses, if any, remain to be determined. The vaccine is not expected to be effective in women already persistently infected with the virus. Any cross protection against other strains is likely to be modest. Sociocultural issues related to the vaccine being protective against a sexually transmitted disease may limit its acceptability. Importantly, immunization status should not create a false complacency resulting in a decline in routine screening for cervical cancer, especially when routine immunization has not been ensured, because this may result in a paradoxical rise in cervical cancer related mortality. Screening programs should therefore continue as per recommendations.

The IAPCOI recommends that the HPV vaccines should be offered to all girls who can afford the vaccine, given prior to sexual debut, as a cervical cancer preventing vaccine and not as a vaccine against a sexually transmitted infection (STI). The recommended age for initiation of vaccination is 10–12 yr, with catch up vaccination permitted up to 26 yr of age (Box 9.14). Both vaccines are contraindicated in patients with history of hypersensitivity to any vaccine and should be avoided in pregnancy. The vaccines may have a lower immunogenicity and efficacy in immunocompromised hosts. At present boosters are not recommended.

Japanese B Encephalitis Vaccine

Japanese encephalitis is an important cause of viral encephalitis in our country; being responsible for 2000–3000 cases and 500–600 deaths annually. In absence of specific therapy, vaccination remains the most important control measure and is indicated in all children between 1–15 yr of age residing in highly endemic areas like Andhra Pradesh, Uttar Pradesh and Karnataka. It should also be given to visitors to endemic areas if duration of stay is expected to be more than 4 weeks. Three types of vaccine are available, the mouse brain-derived inactivated vaccine, the cell culture-derived inactivated vaccine and the cell culture-derived live attenuated vaccine.

The mouse brain-derived vaccine is an inactivated vaccine administered subcutaneously in a dose of 0.5 ml for children between 1–3 yr and 1 ml in an older child. Primary immunization consists of 3 doses; the second and third doses are given 7 and 30 days after the first dose. Booster doses are administered at 1 yr after primary immunization and every 3 yr subsequently. Common adverse events include fever, malaise and local tenderness and redness. Reports of a temporal relationship of vaccination to acute encephalitis and anaphylactic reactions in recipients have resulted in decline in usage of this vaccine. An inactivated vaccine derived from primary hamster kidney cell line was popular in China, but its use was discontinued following availability of the live cell culture derived vaccine.

The cell culture derived live attenuated vaccine is the preferred vaccine in India. The vaccine is based on a stable neuro-attenuated strain of JE virus, the SA–14–14–2, and was first used in China and subsequently elsewhere in Asia. Studies demonstrate that the protective efficacy of on dose of the vaccine is 98–99% (Box 9.15). The vaccine has been used since 2006 in campaigns in hyperendemic districts of Uttar Pradesh, West Bengal, Assam and Karnataka.

Influenza Vaccines

The influenza virus has three antigenic types (A, B and C) and several subtypes (based on the surface antigens hemagglutinin and neuraminidase), with frequent mutations due to antigenic drifts and antigenic shifts, resulting in frequent changes in the strains in circulation. Since the available vaccines elicit a strain specific humoral immune response, this is the only vaccine whose

Box 9.14: Human papillomavirus vaccine

Dose, route	0.5 ml intramuscular
Site	Upper arm (deltoid)
Schedule	
National Program	Not included
IAP 2012	Girls 11–12 yr old (minimum 9 yr*) HPV4: At 0, 2 and 6 mo; HPV2: 0, 1 and 6 mo)
Catch up	Before initiation of sexual activity
Adverse reactions	Local pain, swelling, erythema; fever
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; protect from light

* HPV4 may be given to boys as well

Box 9.15: Japanese B encephalitis vaccine

Dose, route	0.5 ml subcutaneous
Site	Anterolateral thigh or upper arm
Schedule	
National Program	Only in endemic areas; one dose at 9 mo (minimum age 8 mo)
IAP 2012	Only in endemic areas
Catch up	One dose in susceptible children up to 15-yr-old (during disease outbreak or in campaign)
Adverse reactions	Fever, malaise

composition has to be altered yearly according to the expectation of the prevalent strain in the next peak season.

Influenza vaccines are inactivated vaccines derived from viruses grown in embryonated hen's eggs and are of three types. Whole virus vaccines that were available previously were associated with significant adverse effects, especially in children; hence they are no longer used. Split product vaccines are produced from detergent treated highly purified influenza viruses. Surface antigen vaccines are subunit vaccines containing the purified antigens hemagglutinin and neuraminidase. Current vaccines are highly immunogenic and associated with minimal adverse events. The vaccines are usually trivalent, containing two influenza A subtypes and one influenza B strain. The composition of the vaccine is reviewed by the WHO six-monthly to update antigens contained in the vaccine based on the prevalent circulating strains. The vaccine is recommended for use in high-risk children, including those with chronic cardiac or pulmonary disease, immunodeficiency, HIV infection, sickle cell disease, diabetes mellitus, systemic lupus erythematosus, longterm aspirin therapy and children with severe asthma who require oral corticosteroids. Recommendations for administration are listed in Box 9.16.

Meningococcal Vaccine

Neisseria meningitidis is a major cause of bacterial meningitis accounting for 30–40% of cases in children below 15 yr. Endemic cases and severe meningococcal disease are primarily seen in children and adolescents; attack rates are highest in infants between 3 and 12 months of age. Even with treatment, case fatality rates are high (5–15%). The infection is usually due to serogroups A, B, C, Y and W135; serogroup A (and sometimes C) may cause epidemics. In India endemic cases are chiefly due to serogroup B. Infection results in serogroup specific immunity.

Two types of vaccines have been developed: the unconjugated polysaccharide vaccines and a conjugate group C vaccine. Unconjugated vaccines contain group specific capsular polysaccharides, which, like other polysaccharide vaccines, are T cell independent and do not induce immunological memory and are not very immunogenic below 2 yr of age. Bivalent (containing group A and C) and tetravalent (containing groups A, C, Y and W135) vaccines are available.

Box 9.16: Inactivated influenza vaccine

Dose, route	0.5 ml (0.25 ml <3 yr); intramuscular
Site	Anterolateral thigh or upper arm
Schedule	
National Program	Not included
IAP 2012	Only in high-risk categories First time vaccination: Two doses ≥4 weeks apart if 6 mo to 9-yr-old and one dose if >9 yr; annual revaccination with one dose; best administered before rainy season
Adverse reactions	Local pain, redness; anaphylaxis
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; do not freeze

The meningococcal vaccine is indicated in close contacts of patients with meningococcal disease (as an adjunct to chemoprophylaxis), certain high-risk groups (complement deficiency, sickle cell anemia, asplenia, before splenectomy), during disease outbreaks (when caused by a serogroup included in the vaccine) and before travel to the high endemicity belt in Africa.

The vaccine is administered as indicated in Box 9.17. If required, revaccination is considered after 3–5 yr. The vaccine is not recommended for universal immunization in India. During epidemics, children above 2 yr of age may be administered the vaccine, particularly close household contacts.

The conjugated group C vaccine has been marketed in some countries where group C is the most common isolate in meningococcal disease. Three doses of the vaccine are administered 4–8 weeks apart in children below 6 months, while 2 doses suffice for 6–12 months age and 1 dose is enough in older children.

Box 9.17: Meningococcal vaccine

Dose, route	0.5 ml subcutaneous or intramuscular
Site	Anterolateral thigh or upper arm
Schedule	
National Program	Not included
IAP 2012	Single dose in high-risk categories older than 2 yr; repeat after 3–5 yr if required
Adverse reactions	Fever, local pain or redness
Contraindication	Anaphylaxis after previous dose
Storage	2–8°C; protect from light; use within 30 min of reconstitution

Rabies Vaccine

Rabies is endemic in India, accounting for 50% of global mortality associated with the disease. The previously available nerve tissue vaccines are no longer recommended due to poor efficacy and high incidence of adverse effects, like neuroparalytic reactions. Three types of vaccines are available against the virus. The purified duck embryo vaccine (PDEV), available for several decades, is free from myelin basic protein, is safe and its immunogenicity is comparable to modern tissue culture vaccines. Modern tissue culture vaccines include purified chick embryo cell (PCEC) vaccine (Rabipur), human diploid cell vaccine (HDCV) (Rabivax) and purified vero cell vaccine (PVRV) (Verorab, Abhayrab); these vaccines have similar efficacy and safety. The vaccines are available as lyophilized products that are reconstituted before use. The WHO requires each cell culture vaccine to have a potency of at least 2.5 IU per intramuscular dose.

Following an animal bite, the wound should be immediately irrigated with running water for 10 min,

cleaned thoroughly with soap and coated with povidone iodine, 70% alcohol or tincture iodine. All patients with wound category III (WHO recommendations) should receive rabies immunoglobulin (RIG), including transdermal bites or scratches and contamination of mucous membranes with saliva (e.g. licks). RIG is not required in case of licks on intact or broken skin, nibbling of uncovered skin and minor scratches or abrasions without bleeding. Wound suturing should be avoided; if essential, suturing is postponed till after administration of RIG.

RIG provides passive immunity by neutralizing the rabies viruses, thus preventing neural infection. The dose of RIG is 20 U/kg for human (HRIG) and 40 U/kg for equine (ERIG) immunoglobulin. RIG should be infiltrated in and around the wound; in case of large or multiple wounds, RIG may be diluted with normal saline so as to infiltrate all wounded areas. Any remaining immunoglobulin is administered intramuscularly at a site away from vaccine site, usually the deltoid or anterolateral thigh. HRIG is expensive and not widely available. ERIG is associated with a high-risk of adverse effects including anaphylaxis, and requires skin testing prior to its use.

The victim should receive postexposure prophylaxis with rabies vaccine by the intramuscular and intradermal route. The anterolateral thigh and deltoid region are preferred sites for intramuscular administration; the gluteal region should not be used. The dose is 1 ml for all modern tissue culture vaccines except PVRV in which case the dose is 0.5 ml. The intradermal dose is one-fifth of the intramuscular dose. Local pain, swelling or induration are common; less commonly, systemic symptoms may be noted, such as fever, malaise, abdominal pain or headache. The most commonly used schedule for administration is the *Essen Schedule* or *WHO Standard Schedule*, in which the vaccine is administered intramuscularly on days 0, 3, 7, 14 and 30. An additional dose on day 90 is recommended in immunocompromised or severely malnourished individuals. The Zagreb Schedule (two doses on day 0, a dose each on days 7 and 14) induces an early immune response, is now approved for use in India, using either PCEC or PRV, in centers with adequate training and frequent use of the vaccine. "The Thai red Cross Schedule involves administration of two intradermal doses each on days 0, 3 and 7 and one dose each on days 28 and 90.

Pre-exposure prophylaxis is offered to individuals at high-risk of rabies due to contact with animals, e.g. veterinary doctors, wildlife workers, dog handlers, taxidermists, postmen, animal laboratory workers, municipal workers, etc. Three doses are recommended to be given intramuscularly on days 0, 7 and 21 or 28. A booster dose is required after 1 yr and every 5 yr thereafter. In case of re-exposure after completed pre or post-exposure prophylaxis, two doses are recommended on days 0 and 3. The intradermal schedule using MTCV is also acceptable; here the boosters are required yearly. Since HRIG is required in addition to the vaccine for most animal bites and the availability, cost and knowledge regarding use of HRIG is limited, pre-exposure prophylaxis against rabies should be offered to all children at high-risk for rabies.

Combination Vaccines

With the availability of vaccines against several diseases, a child needs to be administered more than twenty antigens in the first two years. A combination vaccine consists of multiple immunogens physically combined in a single preparation, including antigens or serotypes of the same pathogen (e.g. trivalent polio vaccine) or different pathogens (e.g. DTP vaccine). The concept is distinct from simultaneous administration of multiple physically separate vaccines at the same time at separate sites or by different routes. Studies indicate that the immune system of an infant can respond to a large number of antigens simultaneously, and that the efficacy of currently recommended vaccines is not altered by their concurrent administration, if recommended to be given at the same age. Combining vaccines has several benefits. The number of injections at each visit is decreased and fewer visits are required, leading to increased compliance and enhanced immunization coverage. Benefits to the immunization program include decreased requirement of storage space, decreased expenditure on packaging and transportation, and simultaneous vaccination against several diseases for children who have missed previous doses.

However, there are several challenges in the development of combination vaccines. The antigens combined together in a vaccine should be compatible with each other, should not interfere with each other's immunological 'take' (relevant especially for live viral vaccines) and should be indicated at the same time. Some antigens may require an adjuvant to be present in the combination. The total volume of the vaccine should not be excessive and the product should be stable for at least 18–24 months. Before recommending a particular combination vaccine, its efficacy is evaluated in clinical trials and cost benefit analyses. Combination vaccines in common use include DTwP, DTaP, DT, dT, OPV, IPV, MMR and influenza vaccines. Other trivalent, quadrivalent or tetravalent combination vaccines that are available in India and abroad are listed in Table 9.6. Some vaccines are not available as combination vaccines but may be combined in the same syringe of permitted by the manufacturer, as indicated in the table.

VACCINE ADMINISTRATION

Standard precautions should be followed to minimize the risks of spreading infections during the administration of vaccines, including attention to hand washing, safe disposal of needles and vaccine vials and appropriate management of needle stick injury. Vaccine administrators should inspect the vaccine and diluent vials for the date of expiry, storage conditions and appearance.

Table 9.6: Combination vaccines for use in children and infants

Vaccine	Example
dTaP	Boostrix®, Adacel®
DTaP–Hib-IPV	Pentaxim®
DTwP	Multiple brands, e.g.Tripvac®, Triple antigen®, Comvac3®
DTwP-HB	Multiple brands, e.g. Shantetra®, Q-VAC®, Tritanrix-HB®, Tripvac-HB®, Comvac-4-HB®
DTwP–HB-Hib	Multiple brands, e.g. Easy-5®, Pentavac®, Comvac-5®, Shan-5® May combine vaccines if permitted by manufacturer, e.g. Qvac®+HibPro®, Hiberix®+Tratanrix®
DTaP–Hib	May combine Tripacel®+ActHib®, Infanrix®+Hiberix®
DTwP–Hib	Multiple brands, e.g. Easy-4®, Quadrovax®, Shan-4®, TetractHib®; Triple antigen®+HibPro®
HepA–HB	Twinrix®
Meningococcal	A, C, Y and 135 (Mencevax ACWY®); A, C, Y and 135 DT conjugate (Meningococcal A & C®)
Pneumococcal	7 valent (Prevnar®), 23 valent (Pneumo23®), polyvalent polysaccharide (Pneumovax®)

Combination vaccines licensed elsewhere but not in India (common brands)
DTaP–HB (Tritanrix®), DTaP–HB–IPV (Pediatrix®), DTaP–HB–IPV/Hib (Infanrix hexa®), dT-IPV, DTaP–IPV (Quadracel®)
Hib–HB (Comvax), Hib–DT (Vaxem HIB®), Hib-TT conjugate (ActHIB®), Trivalent Hib type A, B, split virion (Vaxigrip®)
HepA–Typhoid (Hepatyrix®); MMR + varicella (Priorix tetra®, Proquad®)
Combined ACW135Y polysaccharide meningitis (ACWY Vax®)

Vaccines available as lyophilized powder may require to be reconstituted in (i) sterile or distilled water, e.g. vaccines against measles, mumps, rubella (with or without varicella), meningococcus (MPSV4), rabies (HDCV, PCECV), varicella or zoster; (ii) normal saline, e.g. Hib vaccine; or (iii) another vaccine, e.g. combination vaccines combining DTaP, polio and Hib vaccines (the diluent contains the DTaP-IPV vaccine) and tetravalent meningococcal vaccine (the diluent contains MenCWY vaccine). The maximum time allowed between reconstitution and use varies from within 30 min (DTaP-IPV-Hib, MMRV, Hib with MenCY, rabies, varicella and zoster), to 8 hr (MMR, MCV4) or 24 hr (Hib, rotavirus vaccines). The reconstituted vaccine should not be used if there is discoloration, extraneous particulate matter and obvious lack of resuspension of the lyophilized powder.

Anxiety and pain are commonly associated with vaccination. Some evidence-based strategies used to reduce these include: (i) the use of antipyretics to ease pain; (ii) age-appropriate nonpharmacologic distraction techniques (reading books, playing music, pretending to blow away the pain, deep breathing); (iii) breastfeeding or ingestion of sweet-tasting liquids before or during vaccination; (iv) administering the most painful vaccine (e.g. MMR, PCV or HPV) last; (v) stroking the skin near the injection site; (vi) administering intramuscular injections rapidly without aspiration; and (vii) the use of topical analgesia (e.g. 5% lidocaine or prilocaine emulsion or spray). Other techniques that may lessen anxiety in older children are explaining the procedure, and administering the vaccine in the sitting position rather than lying down.

Adverse Events following Vaccination

An adverse event following immunization is any untoward effect observed after vaccination, and may be categorized as follows: (i) *Vaccine-induced*: Event is caused by the vaccine or the individual's response to its administration, and would not have occurred without vaccination, e.g. vaccine-associated paralytic poliomyelitis, BCG related adenitis or encephalopathy following DPT; (ii) *Vaccine-potentiated*: Events that are precipitated by vaccination but may have occurred without vaccination, e.g. the first febrile seizure in a predisposed child; (iii) *Programmatic error*: An event caused by technical error in vaccine preparation, handling or administration, e.g. toxic shock syndrome due to bacterial contamination of measles vaccine; and (iv) *Coincidental*: An event that is temporally linked to the vaccination but is expected to have followed vaccine administration only by chance or due to unrelated illness.

Common events following vaccination include fever, irritability and swelling and redness at the injection site. These are self limiting or may require the use of cool compresses or paracetamol. Immediate-type allergic reactions to vaccines are rare and difficult to predict. Severe reactions (e.g. anaphylaxis) are usually IgE mediated, occur in response to vaccine constituents (rather than microbial contamination) and usually appear within minutes. While anaphylaxis may follow administration of any vaccine, the most commonly implicated are the vaccines against yellow fever, MMR and tetanus. Since symptoms may sometimes be delayed, each child should be observed for at least 15 min after vaccine administration. It is important to distinguish anaphylaxis from vasovagal reaction following vaccination. Prior history of syncope with painful stimuli and the presence of pallor and bradycardia, rather than flushing and tachycardia (seen with anaphylaxis) suggest syncope rather than anaphylaxis.

When evaluating for a possible vaccine allergy, one should consider the timing of reaction and history of previous exposure to the vaccine. If a repeat dose of the same or similar vaccine is considered necessary, the child should be evaluated by a dermatologist for the need for a

skin test. Components of vaccines implicated in mediating allergic reactions include (i) Egg protein: yellow fever (skin test mandatory; may also contain chicken protein), measles, MMR, rabies PCEV, influenza killed injectable and live attenuated vaccines; (ii) gelatin: influenza, measles, MMR, rabies, varicella, yellow fever and zoster vaccines; (iii) latex in the rubber of the vaccine vial stopper or syringe plunger; (iv) casein: DTaP vaccine; and (v) *Saccharomyces cerevisiae* yeast: hepatitis B and human papillomavirus vaccines. Antimicrobials added to vaccines in traces (e.g. neomycin) rarely cause allergic reactions. Thimerosal, aluminum and phenoxyethanol, added to some vaccines as preservatives, may cause delayed type hypersensitivity or contact dermatitis. The use of thimerosal has declined due to concerns over mercury exposure. Rare delayed reactions are erythema nodosum and encephalopathy.

Reportable events following vaccination include: (i) anaphylaxis or anaphylactic shock ≤7 days of any vaccine; (ii) adverse effects listed as contraindications to future vaccination in the package insert; (iii) any serious or unusual event; and (iv) any sequelae of reportable events. Vaccine-specific reportable events include: (i) oral polio: paralytic polio or vaccine-strain polio within 1–6 months of vaccine administration; (ii) measles: thrombocytopenic purpura within 7–30 days; measles infection by vaccine strain in an immunodeficient recipient ≤6 months of vaccination; (iii) measles, mumps and/or rubella: encephalopathy or encephalitis <15 days; (iv) tetanus: brachial neuritis ≤28 days; (v) pertussis: encephalopathy or encephalitis ≤7 days; (vi) rotavirus: intussusception ≤30 days; and (vii) rubella: chronic arthritis <6 weeks.

Vaccine Storage and Cold Chain

The cold chain is a system of storing and transporting vaccines at recommended temperatures from the point of manufacture to the point of use. Maintenance of appropriate temperature is critical to the viability and potency of a vaccine. Vaccines such as BCG (especially after reconstitution), OPV and measles are sensitive to heat but can be frozen without harm. In contrast, vaccines like DT, DPT, dT, hepatitis B and tetanus toxoid are less sensitive to heat and are damaged by freezing. Other vaccines that must not be frozen include hepatitis A, Hib and whole cell killed typhoid vaccine. In the refrigerator, OPV vials are stored in the freezer compartment (0 to –4°C). In the main compartment (4–10°C) BCG, measles and MMR are kept in the top rack (below the freezer); other vaccines like DPT, DT, TT, hepatitis A and typhoid are stored in the middle racks; while hepatitis B, varicella and diluents are stored in the lower racks.

IMMUNIZATION PROGRAMS

The *Expanded Program of Immunization (EPI)*, introduced by the World Health Organization (WHO) in 1974, was the first global initiative at immunization and focused on vaccinating young children and pregnant women. When adopted by India in 1978, the EPI included Bacillus Calmette Guérin (BCG), diphtheria and tetanus toxoids and whole cell pertussis (DTwP), oral poliomyelitis (OPV) and typhoid vaccines, and covered chiefly urban areas. The *Universal Immunization Program (UIP)* was introduced in 1985 to improve immunization coverage within India and to extend its focus beyond infancy. Measles vaccine was added to the Program and typhoid vaccine excluded. Further, vitamin A supplementation was introduced in 1990 and Polio National Immunization Days were initiated in 1995. Under the UIP, some states have initiated universal immunization against hepatitis B virus since 2002. A pentavalent vaccine combining *Haemophilus influenza* b (Hib) and hepatitis B vaccines with diphtheria toxoid, whole cell pertussis and tetanus toxoid (DTwP) vaccines has been introduced in some states since 2011. The UIP has remained an essential part of the Child Survival and Safe Motherhood (CSSM) program in 1992, the Reproductive and Child Health (RCH) program I in 1997 and the RCH II and National Rural Health Mission (NRHM) since 2005. The efforts of UIP are also supported by Child Vaccine Initiative (CVI) and Global Alliance for Vaccines and Immunization (GAVI).

The proportion of 1-yr-old children immunized against measles is an important indicator for immunization coverage within the country. While the UIP achieved a significant decline in the incidence of vaccine preventable diseases, the findings of the National Family Health Survey 2005–2006 suggested that only 43.5% of children in India received all the primary vaccines by 12 months of age and this coverage was below 30% in Uttar Pradesh, Rajasthan and Arunachal Pradesh. The Immunization Strengthening Project of the Government of India was launched with the intent to: (i) strengthen routine immunization rates to increase the percentage of fully immunized children to above 80%; (ii) eliminate and eradicate polio; (iii) review and develop a new immunization program based on the availability of newer vaccines, recent advances in vaccine production and cold chain technologies and the changing epidemiology of diseases; and (iv) improve vaccination surveillance and monitoring. This program is being implemented through the National Institute of Health and Family Welfare and regional training centers.

Strengthening of immunization coverage is an important component of the NRHM. Measures proposed to improve vaccination rates include mobilization of children and pregnant women by Accredited Social Health Activist (ASHA) and link workers to increase coverage and decrease dropouts, provision of auto-disable syringes and other disposable and strengthening of cold chain maintenance and immunization monitoring systems.

Recommendations of the Indian Academy of Pediatrics Committee on Immunization (IAPCOI)

The IAPCOI endorses the National Immunization Program, but recommends certain additional vaccines for

Indian view of data available on vaccine preventable diseases (VPDs) and the availability of several vaccines. These include the vaccines for hepatitis A, *Haemophilus influenzae* type b, MMR, typhoid, pneumococcal, varicella, HPV, and rotavirus vaccine. The differences in the National Immunization Program and the recommendations of the IAP are highlighted in Table 9.7.

IMMUNIZATION IN SPECIAL CIRCUMSTANCES

The Indian Academy of Pediatrics also categorizes certain high-risk categories of children that need to be administered additional vaccines (Table 9.8). Some specific aspects are discussed here.

Lapsed immunization. Table 9.9 outlines suggested schedules for children who have missed routine immunization. The vaccination schedule for adolescents is discussed in Chapter 4.

Preterm neonates. Most preterm and low birthweight babies mount adequate immune responses, and should receive immunization at the same chronological age and according to the same schedule and precautions as for full term infants. The dose administered is as for other infants,

Table 9.7: Comparison of the vaccinations scheduled in the National Immunization Program and the 2012 recommendations of the Indian Academy of Pediatrics (IAP)

Age	*National Immunization Program*	*IAP recommendation*
0 (at birth)	BCG, OPV0, Hep B0*	BCG, OPV0, Hep B1
6 weeks	DTwP1, OPV1, Hep B1*, Hib1*	DTwP1/DTaP1, IPV1$, Hep B2, Hib1, Rotavirus1, PCV1
10 weeks	DTwP2, OPV2, Hep B2*, Hib2*	DTwP2/DTaP2, IPV2$, Hib2, Rotavirus2, PCV2
14 weeks	DTwP3, OPV3, Hep B3*, Hib3*	DTwP3/DTaP3, IPV3$, Hib3, Rotavirus3, PCV3
6 mo	–	OPV1/Hep B3
9 mo	Measles, vitamin A1	OPV2, Measles
12 mo	–	Hep A1
15 mo	MMR*	MMR1, Varicella1, PCV B1
16–24 mo	DTwP B1, OPV B1, vitamin A2[6], Japanese encephalitis**	(16–18 mo) DTwP B1/DTaP B1, IPV B1$, Hib B1 (18 mo) Hep A2
2 yr	–	Typhoid1**
5 yr	DTwP B2	DTwP B2/DTaP B2, OPV3, MMR2, Varicella2, Typhoid2
10 yr	TT	TdaP/ Td$$, HPV
16 yr	TT	–

B1 first booster dose; B2 second booster dose; BCG Bacillus Calmette Guérin vaccine; DT diphtheria toxoid with tetanus toxoid; DTwP diphtheria toxoid, tetanus toxoid, whole cell killed pertussis vaccine; DTaP diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine; Td tetanus toxoid with reduced dose diphtheria; Tdap tetanus toxoid with reduced dose diphtheria and pertussis vaccine; Hep B hepatitis B vaccine; Hib *Haemophilus influenzae* b vaccine; HPV human papillomavirus vaccine; MMR measles, mumps and rubella vaccine; OPV oral poliovirus vaccine; PCV pneumococcal conjugate vaccine; TT tetanus toxoid

* Implemented in selected states, districts and cities

** SA 14–14–2 vaccine, in select endemic districts

$ OPV if a inactivated polio vaccine (IPV) is not afforded

$$ dT preferred over TT

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Table 9.8: High-risk conditions in which certain vaccines may be necessary

Circumstances that increase risk of acquiring certain infections	*Vaccines that may be necesssary*
Congenital or acquired immunodeficiency (including HIV infection)	Influenza vaccine
Chronic cardiac, pulmonary*, hematologic, renal (including nephrotic syndrome), liver disease and diabetes mellitus	Meningococcal vaccine
Prolonged therapy with steroids, other immunosuppressive agents	Japanese encephalitis vaccine
Radiation therapy	Cholera vaccine
Diabetes mellitus	Rabies vaccine
Cerebrospinal fluid leak, cochlear implant	Yellow fever vaccine
Malignancies	Pneumococcal polysaccharide vaccine (PPSV 23)
Children with functional/anatomic asplenia/hyposplenia	
During disease outbreaks	
Laboratory personnel and health care workers	
Travelers	

Adapted from the recommendations of the Indian Academy of Pediatrics Committee on Immunization, 2012

*includes asthma if treated with prolonged high-dose oral corticosteroids

Table 9.9: Vaccination of a previously unimmunized child

Visit	*At evaluation*	*After 1 mo*	*After 2 mo*	*After 6 mo*
Age ≤7 yr	BCG[1] Oral poliovirus[1] DTwP/DTaP Hepatitis B	Oral polio virus[1] DTwP/DTaP Hepatitis B	MMR (preferred) or measles Typhoid	DTwP/DTaP Hepatitis B
Age >7 yr	Tdap Hepatitis B	dT[3] Hepatitis B	MMR Typhoid	Hepatitis B

[1]If age is <5-yr-old
[2]Repeat after ≥4 weeks if not received any doses previously
[3]Repeat every 10 yr
Adapted from the recommendations of the Indian Academy of Pediatrics Committee on Immunization, 2012

and use of divided or reduced doses is not recommended. Seroconversion rates following most live and killed vaccines are similar to full term babies, except for hepatitis B vaccine. Seroconversion rates are HBV vaccine are lower among preterm babies with birthweight below 2000 g. If the mother is known to be HBsAg negative, the first dose of the vaccine can be safely postponed to one month of age for such newborns. However, preterm low birthweight neonates born to HBsAg positive mothers or to those with unknown HBsAg status should receive both the HBV vaccine and hepatitis B immunoglobulin within 12 hr of birth for immediate protection.

Primary or secondary immunodeficiency Immunodeficiency may be primary or secondary to malignancy, HIV infection, steroids or other immunosuppressive therapy. Such children are at increased risk of infections with certain pathogens, and the severity of vaccine preventable diseases may be higher than in immunocompetent children. It is recommended that these children receive inactivated influenza and pneumococcal vaccines. Live viral or bacterial vaccines are usually contraindicated due to the risk of serious disseminated disease by the organism in the attenuated vaccine, e.g. with BCG, OPV, measles, MMR, oral typhoid and varicella vaccines. These patients may safely receive toxoid and killed vaccines. However, the vaccine efficacy may be compromised due to immune dysfunction, which may require testing for specific serum antibodies, and administration of further doses. Since household contacts of immunocompromised children may transmit OPV to the patient, IPV is preferred in siblings of immunodeficient children.

Therapy with corticosteroids at 2 mg/kg/day or 20 mg per day of prednisolone or its equivalent is considered as significant immunosuppression during which live vaccines should not be given; killed or inactivated vaccines and toxoids are safe. Live vaccines may be administered if corticosteroids are given for less than 14 days, in lower doses, on alternate days or by inhaled, topical or intra-articular routes. Vaccination with live vaccines may be resumed 4 weeks after stopping therapy with high dose corticosteroids. Wherever possible, vaccination should be completed prior to initiation of chemotherapy, immunosuppressive drugs or radiation. Live vaccines should not be given for at least 3 months after such treatment while inactivated vaccines given during such therapy might need to be repeated afterwards.

Children infected by HIV are susceptible to severe and/or recurrent infections with usual or unusual pathogens. The efficacy and safety of vaccines in such children depends on the degree of immunodeficiency. Most vaccines are safe and efficacious in early infancy as the immune functions are relatively intact, but the longevity of immune response may be affected as the disease advances, The efficacy and safety of vaccines are significantly decreased in advanced HIV disease. Vaccination of a baby born to an HIV positive mother but with an indeterminate HIV status should be as per the normal schedule. Symptomatic infants should not receive BCG vaccine. Measles, MMR and varicella vaccines may be administered if the CD4 count is >15% for the age. Seroconversion should be documented following hepatitis A and hepatitis B immunization; four doses may be required in double doses for achieving seroconversion against hepatitis B.

Splenectomy. Children with splenectomy or anatomical or functional asplenia (e.g. sickle cell disease) are at an increased risk of infections with encapsulated organisms (e.g. *S. pneumoniae, N. meningitidis, H. influenzae b).* Where possible, vaccines against these organisms should be considered at least two weeks before elective splenectomy.

Passive Immunization

Passive immunity is resistance based on antibodies preformed in another host. Preformed antibodies to certain viruses (e.g. varicella, hepatitis B) can be injected during the incubation period to limit viral multiplication. Nonspecific normal human immunoglobulin serves the same purpose when specific immunoglobulin is not available, e.g. to protect from hepatitis A or measles. Passive-active immunity involves giving both preformed antibodies immune globulins to provide immediate protection and a vaccine to provide longterm protection, e.g. in preventing tetanus and hepatitis B. These pre-

Table 9.10: Passive immunization

Infection	*Target population*	*Dose**
Normal human immunoglobulin		
Hepatitis A	Institutional outbreak; unimmmunized contact of infected individual; travel to endemic area	0.02 ml/kg (3.2 mg/kg); repeat every 4 mo if travel is prolonged
Measles	Immunocompromised person or an infant <1-yr-old exposed to infected person <6 days back	0.5 ml/kg (immunocompromised individual); 0.25 ml/kg (infant)
Specific (hyperimmune globulin)		
Hepatitis B	Newborn of HBsAg positive mother	0.5 ml (>100 IU) within 24 hr of birth
	Percutaneous or mucosal exposure; sexual contact	0.06 ml/kg (32–48 IU/kg; maximum 2000 IU) within 7 days (preferably 48 hr) of exposure
Varicella	Newborn of infected mother with lesions noted ≤6 days of birth; infant <1-yr-old or immunocompromised child exposed to infected person <6 days back	12.5 (5–25) U/kg (maximum 625 units)
Rabies	Bite by rabid animal	20 units/kg
Tetanus	Wound/exposure in unimmunized or incompletely immunized individual; treatment of tetanus	250 units for prevention; 3000–6000 units for therapy
Antisera/Antitoxin		
Diphtheria antitoxin	Susceptible contact	500–1000 units
Anti-tetanus serum (horse)	Wound/exposure in unimmunized or incompletely immunized individual	1500 units subcutaneous or intramuscular
Rabies antiserum	Bite by rabid animal	40 IU/kg

*Administered intramuscularly unless specified

parations should be given at different sites in the body to prevent the antibodies from neutralizing then immunogens in the vaccine. Administration of antibody against diphtheria or tetanus allows large amounts of antitoxin to be immediately available to the host to neutralize the toxins. Table 9.10 tabulates common indications in which passive immunization provides protection from disease.

Suggested reading

Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus Recommendations on Immunization and IAP Immunization Timetable 2012. Indian Pediatr 2012;49: 549–64.
www.iapcoi.com/hp/pdf/IAPCOI
www.aapredbook.aappublications.org/site/resources
www.immunize.org/catg.d/p3040.pdf
www.aap.org/immunization/IZSchedule.html

Infections and Infestations

10

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FEVER

Definition and Measurement

Fever is a controlled increase in body temperature over the normal values for an individual. The normal body temperature in children is higher as compared to adults, varies between 36.1°C and 37.8°C (97–100°F) on rectal measurement and exhibits a normal circadian diurnal variation, being lowest between midnight and 6 am and maximum between 5 pm and 7 pm.

The core body temperature can be measured inside the oral cavity, axilla, rectum, ear canal and over the temporal artery. The rectal method is the most accurate method for measuring temperature and fever is defined as rectal temperature of more than 38°C or 100.4°F. However, measurement of rectal temperature is not always possible. In children below the age of 4–5 yr, axillary temperature may be used. The axillary temperature is on an average 0.5–1°C or 1–2°F lower than the rectal temperature and fever is defined as axillary temperature over 37.2°C or 99°F. In infants below the age of 3 months, if the axillary method shows fever, it should be confirmed by rectal temperature as this is of serious concern and mandates investigations. In children above the age of 4–5 yr, the oral method is suitable. The oral temperature is 0.5–1°F or 0.25–0.5°C lower than rectal temperature and fever is defined as oral temperature more than 37.5°C or 99.5°F.

Both mercury and electronic thermometers are available. The electronic thermometers are convenient and take only 30 seconds to record temperature but are subject to calibration errors. The mercury thermometers take 2–4 min to record temperature, are inexpensive and especially suitable for home use where regular calibration of electronic thermometers is not possible. Infrared thermometers, used for measuring ear or temporal artery temperatures, measure rapidly and closely approximate rectal temperature, but are expensive.

Etiopathogenesis

Causes of fever are varied, including infections, vaccination, biologic agents, tissue injury, malignancy, drugs, autoimmune diseases, granulomatous diseases, metabolic disorders (gout) and inherited disorders such as familial Mediterranean fever. These may result in the production of endogenous pyrogens, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, interferon-β, interferon-γ and lipid mediators such as prostaglandin E2, which alter the temperature set point in the anterior hypothalamus, leading to elevated body temperature.

In contrast to fever, the high body temperature in *heat illness* is due to increased heat production or reduced heat loss, with the hypothalamic set point being normal. Here, the core temperatures can rise to beyond 106°F. Causes of heat illness include hyperthyroidism, anhidrotic ectodermal dysplasia, anticholinergic agents and phenothiazines, heat stroke and malignant hyperthermia.

Evaluation

Fever is a symptom and not a disease; hence, evaluation for cause is important. Heat illness should be suspected if temperatures are very high. It is useful to classify fever as short duration fever and prolonged fever since etiology and management strategies differ. The pattern of fever is only sometimes useful in arriving at a diagnosis. Intermittent fevers are characteristic of malaria; biphasic fevers are seen in illnesses such as dengue and leptospirosis and periodic fevers (fever syndromes with regular periodicity) are seen in cyclic neutropenia, periodic fever, adenopathy, pharyngitis and aphthous ulcers (PFAPA) syndrome and hyperimmunoglobulin D syndromes.

Management

Since fever is only a symptom, treatment of the underlying cause is important. Fever *per se* may not always be treated. While fever is shown to improve the immunologic response to certain infections, its clinical significance is

unknown. However, fever may also be associated with adverse effects, such as increased insensible water losses, cardiopulmonary stress, paradoxical suppression of immune response and triggering of febrile seizures in predisposed patients. Reduction of fever is essential in patients with past or family history of febrile seizures and patients with critically illness, cardiorespiratory failure, disturbed fluid and electrolyte balance and those with temperature exceeding 40°C (104°F). Treatment should be individualized in other patients and parental counseling is important.

The two antipyretic drugs commonly used in children are paracetamol and ibuprofen. Other agents such as aspirin, nimesulide and mefenamic acid are associated with high incidence of adverse effects and are better avoided. Therapy with ibuprofen decreases fever at the same rate as paracetamol, but therapy with ibuprofen shows a slightly lower nadir and prolonged duration of action (6 hr) as compared to paracetamol (4 hr). However, the risk of side effects such as acute renal failure and gastrointestinal bleeding is theoretically higher with ibuprofen. Conversely, the consequences of overdose with paracetamol (hepatic failure) are more sinister than those with ibuprofen (renal failure, neurological depression). Considering all factors, it is reasonable to use paracetamol at a dose of 15 mg/kg every 4 hr (maximum 5–6 doses/day) as the first-line drug for fever management. Patients who have not adequately responded to paracetamol may receive ibuprofen at a dose of 10 mg/kg every 6 hr. There is marginal benefit on amelioration of fever by combining paracetamol and ibuprofen as compared to using either drug alone without increase in toxicity. Tepid water sponging may be used as a complementary method to drug therapy in bringing down fever quickly.

Heat illness is a medical emergency. High temperatures can cause irreversible organ damage and should be brought down quickly. Since the hypothalamic set point is not altered, nonsteroidal anti-inflammatory drugs, which act by reducing prostaglandin production, are ineffective. External cooling with ice water sponging, cooling blankets, cold water enemas and gastric washes are helpful. Simultaneously, measures to correct the underlying condition are required.

Suggested Reading

Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: Have parental misconceptions about fever changed in 20 yr? Pediatrics 2001;107:1241–6

Sherman JM, Sood SK. Current challenges in the diagnosis and management of fever. Curr Opin Pediatr 2012;24(3):400–6

10

Short Duration Fevers

Short duration fever lasting for less than 5–7 days are among the most common reasons for pediatric outpatient visits. While the overwhelming majority are due to viral infections, fever without localizing signs or focus in children below the age of 3 yr (especially below 3 months) are of great concern as they may indicate a serious bacte infection. Since *H. influenzae* and *S. pneumoniae* important causes of serious bacterial infection, algorithms suggested below may change with increasi rates of immunization with *H. influenzae* and *S. pneumon* vaccines.

Fever without Focus in Newborns

Fever in a neonate is a medical emergency, since thes infants have 5–15% risk of serious bacterial infection suc as sepsis, bacteremia, urinary tract infections, pneumonia enteritis and bacterial meningitis and may look wel despite carrying a serious infection, delaying the diagnosis of sepsis.

Sometimes neonates develop fever due to over clothing or warm weather ('dehydration fever'). The baby looks well and active and only requires observation with frequent feeding and nursing in less warm environment. The infant is observed for signs of sepsis and, if diagnosis is doubtful, investigated.

A febrile neonate requires a detailed assessment (Fig. 10.1). A neonate with toxic appearance has high-risk of serious bacterial infections and should be treated aggressively. He/She should be admitted to undergo a complete sepsis evaluation. Therapy with antibiotics (third generation cephalosporins, e.g. cefotaxime or ceftriaxone, with or without an aminoglycoside) should be initiated while awaiting results of investigations. Supportive therapy is instituted, as required. The management of a well-appearing febrile neonate is controversial. For fever suspected to be due to overdressing, temperature assessment should be repeated 15–30 min after undressing. Most guidelines recommend hospitalization of well-appearing febrile infants below 1 month of age as they may have serious bacterial infection. These infants should undergo basic evaluation including blood counts and C reactive protein. Cultures should be sent if possible. Patients with positive septic screen should receive IV antibiotics after lumbar puncture and CSF examination. If the screen is negative, the baby is observed and a screen

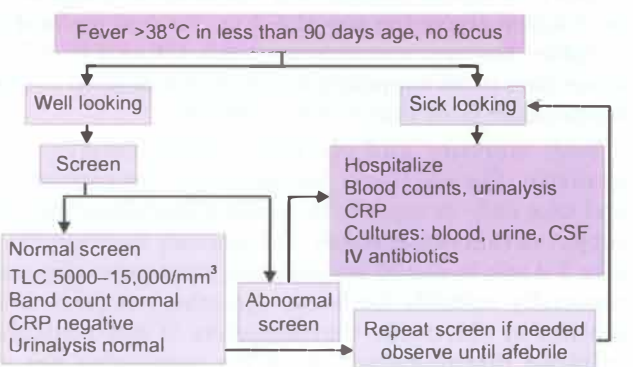


Fig. 10.1: Evaluation of fever in a patient less than 3-month-old; CRP C-reactive protein; CSF cerebrospinal fluid; IV intravenous; TLC total leukocyte count

repeated 6–12 hr later. If repeat screen is also negative, observation is continued till the baby is afebrile and culture reports are available. By then most babies would have either become afebrile or a focus would have developed.

Fever without Focus in an Infant 1–3-Month-Old

Similar to neonates, 10% infants in this age group may have serious bacterial disease, with 2–3% risk of bacteremia. Also, they may look well but still have bacteremia. The algorithm for management of these babies is similar to newborns (Fig. 10.1) and includes a detailed clinical assessment. As fever may relate to immunization, history must include that of recent vaccination.

Toxic or ill-appearing babies require management similar to sick febrile neonates. One to 3-month-old febrile infants who appears well should undergo a complete sepsis evaluation through the outpatient department including leukocyte and platelet counts, band cell count, C-reactive protein, urinalysis, urine and blood cultures and, if indicated, smear for malarial parasite, and chest X-ray. CSF examination is undertaken if there is no clue to focus of infection. If the screen is positive, the patient is hospitalized and treated with antibiotics. A well-looking infant with no clinical focus of infection and a negative screen (leukocyte count <15,000 mm^3, band count <20%, negative C-reactive protein, urine white cells <10/HPF) can be observed at home without antibiotics, provided the care takers are reliable and agree to bring the infant for reassessment 24 hr and 48 hr later.

Fever without Focus in Children 3–36-Month-Old

The risk of serious bacterial infections decreases to 5% in this age group. Detailed history is taken about vaccination, history of sick contacts in the family and the condition of the child when fever is down. If the child looks toxic, he requires hospitalization and appropriate evaluation and treatment. In a nontoxic child with fever less than 39°C, one can merely observe. Children with fever more than 39°C have a high-risk of bacteremia and testing with leukocyte count and examination of smear for malarial parasite are recommended. If the leukocyte count is >15,000/mm^3, blood culture should be sent and the patient administered IV ceftriaxone on either an inpatient or outpatient basis. A count below 5000/mm^3 suggests a viral infection or enteric fever. If the count is below 15,000 mm^3, observation is continued; if fever persists beyond 48 hr without development of a focus, evaluation should include complete blood counts, smear for malaria, urine microscopy and blood culture.

Suggested Reading

Baker MD. Evaluation and management of infants with fever. Pediatr Clinics North Am 1999;46:1061–72

Jhaveri R, Byington CL, Klein JO, Shapiro ED. Management of the non-toxic appearing acutely febrile child. J Pediatr 2011;159:181–5

Section on clinical pharmacology and therapeutics. Fever and antipyretic use in children. Pediatrics 2011;127:530–7

Fever of Unknown Origin

Fever of unknown origin (FUO) is defined as fever >101°C lasting for 3 weeks or more for which no cause is apparent after 1 week of outpatient investigation. A practical definition is fever >101°F measured on several occasions over a 7-day period.

Causes

The principal causes are listed in Table 10.1. Infections account for 60–70% cases in children. Most common infectious causes include enteric fever, malaria, pulmonary or extrapulmonary tuberculosis and urinary tract infections. The remaining cases are due to malignancies, chiefly leukemia and autoimmune diseases, chiefly juvenile rheumatoid arthritis. Uncommon causes include drug fever, temperature dysregulation, diabetes insipidus, sarcoidosis, ectodermal dysplasia and sensory autonomic neuropathies. Even with extensive investigations, the cause remains undiagnosed in 10–20% cases.

Approach to Evaluation

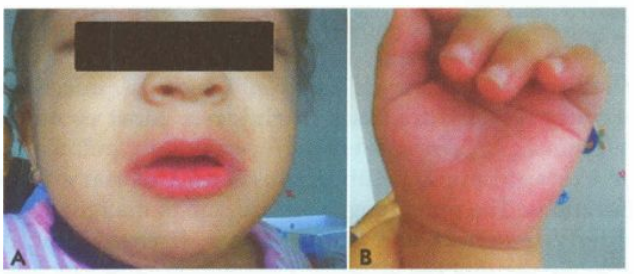
The first step is to identify sick patients who need stabilization and urgent referral. Subsequently, all attempts are made to identify the etiology. A detailed history is of paramount importance. This should include: (i) whether and how fever was documented (not uncommonly, children with history of prolonged fever do not have fever documented on a thermometer); (ii) duration and pattern of fever (to distinguish from recurrent fever); (iii) symptoms referable to various organ systems, weight loss; (iv) recurrent infections and/or oral thrush (suggests HIV infection); (v) joint pain, rash, photosensitivity (autoimmune disease); (vi) contact with person with tuberculosis; animals (brucellosis); (vii) travel to endemic zones (kala-azar); and (viii) history of intake of anticholinergics (drug fever).

Complete physical examination should include documentation of fever, followed by assessment of general activity, nutrition and vital signs. Physical examination, including head to toe examination, should be repeated

Table 10.1: Causes of fever of unknown origin

Infectious	
Enteric fever, malaria, urinary tract infections, tuberculosis, chronic hepatitis, HIV, occult abscesses (liver, pelvic), mastoiditis, sinusitis, osteomyelitis, meningitis, infectious mononucleosis, infective endocarditis, brucellosis, CMV, toxoplasmosis, kala-azar	
Autoimmune	
Systemic onset juvenile rheumatoid arthritis, Kawasaki disease, systemic lupus erythematosus, inflammatory bowel disease, polyarteritis nodosa	
Malignant	
Leukemia, lymphoma, Langerhans cell histiocytosis	

daily as new findings may emerge that provide a clue to the etiology. Kawasaki disease, though relatively uncommon, must be kept in mind as diagnosing the illness before the tenth day of fever is crucial to prevent coronary complications (Figs 10.2A and B).



Figs 10.2A and B: Kawasaki disease: (A) Red and cracked lips; (B) palmar rash and swelling

Preliminary investigations which should be done in all patients with FUO include complete blood counts, peripheral smear, malarial parasite, erythrocyte sedimentation rate, blood culture, Widal, chest X-ray, tuberculin test, urinalysis and culture, hepatic aminotransaminases and abdominal ultrasound. Specialized investigations are based on clinical clues.

If the above approach yields a diagnosis, appropriate treatment should be instituted. Inability to make a specific diagnosis merits reassessment and further investigations. While second line investigations are planned, treatment with intravenous (IV) ceftriaxone may be initiated since enteric fever is an important cause of FUO in India, particularly in cases where preliminary investigations are noncontributory.

Second-line investigations include HIV ELISA, contrast enhanced CT of chest and abdomen, bone marrow smear, biopsy and cultures, 2D echocardiogram, complement C3 level, antinuclear antibody, rheumatoid factor and specific tissue biopsies, if indicated. Other serologic tests may include serology for brucellosis, HBsAg and Paul Bunnel test, Monospot test or IgM antibody to viral capsid antigen for infectious mononucleosis. Tests of no clinical value include serology and PCR for *M. tuberculosis*.

It should be possible to determine the etiology of FUO in most cases. In a small number of cases, no cause is found. In such cases, periodic reassessment is useful as lymphoma or systemic onset juvenile rheumatoid arthritis may finally surface. Some cases are self limiting. Uncommonly, use of antitubercular therapy with four drugs for a month is advised in sick patients. Empirical use of corticosteroids should be avoided.

Suggested Reading

Tolan RW. Fever of unknown origin: A diagnostic approach to this vexing problem. Clin pediatr 2010;49:207–13.

Fever with Rash

Fever with rash is a common and vexing problem. It may signify serious disorders such as meningococcemia or dengue hemorrhagic fever or may be associated with minor drug allergy. The common infectious and non-infectious causes of fever with rash are listed in Table 10.2.

Evaluation

The nature of the rash often provides clues to determine the etiology of the exanthematous febrile illness (Fig. 10.3). Rashes may be macular, maculopapular, vesicular, nodular, urticarial or purpuric (Table 10.2) and considerable overlap may occur with varying presentations of the same etiology. Other factors that assist in diagnosis include epidemiological factors, season, history of exposure, incubation period, age, vaccination status, previous exanthems, prodromal symptoms, relation of rash with fever, distribution and progression of the rash, involvement of mucous membranes, drug intake and associated symptoms.

Table 10.2: Common exanthematous illnesses in Indian children

Macular or Maculopapular rash	
Common:	Measles, rubella, dengue, roseola infantum, erythema infectiosum, drug rash, adenoviral or enteroviral infections
Less common:	Infectious mononucleosis, chikungunya, HIV, *Mycoplasma pneumoniae*, secondary syphilis, brucellosis, scrub typhus, chronic hepatitis B, cytomegalovirus, lupus, systemic onset juvenile rheumatoid arthritis
Diffuse erythema with peeling or desquamation	
Common:	Stevens-Johnson syndrome, drug induced toxic epidermolysis, Kawasaki disease
Less common:	Scarlet fever, staphylococcal and streptococcal toxic shock syndrome
Vesicular rash	
Common:	Chickenpox, enteroviral infections (hand-foot-mouth disease)
Less common:	Herpes simplex, herpes zoster, papulonecrotic tuberculosis
Petechial and/or Purpuric rash	
Common:	Meningococcemia, dengue hemorrhagic fever, Henoch-Schönlein purpura
Less common:	Indian spotted fever, gonococcemia, hemorrhagic measles, chickenpox, cutaneous vasculitis
Urticarial rash	
Common:	Scabies, insect bites
Less common:	Cutaneous larva migrans due to hookworm, strongyloides, pediculosis
Nodular rash	
Common:	Erythema nodosum due to tuberculosis, drugs, sarcoid, inflammatory bowel disease, lepromatous leprosy; *Molluscum contagiosum*
Less common:	Disseminated histoplasmosis, cryptococcosis

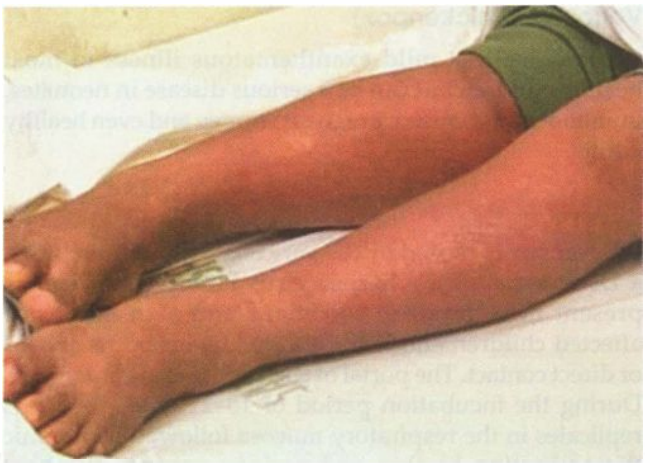


Fig. 10.3: Diffuse erythematous rash seen in a patient with dengue

Examination should include nature of the rash and its distribution, involvement of palms and soles (seen with dengue, spotted fever, Kawasaki disease and Stevens-Johnson syndrome), involvement of mucous membranes, lymphadenopathy, organomegaly and signs of meningeal irritation. Laboratory investigations that may assist include complete blood counts, C-reactive protein, ESR, blood culture, specific serologies and sometimes, biopsy.

Management

All efforts should be made to diagnose serious entities earlier and institute immediate treatment. For stable children, a specific diagnosis may not be always possible. In this situation, symptomatic therapy, close observation, explanation of danger signs to parents and staying away from school until the rash resolves, is recommended.

Often a child receives drugs and antibiotics for fever which is followed by a rash. Distinguishing this rash as a viral exanthem from drug related rash is difficult. Intense itching is more commonly seen with a drug rash. Withholding the drug, symptomatic therapy and observation is the usual practice. Rechallenge with the same drug later under observation is permitted if the rash was mild.

Suggested Reading

Sarkar R, Mishra K, Garg VK. Fever with rash in a child in India. Indian J Dermatol Venereol Leprol 2012;78(3):251–62.

COMMON VIRAL INFECTIONS

Measles

Measles is a common and serious exanthematous illness, which still causes 350,000 childhood deaths annually in developing countries of which 80,000 occur in India alone.

Etiopathogenesis

Measles is caused by an RNA virus belonging to the Paramyxovirus family. The virus is transmitted by droplet spread from the secretions of the nose and throat, usually 4 days before to 5 days after the rash. The disease is highly contagious with secondary attack rates in susceptible household contacts exceeding 90%. The portal of entry is the respiratory tract where the virus multiplies in the respiratory epithelium. Primary viremia occurs resulting in infection of the reticuloendothelial system, followed by secondary viremia, which results in systemic symptoms. The incubation period is around 10 days.

Clinical Features

The disease is most common in preschool children; infants are protected by transplacental antibodies, which generally decay by 9 months (hence the rationale for vaccination at this age). The prodromal phase is characterized by fever, rhinorrhea, conjunctival congestion and a dry hacking cough. Koplik spots, considered as pathognomonic of measles, appear opposite the lower second molars on the buccal mucosa on the second or third day of the illness as gray or white lesions resembling grains of sand with surrounding erythema. The rash, usually apparent on the fourth day with rise in fever, appears as faint reddish macules behind the ears, along the hairline and on the posterior aspects of the cheeks (Fig. 10.4). The rash rapidly becomes maculopapular and spreads to the face, the neck, chest, arms, trunk, thighs and legs in that order over the next 2–3 days. It then starts fading in the same order that it appeared and leaves behind branny desquamation and brownish discoloration, which fade over 10 days.

Modified measles, seen in partially immune individuals, is a milder and shorter illness. Hemorrhagic measles is characterized by a purpuric rash and bleeding from the nose, mouth or bowel.

Complications

Widespread mucosal damage and significant immunosuppression induced by measles account for the frequent complications seen with this viral infection. Complications are more frequent in the very young, malnourished and the

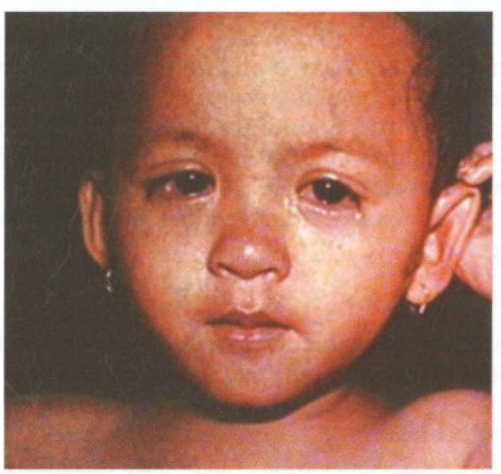


Fig. 10.4: Conjunctival congestion and morbilliform rash in a child with measles

immunocompromised. The most common complications are otitis media and bacterial bronchopneumonia. The usual bacterial pathogens are pneumococcus, *Staphylococcus aureus* and sometimes gram-negative bacteria. Other respiratory complications include laryngitis, tracheitis, bronchitis, giant cell pneumonia, bronchiectasis and flaring up of latent *M. tuberculosis* infection. Transient loss of tuberculin hypersensitivity reaction is common following measles. Gastrointestinal complications include persistent diarrhea, appendicitis, hepatitis and ileocolitis. Measles can precipitate malnutrition and can cause noma or gangrene of the cheeks.

Acute encephalitis occurs in measles at a frequency of 1–2 per 1000 cases, most commonly during the period of the rash, consequent to direct invasion of the brain. Post-measles encephalitis occurs after recovery and is believed to be due to an immune mechanism, similar to other para-infectious or demyelinating encephalomyelitis. Measles is also responsible for the almost uniformly fatal subacute sclerosing panencephalitis (SSPE), seen several yr after infection at a frequency of 1 per 100,000 cases.

Diagnosis

The diagnosis is clinical and may be confirmed by estimating the levels of IgM antimeasles antibody that is present 3 days after the rash and persists for 1 month. Measles needs to be differentiated from other childhood exanthematous illnesses. The rash is milder and fever less prominent in rubella, enteroviral and adenoviral infections. In roseola infantum, the rash appears once fever disappears while in measles the fever increases with rash. In rickettsial infections, the face is spared which is always involved in measles. In meningococcemia, the upper respiratory symptoms are absent and the rash rapidly becomes petechial. Drug rashes have history of antecedent drug intake. In Kawasaki disease, glossitis, cervical adenopathy, fissuring of lips, extreme irritability, edema of hands and scaling are distinguishing clinical features.

Treatment

Treatment is supportive and comprises antipyretics, maintenance of hygiene, ensuring adequate fluid and caloric intake and humidification. Vitamin A reduces morbidity and mortality of measles; a single oral dose of 100,000 units below 1 yr and 200,000 units over the age of 1 yr is recommended. Complications should be managed appropriately.

Prevention

Measles is a preventable and potentially eradicable disease through universal immunization (*see* Chapter 9).

Suggested Reading

Measles vaccines: WHO position paper. Wkly Epidemiol Rec 2009; 84:349–60

Scott LA, Stone MS. Viral Exanthems. Dermatol Online J 2003;9:4

Varicella (Chickenpox)

Chickenpox is a mild exanthematous illness in most healthy children but can be a serious disease in neonates, immunocompromised, pregnant women and even healthy adults.

Etiopathogenesis

Chickenpox is caused by the varicella zoster virus (VZV), a DNA virus of the herpes virus family. The virus is present in respiratory secretions and skin lesions of affected children and is transmitted by air-borne spread or direct contact. The portal of entry is the respiratory tract. During the incubation period of 10–21 days, the virus replicates in the respiratory mucosa followed by viremic dissemination to skin and various organs. The host immune responses limit infection and promote recovery. In immunocompromised children, unchecked replication and dissemination of virus leads to complications. During the latter part of the incubation period, the virus is transported to the respiratory mucosa and leads to infectivity even prior to appearance of the rash. The period of infectivity lasts from 24 to 48 hr before the rash until all the vesicles are crusted (the scabs are not infective, unlike small-pox). The disease is highly contagious with secondary attack rates of 80% among household contacts. VZV establishes lifelong latent infection in the sensory ganglia. *Reactivation, especially during periods of depressed immunity, leads to the dermatomal rash of herpes zoster.*

Clinical Features

Chickenpox is rarely subclinical; however, in some children only a few lesions may be present. The peak age of disease is 5–10 yr. The prodromal period is short with mild to moderate fever, malaise, headache and anorexia. The rash appears 24–48 hr after the prodromal symptoms as intensely pruritic erythematous macules, seen first on the trunk. The rash rapidly spreads to the face and extremities while it evolves into papules, clear fluid-filled vesicles, clouded vesicles and then crusted vesicles (Fig. 10.5). Several crops of lesions appear and simultaneous presence of skin lesions in varying stages of evolution is characteristic of varicella. The median number of lesions is around 300 but may vary from 10 to 1500. Systemic symptoms persist for 2–4 days after appearance of the rash. The rash lasts 3–7 days and leaves behind hypopigmented or hyperpigmented macules that persist for days to weeks. Scarring is unusual unless lesions are secondarily infected.

Complications

Secondary bacterial infections of the skin lesions is fairly common; necrotizing fasciitis is rare. Neurologic complications include meningoencephalitis, acute cerebellar ataxia, transverse myelitis, Landry-Guillain-Barré syndrome and optic neuritis. Other complications include purpura fulminans due to antibodies against protein C, CNS vasculitis

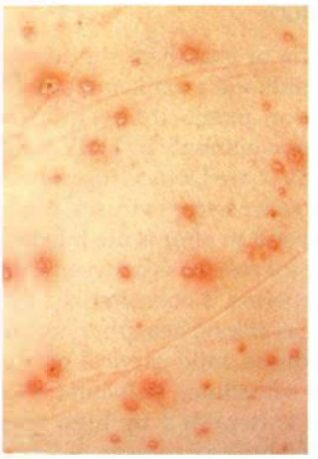


Fig. 10.5: Polymorphic rash of chickenpox

leading to stroke, autoimmune thrombocytopenic purpura and Reye syndrome.

The progressive varicella syndrome is a dreaded complication in immunocompromised individuals, neonates, pregnant women and even healthy adults and adolescents. This syndrome is characterized by continued development of lesions, hemorrhagic lesions, coagulopathy and visceral organ involvement including hepatitis, pneumonia and encephalitis. Mortality rate are high despite therapy.

Chickenpox in pregnancy is associated with an increased risk of severe disease in the mother. Congenital varicella syndrome may occur following infection in the first and second trimester at a frequency of 0.4–2%. It is characterized by skin scarring, malformed extremities, cataracts and brain abnormalities (e.g. aplasia, calcifications). Finally, if the disease occurs in the mother 5 days before to 2 days after delivery, severe and often fatal neonatal disease may result.

Herpes zoster in children is characterized by a mild vesicular rash with dermatomal distribution. Unlike in adults, pain is less and postherpetic neuralgia unusual. The risk of herpes zoster is more in immunocompromised children, children who acquire chickenpox in infancy and those whose mothers developed varicella in the third trimester.

Diagnosis

The diagnosis is clinical and usually not difficult. Chickenpox should be differentiated from other vesicular exanthemata such as herpes simplex, enteroviral infections (hand-foot-mouth disease), insect bites and drug reactions. In atypical cases, the diagnosis is made on Tzanck smear of the lesions, which shows multinucleated cells and by demonstrating IgM antibodies to varicella.

Treatment

Management is symptomatic and includes antipyretics, antipruritic agents and good hygiene. Aspirin is contraindicated due to risk of Reye syndrome. The child should not attend school until new lesions stop appearing and all lesions have crusted. Administration of oral acyclovir (20 mg/kg/dose four times a day for 5 days) within 24 hr of onset of rash in healthy children reduces the duration of rash by one day and lesions by 25%. IV acyclovir (10 mg/kg every 8 hr for 7 days) is given to patients with complicated varicella and for illness in high risk patients (neonates, immunocompromised children, pregnant women).

Prevention

Prevention against varicella with the live attenuated varicella vaccine and use of varicella zoster immune globulin (VZIG) for postexposure prophylaxis are detailed in Chapter 9. VZIG is fairly expensive and not always available.

Suggested Reading

Gershon AA: Varicella-zoster virus infections. Pediatr Rev 2008;29(1): 5–10

Whitley RJ. Therapy of herpes virus infections in children. Adv Exp Med Biol 2008;609:216–32

Infectious Mononucleosis

Infectious mononucleosis, a syndrome characterized by fever, fatigue, sore throat and lymphadenopathy, is most often caused by a herpes virus, Epstein-Barr virus (EBV). Infectious mononucleosis-like illness can also be caused by toxoplasma, CMV, adenoviruses and primary HIV infection.

Epidemiology

The EBV virus, a DNA virus of the herpes virus family, is transmitted in oral secretions by close intimate contact like kissing or exchange of saliva from close child contact. The virus replicates in the oral epithelial cells then spreads to salivary glands with eventual viremia to the B lymphocytes in the blood and lymphoreticular system including liver and spleen. The CD8 lymphocytes proliferate to check this replication of virus in the B lymphocytes and represent the atypical lymphocytes seen in EBV infection. Like other herpes viruses, EBV establishes lifelong latent infection after the primary infection with frequent asymptomatic reactivations.

The epidemiology is related to the age of primary acquisition of EBV infection. In developing countries, most of EBV infection occurs in infancy and early childhood, when it is either asymptomatic or similar to other childhood infections. For this reason, infectious mononucleosis is uncommonly seen or reported in India. In developed countries, the age of acquisition of EBV infection shifts upwards and thus the illness is seen more commonly.

Clinical Features

Symptomatic EBV infections in older children and adults are characterized by insidious onset of malaise, fatigue,

fever, headache, nausea, sore throat, abdominal pain and myalgia. Examination shows pharyngeal inflammation with exudates and petechiae at the junction of soft and hard palate, generalized lymphadenopathy (cervical, less often axillary and inguinal), mild splenomegaly (50%) and hepatomegaly (10%). Maculopapular rashes are seen in 3–15% cases and in 80% of those who have received ampicillin or amoxicillin.

Complications are rare and include splenic rupture following minor trauma, airway obstruction due to enlargement of oropharyngeal lymphoid tissue, meningitis, seizures, ataxia, myocarditis, hemolytic anemia, thrombocytopenia, neutropenia, aplastic anemia, interstitial pneumonitis and pancreatitis.

Diagnosis

Most patients show leukocytosis and absolute lymphocytosis, with presence of atypical lymphocytes on peripiheral smear. The platelet count is slightly low and hepatic transaminases mildly elevated in 50% patients. The Paul Bunnel (heterophile antibody) test is used for screening. This test is based on agglutination of sheep/horse red cells by heterophile antibodies present in the serum of patients with EBV infection. This test may have false negative rates of 10% and remains positive for few months to 2 yr after infection. IgM antibody to viral capsid antigen (IgM VCA) is a confirmatory test to diagnose acute EBV infection.

Infectious mononucleosis should be differentiated from other causes of mononucleosis like illness, streptococcal pharyngitis and acute leukemia.

Treatment

Rest and symptomatic therapy are advised. Participation in strenuous activities and contact sports should be prohibited in the first 2–3 weeks of illness due to risk of splenic rupture. Treatment with prednisolone (1 mg/kg/day for 7 days) is advised for complications such as hemolytic anemia, airway obstruction, meningitis and thrombocytopenia with bleeding.

Other Manifestations of EBV Infections

EBV has oncogenic potential and is causally associated with proliferative disorders such as virus associated hemophagocytic syndrome, oral hairy leukoplakia and lymphoid interstitial pneumonitis in patients with AIDS, nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, tumors in immunocompromised patients (e.g. X-linked lymphoproliferative disease, leiomyosarcoma, CNS lymphoma) and post-transplantation lymphoproliferative disease.

10

Suggested Reading

Bell AT, Fortune B, Sheeler R. What is the best test for diagnosing infectious mononucleosis? J Fam Pract 2006;55(9):799–802

Roseola Infantum

Roseola infantum or exanthem subitum or Sixth disease is a common childhood exanthematous illness caused by primary infection primarily by human herpes virus (HHV)-6 and less commonly by HHV-7 and echovirus 16. HHV-6 and HHV-7 are DNA viruses that target the CD4 T cells, and like other herpes viruses, can remain latent in the body for several yr after acute infection.

The peak age for roseola is between 6 months and 3 yr. The prodromal period is characterized by upper respiratory signs such as rhinorrhea, pharyngeal inflammation, conjunctival redness, mild cervical or occipital lymphadenopathy and sometimes, palpebral edema. The classic clinical illness is heralded by high fever of 38–40°C, associated with febrile seizures in 5–10% cases, and lasts 3–4 days. Fever declines abruptly and is followed by development of a rash within 12–24 hr. The rash is discrete erythematous and maculopapular which first appears on the trunk and then spreads to the face, neck and proximal extremities. The rash is nonpruritic, rarely becomes confluent and fades in 3–4 days. Infectiousness is low and outbreaks have not occurred. Roseola should be differentiated from childhood illnesses such as rubella, measles, enteroviruses and drug hypersensitivity. Treatment is symptomatic and prognosis excellent.

Suggested Reading

Caserta MT, Mock DJ, Dewhurst S. Human herpes virus 6. Clin Infect Dis 2001;33:829–33

Erythema Infectiosum

Erythema infectiosum or Fifth disease is a common exanthematous illness of childhood caused by a small DNA virus, parvovirus B19. This virus has tropism for cells of the erythroid lineage at the pronormoblast stage.

The peak age for erythema infectiosum is between 5 and 15 yr. Transmission of infection is by the respiratory route and the incubation period is 4–28 days (average 16–17 days). The prodromal phase is mild and consists of low-grade fever, headache and symptoms of mild upper respiratory tract infection. The characteristic rash first appears as erythematous flushing on the face in a 'slapped cheek' appearance (Fig. 10.6). It spreads rapidly to the trunk and proximal extremities as a diffuse erythematous macular rash that rapidly undergoes central clearing to give it a lacy or reticulated pattern. The rash gradually fades over a 1–3 week period. Complications include arthropathy, idiopathic thrombocytopenic purpura and aseptic meningitis. Fifth disease should be differentiated from measles, roseola, rubella and drug rash. Treatment is symptomatic.

Other serious manifestations of parvovirus B19 infection include arthralgia and arthropathy in adolescents or adults, transient aplastic crises in patients with chronic hemolytic anemias, chronic anemia, pancytopenia or marrow suppression, virus associated hemophagocytic

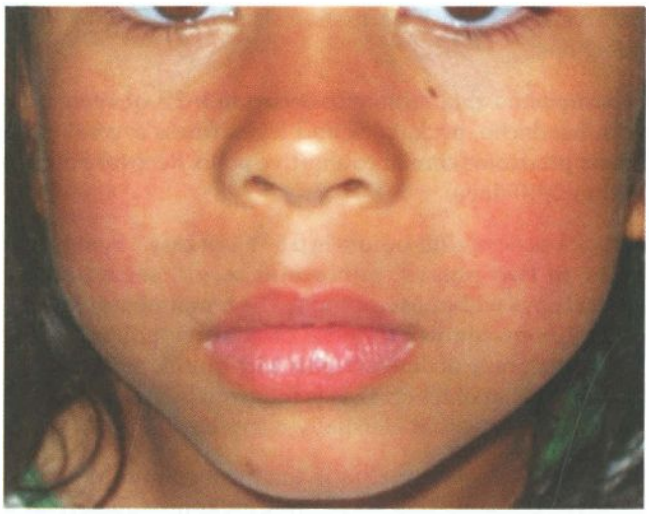


Fig. 10.6: The rash resembles a 'slapped cheek' in erythema infectiosum

syndrome in the immunocompromised, hydrops fetalis in pregnant women and rare episodes of myocarditis in healthy children or adults.

Suggested Reading

Servant-Delmas A, Lefrere JJ, Morinet F, Pillet S. Advances in human B19 erythrovirus biology. J Virol 2010;84:9658–65

Servey JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19 infections. Am Fam Physician 2007;75:373–6

Mumps

Mumps is an acute viral infection characterized by painful enlargement of the salivary glands, most characteristically the parotid glands. Mumps is caused by an RNA virus of genus *Paramyxovirus* in the family Paramyxoviridae; only one serotype is known.

Epidemiology

Most cases occur between the ages of 5 and 15 yr; infants are rarely affected due to presence of transplacentally acquired maternal antibodies. Man is the only reservoir of infection; carrier state does not exist. The incidence is higher in winter and spring.

The virus is spread from human reservoir by direct contact, air-borne droplets and fomites contaminated by saliva and urine. The virus proliferates in the respiratory epithelium to enter the circulation and then gets localized to the glandular and neural tissue. The virus has been isolated from saliva as long as 6 days before to 9 days after appearance of salivary gland swelling. The secondary infection rate is as high as 80%. Mumps infection or immunization is believed to confer lifelong immunity. The disease is mild in the majority; in 10% cases, the infection is associated with aseptic meningitis or encephalitis.

Clinical Features

Following an incubation period of 2–4 weeks, symptoms begin acutely with fever, malaise and headache. Mumps infection is characterized by unilateral or bilateral parotitis. This presents as earache, jaw tenderness while chewing, dryness of mouth and swelling at the angle of jaw. The ear lobe may appear to be pushed upwards and outwards. The defervescence and resolution takes about a week. Occasionally, other salivary glands, including the submaxillary and sublingual glands, are affected.

The occurrence of epididymoorchitis is more common in adolescent boys or postpubertal men. The condition is unilateral in 85% cases and occurs 1–2 weeks after parotitis. The testes are enlarged and tender. Some degree of atrophy follows the inflammation but sterility is rare.

Aseptic meningitis is seen in about 1–10% patients with parotitis. Mumps is perhaps the commonest cause of aseptic meningitis in children. Recovery is generally uneventful. The risk of encephalitis is between 0.02 and 0.3% cases. Mumps encephalitis has a satisfactory prognosis with a mortality rate of less than 2%. Other neurological manifestations include auditory nerve damage leading to deafness, cerebellar ataxia, facial neuritis, transverse myelitis and Guillain-Barré syndrome. Uncommon presentations include pancreatitis (5% may trigger insulin dependent diabetes mellitus), mastitis, oophoritis, nephritis and myocarditis.

Diagnosis

The diagnosis is based on clinical features and may be confirmed by ELISA for IgM. Serum amylase is elevated in almost 90% cases. Mumps parotitis needs to be differentiated from suppurative parotitis, submandibular lymphadenitis, recurrent juvenile parotitis, calculus in Stensen duct and other viral infections causing parotitis, e.g. coxsackie A and cytomegalovirus.

Treatment

Symptomatic treatment is given in the form of antipyretics and warm saline mouthwashes. Orchitis is treated by bed rest and local support. Steroids may be used for symptomatic relief of orchitis and arthritis but does not alter the course of disease.

Prevention

The affected patient should be isolated until the parotid swelling has subsided. Mumps can be prevented by timely immunization (Chapter 9).

Suggested Reading

MacDonald N, Hatchette T, Elkout L, Sarwal S. Mumps is back: Why is eradication not working, Adv Exp Med biol 2011;697:197–220

WHO position paper on mumps and vaccines. Weekly Epidemiologic Record 2001;76:345–56

Poliomyelitis

The polioviruses belong to the genus *Enterovirus* in the family Picornaviridae and comprise three related

serotypes: types 1, 2 and 3, all of which can cause paralysis. Type 1 is most frequently responsible, type 3 is less commonly causative and type 2 is only rarely implicated.

Epidemiology

The disease is seasonal, occurring more commonly in summer and early autumn in temperate climates. In tropical countries, seasonality is less clearly defined; some areas experience increase in incidence during the rainy season. Feco-oral route is the predominant mode of transmission in developing countries with poor sanitation, whereas oral-pharyngeal transmission predominates in industrialized countries and during outbreaks. The average incubation period of disease is 7–10 days, ranging from 4 to 35 days. The virus is shed in the stools for 6–8 weeks after infection.

Humans are the only reservoir of poliovirus and infection is spread from person-to-person. The virus spreads rapidly to nonimmune persons. Transmission is usually widespread in the community by the time of onset of paralysis in a child. Infants born to mothers with antibodies are protected naturally against paralytic disease for a few weeks. Immunity is acquired through infection with the wild virus and through immunization.

The Global Polio Eradication initiative was launched in 1988 using oral polio vaccine (OPV) as the eradication tool and employing a four pronged strategy comprising (i) maintaining high routine immunization coverage, (ii) supplementary immunization activities (SIAs)/pulse immunization, (iii) acute flaccid paralysis (AFP) surveillance, and (iv) outbreak response immunization. The initiative was hugely successful with reduction of polio cases from 350,000 worldwide in 1988 to 650 in 2011 and only 215 cases in 2012 (as of 25th December 2012). Only 3 countries, Afghanistan, Nigeria and Pakistan remain polio endemic; 210 of the 215 cases in 2012 were reported from these countries. The last wild polio case was reported from India on 13 January, 2011 and India is no more considered endemic for poliovirus.

Pathogenesis

The mouth is the usual portal of entry. The virus is usually present in the pharynx and stools before the onset of paralytic illness. It invades local lymphoid tissue, enters the bloodstream to invade certain nerve cells and may damage or destroy these cells.

10

Clinical Features

In 90–95% of individuals, poliovirus infection is inapparent. In the remaining 5–10% of individuals, one of the following syndromes may occur.

Abortive polio occurs in 4–8% of infections and is characterized by a minor illness with low grade fever, sore throat, vomiting, abdominal pain, loss of appetite and malaise. Recovery is rapid and complete; there is no paralysis. It cannot be distinguished from other viral infections.

Nonparalytic aseptic meningitis occurs in 1–2% of infections, with headache, neck, back and leg stiffness several days after a prodrome similar to abortive polio. Recovery occurs within 2–10 days.

Paralytic poliomyelitis occurs in 0.5–1% of cases. Symptoms occur in two phases, minor and major, separated by several days without symptoms. The minor phase consists of symptoms similar to those of abortive poliomyelitis. The major phase of illness begins with muscle pain, spasms and the return of fever. This is followed by rapid onset of flaccid paralysis that is usually complete within 72 hr.

Spinal paralytic poliomyelitis is the most common form of paralytic poliomyelitis, accounting for approximately 80% cases. It results from a lower motor neuron lesion of the anterior horn cells of the spinal cord and affects the muscles of the legs, arms and/or trunk. Severe cases may develop quadriplegia and paralysis of the trunk, abdominal and thoracic muscles. The affected muscles are floppy and reflexes are diminished. The sense of pain and touch are normal. Paralysis is often asymmetrical, affecting legs more often than arms. Paralysis in extremities begins proximally and progresses to involve distal muscle groups (i.e. descending paralysis). Residual flaccid paralysis is usually present after 60 days. *Bulbar polio* accounts for 2% cases and results from a cranial nerve lesion, resulting in respiratory insufficiency and difficulty in swallowing, eating or speaking. *Bulbospinal polio* accounts for 20% cases and is a combination of spinal paralytic and bulbar polio.

Polio encephalitis is characterized by irritability, delirium and loss of consciousness; seizures may occur. The paralysis may be of the upper motor neuron type.

Depending on the strain of poliovirus, the ratio between subclinical and clinical cases is estimated to range between 100:1 and 1000:1. Older children and adults run a greater risk of developing paralytic illness. The case fatality rate among persons who develop the paralytic form of the disease is 2–20%. However, the case-fatality rate may be as high as 40% in those with bulbar or respiratory involvement.

Residual Paralysis

Following an acute phase of illness lasting 1–4 weeks, the recovery of paralyzed muscles begins. The extent of recovery is variable ranging from mild to severe residual paresis at 60 days, depending upon the extent of damage caused to the neurons by the virus. Maximum neurological recovery takes place in the first 6 months of the illness; slow recovery continues up to two yr. After two year, no more recovery is expected and the child is said to have *postpolio residual paralysis*, which persists throughout life.

Diagnosis

The diagnosis is based on the history and the characteristic clinical manifestations of asymmetric flaccid paralysis. *Stool examination* is recommended in every case of acute flaccid paralysis (AFP). Virus can be detected from onset to 8 or more weeks after paralysis; the highest probability of detection is during the first 2 weeks after onset of paralysis. Examination of the *cerebrospinal fluid* (cell count, Gram stain, protein and glucose) is useful in eliminating other conditions that cause AFP. Current *serologic tests* cannot differentiate between wild and vaccine virus strains. Collection of blood specimens for culture or serology is not recommended.

Differential Diagnosis

The two diseases most commonly confused with polio are Guillain-Barré syndrome and transverse myelitis. Other conditions with a presentation similar to those of paralytic poliomyelitis include traumatic neuritis and less frequently, meningitis, encephalitis and illnesses produced by toxins (diphtheria, botulism) (*see* Chapter 19).

Treatment

Treatment should be early and appropriate to the stage and degree of paralysis. Children with bulbospinal polio and respiratory paralysis require hospitalization. In the acute stage, children with isolated paralysis of one or more limbs can be managed at home. They should be advised complete rest, proper positioning of the affected limb and passive range of movement at the joints. Massage and intramuscular injection should be avoided during acute phase of illness. Frequent change of the posture of the patient is must. The child should be made to lie on a firm bed and maintain limbs in neutral position. The child should lie with trunk and hip straight with slight flexion (5–10°) at knees and feet at right angle at the ankle joint. This position can be maintained with pillows, rolled towels or sand bags. Warm moist fomentations can be given with soft towels, dipped in warm water to relieve pain and spasms. Analgesics can also be given to relieve pain and fever. All the joints of affected limb/limbs should be moved through their passive range of movements, 2–3 times a day for 10 times at each joint, to prevent joint stiffness. This helps to stimulate proprioceptive impulses from muscles and tendons, helping improve muscle power.

As the acute phase of illness subsides, recovery in muscle power is helped by giving physiotherapy, helping ambulation and prevention of deformities. Some children require orthosis at some stage for ambulation. Others with fixed deformities and contractures require orthopedic intervention.

Prevention of Poliomyelitis

The available vaccines and the recommended schedule are discussed in Chapter 9.

Eradication of Polio

Eradication is possible because polio affects only man, immunity is lifelong, a safe vaccine is available and there are no carriers or reservoirs of the infection. The strategies for achieving this goal are:

Attaining high rates of routine immunization. Every child less than 1-yr-old should be immunized with at least three doses of oral poliovirus vaccine (OPV).

National immunization days (NIDs). On these days, under the pulse polio immunization (PPI) program, additional OPV doses are administered to every child <5-yr-old. The aim of NIDs/PPI is to 'flood' the community with OPV within a very short period, thereby interrupting transmission of virus throughout the community. Intensification of the PPI program is accomplished by the addition of extraimmunization rounds, adding a house-to-house 'search and vaccinate' component in addition to providing vaccine at a fixed post. The number of PPI rounds conducted during any particular yr is determined by the extent of poliovirus transmission in the state or district.

Mopping-up immunization. When poliovirus transmission is reduced to well-defined and focal geographic areas, intensive house-to-house, child-to-child immunization campaigns are conducted over a period of days to break the final chains of virus transmission.

Acute flaccid paralysis surveillance. Under the global polio eradication initiative, surveillance for polio is conducted through investigation of patients with AFP. AFP surveillance helps to detect reliable areas where poliovirus transmission is occurring. Acute flaccid paralysis (AFP) is defined as sudden onset of weakness and floppiness in any part of the body in a child <15-yr-old or paralysis in a person of any age in whom polio is suspected. In other parts of the world, at least one case of AFP (excluding polio) occurs annually for every 100,000 children less than 15 yr of age (background AFP rate). The nonpolio causes of AFP account for this background rate. Sensitive surveillance will detect a background AFP rate of 1 per 100,000 children. In our country, where the incidence of conditions such as traumatic neuritis and AFP caused by other nonpolio enteroviruses is very high, the background nonpolio AFP rate is higher.

Details on the AFP surveillance are mentioned in Chapter 19.

Suggested Reading

National Polio Surveillance Project, at: http://www.npspindia.org/index.asp. accessed on May 21,2012

WHO position paper. Poliovaccines and immunization. Weekly epidemiologic record 2010;85:213–28

Hand-Foot-Mouth Disease

Hand-foot-mouth disease is a common viral illness primarily affecting children below 5 yr. It is caused by

viruses of the genus *Enterovirus* belonging to family Picornaviridae, including polio, ECHO, coxsackie virus and enteroviruses. The most common causes of hand foot mouth disease are coxsackie virus A16 and enterovirus 71. The disease usually presents as outbreaks, often in preschool children and transmission is by direct contact with an affected patient or infected fomites.

Clinical Features

The onset is with a prodrome characterized by low grade fever, feeling of being unwell and sore throat. This is followed by development of ulcers or blisters in the oral cavity, mostly on the posterior aspect and then a papulovesicular skin rash on the palms and soles and less commonly, on buttocks, knees, elbows and genital area (Fig. 10.7). All manifestations may not be present in all patients. The illness resolves quickly over 4–5 days.

Complications include temporary loss of toe nails or finger nails about 4 weeks after onset of disease. Rare complications include aseptic meningitis, encephalitis, polio like paralysis, myocarditis and respiratory distress syndrome. Outbreaks, particularly due to enterovirus 71, are reported from China, Vietnam, Taiwan and Malaysia, in which neurologic complications are common and mortality significant. Some experts believe that enteroviruses cause hand-foot-mouth disease now occupy the ecologic niche vacated by eradication of polioviruses.

Diagnosis is clinical and requires differentiation from other illnesses causing oral ulcers like herpangina, herpetic gingivostomatitis and aphthous ulcers and from chickenpox.

Treatment and Prevention

Treatment is mainly symptomatic and includes analgesics and soft diet. Isolation of affected children at home and promotion of hand hygiene to prevent disease spread is important. No vaccine is available against this disease.

Suggested Reading

Wong SS, Yip CC, Lau SK, Yuen KY. Human enterovirus 71 and hand, foot and mouth disease. Epidemiol Infect 2010;138:1071–89

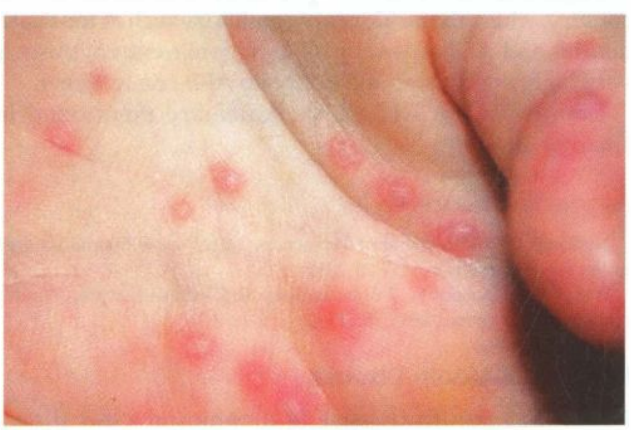


Fig. 10.7: The vesicular rash of hand-foot-mouth disease

VIRAL HEPATITIS

Hepatitis, meaning inflammation of the liver, can be caused by a variety of different hepatotropic viruses such as hepatitis A, B, C, D and E. Hepatitis A and E are responsible for most of the water-borne (community acquired) hepatitis while B, C and D are responsible for post-transfusion hepatitis. Since a considerable number of cases of post-transfusion and community-acquired hepatitis are not identified as being caused by hepatitis A–E, other hepatotropic viruses are also incriminated, including hepatitis G, TT virus and SEN virus.

Hepatitis A

Hepatitis A is caused by infection with the hepatitis A virus (HAV), a nonenveloped RNA virus. A single serotype of HAV infects humans and infection induces lifelong immunity. HAV is extremely resistant to degradation by environmental conditions. Hence, it spreads readily by the feco-oral route through contaminated food and water and from person-to-person living with poor sanitation. Disease severity increases with age at infection; children below 5 yr age have asymptomatic infection or present with an acute undifferentiated febrile illness, while older children, adolescents and adults suffer from classic hepatitis. Symptomatic disease is uncommon and outbreaks rare in developing countries with poor hygiene since most individuals are infected in childhood. In regions with intermediate endemicity like India, a significant proportion of people escapes infection in childhood and may develop symptomatic disease as adults.

Clinical Features

During an *incubation or preclinical period* of average 30 (range 10–50) days, the virus replicates actively. This is followed by a short prodromal phase lasting up to a week, which is characterized by loss of appetite, fatigue, abdominal pain, nausea and vomiting, fever, diarrhea, dark urine and pale stools. Older individuals then have an *icteric phase*, during which jaundice develops, with total bilirubin levels exceeding 2–4 mg/dl. Fever improves after the first few days of jaundice. In the subsequent few weeks of *convalescence*, patients show complete recovery.

In around 0.1–1% of patients, extensive necrosis of the liver occurs during the first 6–8 weeks of illness. In this case, high fever, marked abdominal pain, vomiting, jaundice and the development of hepatic encephalopathy associated with coma and seizures occur. These are the signs of fulminant hepatitis which is more common as age advances and leads to death in 70–90% of the patients. In patients who survive, neither functional nor pathologic sequelae are common despite the widespread necrosis. Infection with HAV does not lead to chronic or persistent hepatitis. Relapsing hepatitis may occur in 3–20% of patients 4 to 15 weeks after the initial symptoms have resolved.

Diagnosis

The specific diagnosis of acute hepatitis A is made by detecting serum anti-HAV IgM. Anti-HAV IgM is detectable about 3 weeks after exposure, by which time symptoms have already appeared. Its titer increases over 4–6 weeks, then declines to nondetectable levels within 6 months of infection. As IgG anti-HAV persists lifelong after acute infection, detection of IgG anti-HAV alone indicates past infection. Laboratory evaluation of liver function includes estimation of total and direct bilirubin, transaminases, alkaline phosphatase, prothrombin time, total protein and albumin.

Treatment

Therapy is supportive and is aimed at maintaining adequate nutrition. There is no evidence to suggest that restriction of fats has any beneficial effect on the course of the disease. Eggs, milk and butter may actually help provide an appropriate caloric intake. Antiviral agents have no role because the hepatic injury appears to be immunologically mediated. Referral to a liver transplant center is appropriate for patients with fulminant hepatitis.

Prevention

The ideal preventive strategy is improvement in sanitation, hygiene and water supply. Immunization is very effective and discussed further in Chapter 9. Immunoglobulin G may be used for postexposure prophylaxis. If administered within two weeks of exposure it either prevents development of disease or reduces its severity.

Suggested Reading

Mathur P, Arora NK. Epidemiological transition of hepatitis A in India: issues for vaccination in developing countries. Indian J Med Res 2008;128:699–704

Hepatitis B

Hepatitis B virus is a 3.2 kb, circular, partially double stranded DNA virus. HBV contains four open reading frames, which encode major structural and nonstructural proteins for HBV.

Epidemiology

HBV infection is prevalent in Asia, Africa, Southern Europe and Latin America, where the HBsAg seropositivity ranges from 2 to 20%. In hyperendemic areas, HBV infections occur mainly during infancy and early childhood. In Asia, perinatal transmission from HBsAg carrier mothers to their infants is an important route of transmission leading to chronicity. Approximately 90% of infants of HBeAg seropositive carrier mothers become HBsAg carriers, irrespective of a high or low HBsAg carrier rate in the population. In areas of low endemicity, horizontal infection is the main route of transmission.

Pathogenesis and Natural Course

HBV has an incubation period of 2–6 months. Following primary HBV infection, an acute, fulminant or chronic course may be noted.

Acute and fulminant hepatitis. Acute hepatitis is marked by symptoms similar to other acute hepatitis illnesses, i.e. fever, vomiting, jaundice and anorexia. Recovery is marked by hepatitis B surface antibody (anti-HBs) seroconversion. Fulminant hepatitis is heralded by pathologic mental status changes within 2 to 8 weeks after the initial symptoms in an otherwise healthy child. About two-thirds of children with fulminant hepatitis B present in infancy.

Chronic infection. Children with chronic HBV infection are mostly asymptomatic. They are generally active and grow well. Although liver damage is usually mild during childhood, serious sequelae, including cirrhosis and hepatocellular carcinoma, may develop insidiously at any age. An immune-mediated process is the main mechanism for cell damage. During acute exacerbations of chronic HBV infections, CD8+ T lymphocytes are the predominant cells in the liver in the areas of piecemeal necrosis. Since HBeAg is an important marker reflecting active viral replication and infectivity, its clearance is used as a marker for the success of antiviral therapy. Children with chronic HBV infection are HBeAg seropositive at the initial stage of infection; this antigenemia can persist for yr after primary infection (Fig. 10.8). Spontaneous clearance of HBeAg occurs gradually with increasing age. Viral replication is reduced during this process. This process of HBeAg seroconversion takes place subclinically in most individuals for a period of 2 to 7 yr (Table 10.3). This process is usually preceded by an elevation of aminotransferases. After HBeAg clearance, aminotransferase

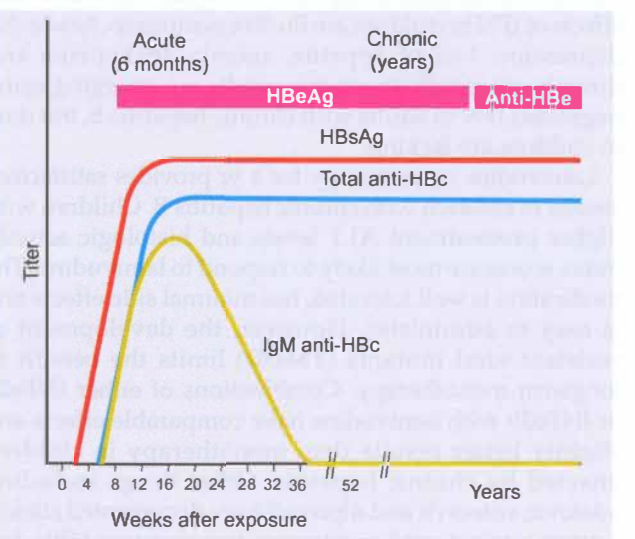


Fig. 10.8: Serological response in hepatitis B virus infection

Table 10.3: Common seropatterns of hepatitis B infection

HBsAg	*Anti-HBs*	*Anti-HBc*	*HBeAg*	*Anti-HBe*	*Interpretation*
+	–	IgM	+	–	Acute infection
–	–	IgM	+/–	+/–	Acute infection; anti-HBc window
+	–	IgG	+	–	Chronic infection; high infectivity
+	–	IgG	–	+	Chronic infection; low infectivity
+	–	+/–	–	–	Precore/Core mutant infection
+	–	IgG	–	+/–	Hepatitis B carrier
–	+	IgG	–	+/–	Recovery from infection
–	+	–	–	–	Immunization; false positive; infection in remote past

levels return to normal levels and anti-HBe develops. Longterm followup of HBsAg carrier children shows that the rate of HBsAg clearance is low (0.6% annually), and occurs only after clearance of HBeAg.

During the early phase of infection, the amount of virus in the liver and blood is usually large, whereas the liver damage is mostly mild. The host immune system gradually recognizes the virus and starts to clear the virus. It results in active inflammation of the liver and elevation of serum aminotransferases. Repeated episodes of elevation of aminotransferases is followed by HBeAg seroconversion. After HBeAg seroconversion, viral replication declines and the liver inflammation gradually becomes inactive.

Treatment

There are two approved therapies for *chronic hepatitis B* in children: interferon (IFN) and lamivudine. Interferons are a group of naturally occurring agents with antiviral, antineoplastic and immunomodulatory properties. IFNα2a achieves seroconversion in approximately one-third of cases; those most likely to respond have high ALT activity and a greater histological activity index score in the liver biopsy before treatment. Children younger than 6 yr have an enhanced response to IFNα2b treatment. Side effects of IFN in children are flu-like symptoms, headache, depression, loss of appetite, anemia, leukopenia and thrombocytopenia. Promising results are emerging using pegylated IFN in adults with chronic hepatitis B, but data in children are lacking.

Lamivudine monotherapy for 1 yr provides satisfactory results in children with chronic hepatitis B. Children with higher pretreatment ALT levels and histologic activity index scores are most likely to respond to lamivudine. The medication is well tolerated, has minimal side effects and is easy to administer. However, the development of resistant viral mutants (YMDD) limits the benefit of longterm monotherapy. Combinations of either INFα2a or INFα2b with lamivudine have comparable effects and slightly better results than monotherapy in children affected by chronic hepatitis. Other drugs including adefovir, entecavir and dipivoxil have documented clinical activity against wild and lamivudine resistant HBV, but needs to be further evaluated in children.

Immunoprophylaxis

Hepatitis B immunoglobulin is used in the postexposure prophylaxis of newborns of HBV infected women. It is administered intramuscularly and may be given concurrently with HBV vaccine, at a different site. The dose for infants is 0.5 ml. Combination of the immunoglobulin and HBV vaccination in infants born to HBsAg positive mothers prevents transmission in approximately 95% of those at risk.

Hepatitis D

Hepatitis delta virus (HDV) was first detected as a new nuclear antigen in the hepatocytes of patients infected with hepatitis B virus (HBV) and was frequently associated with severe acute or chronic hepatitis. Transmission of hepatitis delta virus requires either coinfection with HBV or superinfection in individuals who are HBV carriers.

Hepatitis C

Hepatitis C virus (HCV) was recognized in 1989 as a major cause of non-A, non-B hepatitis. HCV is an enveloped, single-stranded, positive-sense ribonucleic acid virus, classified as an independent genus (*Hepacivirus*) within the Flavivirus family.

Viral Variants

The HCV RNA-dependent RNA polymerase lacks proofreading ability, which results in HCV being genetically heterogeneous. Based on analysis of HCV sequences, six major HCV genotypes are recognized. HCV genotypes 1 and 2 are the most prevalent worldwide. HCV genotype 3 is most common in Australia and the Indian subcontinent. The viral genotypic distribution in children generally parallels that reported regionally in adults. HCV genotype 1 correlates with higher serum viral levels and a less favorable response to antiviral treatment.

Epidemiology

The worldwide prevalence of HCV infection is approximately 3%, which represents an estimated 170 million infected persons. Children who received transfusions of potentially contaminated blood products prior to the institution of routine screening have seroprevalence rates up to 95%.

Clinical Features

The mean incubation period of post-transfusion acute HCV infection is 7 to 8 weeks, with a range of 2 to 26 weeks. Acute HCV is usually anicteric or subclinical and only one-third of patients develop jaundice or symptoms. Fulminant hepatic failure due to HCV is rare. In adults, 85% of patients exposed to HCV will develop chronic infection, of which approximately 10 to 20% develop cirrhosis. In children, the course of HCV infection is generally benign. Most children with acute hepatitis C are asymptomatic.

When symptoms are present, they are often nonspecific (malaise, anorexia) or mild; jaundice is present in 25%. Most children exposed to HCV are at risk to become chronically infected based on persistently detectable serum anti-HCV antibodies and HCV RNA. Children with chronic HCV infection may also remain asymptomatic. Progression to decompensated liver disease in children is rare. Biochemical markers such as serum alanine aminotransferase typically fluctuate in HCV patients. Normal or only minimally increased transaminase levels are reported with chronic HCV infection and these can remain elevated despite anti-HCV seronegativity. Liver histology shows portal lymphoid aggregates, bile duct injury and steatosis; necroinflammatory activity is mild.

Perinatal Transmission

The rate of vertical transmission is approximately 5–6%, which is low compared to that for hepatitis B virus and human immunodeficiency virus. High-titer maternal viremia correlates with higher transmission rates. Breastfeeding is permitted unless the mother has bleeding nipples.

Diagnosis

The diagnosis of HCV infection is based on detection of antibodies against recombinant HCV antigens by enzyme immunoassay or recombinant immunoblot assay or by detection of HCV RNA using nucleic acid tests. Enzyme immunoassay is limited by frequent false-positive results, particularly in patients with elevated globulin levels such as those with autoimmune hepatitis. Recombinant immunoblot assays are less sensitive but more specific than enzyme immunoassay in detecting anti-HCV antibodies. Recombinant immunoblot assay is, therefore, not recommended for initial HCV screening and are useful to confirm viral infection. Nucleic acid tests identify the presence of HCV very early in the course of infection and therefore, are used to diagnose infection even before the anti-HCV antibodies have appeared. These tests are also necessary to detect HCV in infants born to infected mothers, in whom HCV antibodies may be of maternal origin and in immunocompromised patients whose ability to produce HCV antibodies may be impaired.

Therapy

Sustained virologic responses are achieved in only 8–35% of patients given recombinant interferon monotherapy. However, significantly higher sustained virologic responses are attained (30–40%) by combining interferon with ribavirin at 15 mg/kg/day. Longer-acting pegylated interferons have been subsequently developed based on the premise that more sustained drug levels would result in greater antiviral activity. Several randomized clinical trials in adults verify considerably better virologic responses (50–60%) with the use of pegylated interferons, particularly when given in conjunction with ribavirin. However, in general, sustained virologic response rates in children treated with interferon alone (30–60%) appear to be two- to three-fold higher than in similarly treated adults. Importantly, biochemical and virologic responses have been accompanied by significant histologic improvement in all treated patients included in these trials, and interferon has been well tolerated in children.

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Hepatitis E

Hepatitis E virus was first described in 1978 after an epidemic affecting 52,000 individuals in Kashmir. Hepatitis E is caused by infection with the hepatitis E virus (HEV), a single-stranded RNA virus. Just like hepatitis A virus, HEV is transmitted via the fecal oral route. It is usually transmitted through contaminated drinking water. Hepatitis E virus causes acute sporadic and epidemic viral hepatitis. Symptomatic HEV infection is most common in young adults aged 15–40 yr and is uncommon in children since it is mostly asymptomatic and anicteric.

Clinical Features

The incubation period following exposure to HEV ranges from 3 to 8 weeks, with a mean of 40 days. The clinical presentation of hepatitis E is similar to hepatitis A. The severity of an HEV infection is generally greater than the severity of an HAV infection. In pregnant women, the disease is particularly severe where mortality approaches 20% with infections in the third trimester. Premature deliveries with high infant mortality up to 33% are observed. No evidence of chronic inflammation or of a healthy chronic carrier state has been detected and no recurrence of hepatitis E has been reported.

Diagnosis

Laboratory evaluation of HEV is similar to that of HAV and is based on detection of IgM antibodies. These

antibodies (IgM and IgG) develop at the time symptoms occur, usually before the development of jaundice. IgM anti-HEV titer declines rapidly during early convalescence, while IgG anti-HEV persists for long duration and provides protection against subsequent infections.

Treatment

As no specific therapy is capable of altering the course of acute hepatitis E infection, prevention is the most effective approach against the disease.

Prevention

Good personal hygiene, high quality standards for public water supplies and proper disposal of waste have resulted in a low prevalence of HEV infections in developed countries. At present, there are no commercially available vaccines for the prevention of hepatitis E.

Hepatitis due to other Viruses

Certain cases of post-transfusion (10%) and community acquired hepatitis (20%) are of unknown origin. Three viruses are potentially associated with liver disease but no conclusive evidence exists to support them as a cause for these cases. These viruses are HGV/GB virus C, TT virus and SEN virus.

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Dengue Infections

Dengue fever is an acute illness characterized by fever, myalgia, arthralgia and rash. Severe dengue infection is characterized by abnormalities in hemostasis and by marked leakage of plasma from the capillaries; the latter may lead to shock (dengue shock syndrome).

Epidemiology

The global prevalence of dengue has grown dramatically in recent decades. The disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. WHO currently estimates there may be 50 million cases of dengue infection worldwide every year. During epidemics of dengue, attack rates among susceptible are often 40–50%, but may reach 80–90%. An estimated 500,000 cases of severe dengue infection require hospitalization each year, of which very large proportions are children. Without proper treatment in severe dengue infection [earlier called dengue hemorrhagic fever (DHF) dengue shock syndrome (DSS)] case fatality rates can exceed 20%.

The spread of dengue is attributed to expanding geographic distribution of the four dengue viruses and of their mosquito vectors, the most important of which is the predominantly urban species *Aedes aegypti*. A rapid rise in urban populations is bringing ever greater numbers of people into contact with this vector, especially in areas that are favorable for mosquito breeding, e.g. where household water storage is common and where solid waste disposal services are inadequate.

Virus. Dengue fever is caused by infection due to any of the four serotypes of dengue viruses. Dengue viruses are arboviruses that belong to the family Flaviviridae. The envelop protein bears epitopes that are unique to the serotypes; the antibodies to these unique epitopes neutralize by interfering with the entry of the virus into the cells.

Transmission. Dengue viruses are transmitted to humans through the bites of infected female Aedes mosquitoes. Mosquitoes generally acquire the virus while feeding on the blood of an infected person. After incubation for 8–10 days, an infected mosquito is capable, during probing and blood feeding, of transmitting the virus, to susceptible individuals for the rest of its life. Infected female mosquitoes may also transmit the virus to their offspring by transovarial transmission, but the role of this in sustaining transmission of virus to humans has not yet been delineated. Humans are the main amplifying host of the virus, although studies have shown that in some parts of the world monkeys may become infected and perhaps serve as a source of virus for mosquitoes. The virus circulates in the blood of infected humans for two to seven days, at approximately the same time as they have fever; Aedes mosquitoes may acquire the virus when they feed on an individual during this period.

Pathophysiology

The major pathophysiologic changes that determine the severity of disease in severe dengue infection and differentiate it from dengue fever are plasma leakage and abnormal hemostasis leading to rising hematocrit values, moderate to marked thrombocytopenia and varying degrees of bleeding manifestations. The cause of abnormal leakage of plasma is not entirely understood. However, rapid recovery without residual abnormality in vessels suggests it to be the result of release and interaction of biological mediators, which are capable of producing severe illness with minimal structural injury.

It has been observed that sequential infection with any two of the four serotypes of dengue virus results in severe dengue infections in an endemic area. How a second dengue infection causes severe disease and why only some patients get severe disease remains unclear. It is suggested that the residual antibodies produced during the first infection are able to neutralize a second viral infection with the same serotype. However, when no neutralizing antibodies are present (i.e. infection due to another serotype of dengue virus), the second infection is under the influence of *enhancing antibodies* and the resulting infection and disease are severe. An alternative explanation is that certain strains (South-East Asian) of the dengue virus may be inherently capable of supporting

severe antibody-enhanced infection than viruses in other geographic area. Serotype cross-reactive antibodies generated from previous primary infection with a particular dengue viral serotype are not highly specific for the other serotypes involved in secondary infections. Hence, they bind to the virions but do not neutralize them, and instead increase their uptake by cells, which express Fc. receptors on their surfaces, like tissue dendritic cells, monocytes and macrophages. Such antibody-coated virions are taken up more rapidly than uncoated virus particles and this leads to enhanced antigen presentation by the infected dendritic cells to the T cells, leading to the more rapid activation and proliferation of memory T cells.

The cytokines produced by the activated T cells have several important effects that lead to the pathogenesis of the severe dengue infections (DHF/DSS). Cytokines are also implicated in the pathogenesis of vascular compromise and hemorrhage in dengue virus infection. Endothelial cell dysfunction in dengue virus infection manifests as diffuse increase in capillary permeability, which is responsible for the microvascular leakage, hemoconcentration and circulatory insufficiency. The transient nature of plasma leakage suggests that it could be mediated by a soluble mediator.

Dengue viral infection is commonly associated with thrombocytopenia, the cause of which is molecular mimicry between dengue virus proteins and endogenous self proteins. There is generation of antibodies against dengue virus proteins (especially NS1), which cross-react with platelet surface proteins and thus cause thrombocytopenia. There is activation of blood clotting and fibrinolytic pathways. Mild disseminated intravascular coagulation, liver injury and thrombocytopenia together contribute to hemorrhagic tendency. Central nervous system involvement also has been identified and has been attributed to direct neurotropic effect of dengue virus.

Pathology

There are usually no gross or microscopic lesions that may account for death, except when massive gastrointestinal or intracranial bleeding causes death. Presence of viruses in tissues mainly leads to hemodynamic alterations with generalized vascular congestion and increased permeability, and mast cell recruitment in lungs. These findings have also been seen in animal models. Variable hepatic involvement has been reported—diffuse hepatitis with midzonal necrosis and steatosis, focal areas of necrosis and normal histology in some children. Dengue virus antigen can be detected using immunohistochemistry in hepatocytes from necrotic areas. Absence of recruitment of polymorphonuclear cells and lymphocytes has been observed in the liver lesions of patients who died from DHF.

Clinical Manifestations

Dengue infection has varying clinical presentations and often with unpredictable clinical evolution and outcome. Incubation period is 4–10 days. Most infections are subclinical. Infants and young children may present with an undifferentiated febrile illness. The classic presentation of dengue fever is usually seen in older children, adolescents and adults and can be described under three phases.

Febrile phase. It is characterized by sudden onset high-grade fever that may last for 2–7 days. There may be facial flushing, skin erythema, generalized bodyache, myalgia, arthralgia, headache, anorexia, nausea and vomiting. Occasionally, child may have sore throat, injected pharynx and conjunctival injection. A positive tourniquet test may be seen in some patients. Minor hemorrhagic manifestations: petechiae and mucosal bleeding (e.g. nose and gums) may be seen in some patients. Liver may be enlarged and tender from 2–5 days and indicates risk for development of severe illness. There is progressive decrease in total white cell count and platelet count.

Critical phase. This phase is between 3 and 7 days of onset of fever when defervescence sets in. Child may develop bleeding and shock with fall in platelet count and increase in packed cell volume. Some children may develop organ dysfunction such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding (may also develop without obvious plasma leakage or shock).

Recovery phase. After 24–48 hr in critical phase, a gradual reabsorption of extravascular compartment fluid takes place in 48–72 hr. General wellbeing improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of "isles of white in the sea of red". Some may experience generalized pruritus, bradycardia and electrocardiographic changes; respiratory distress may occur due to pulmonary edema. The packed cell volume stabilizes or may be lower due to the dilution; leukocyte count starts to rise soon after defervescence, while recovery of platelet count takes longer.

Differential Diagnosis

Differential diagnosis for dengue infection includes other hemorrhagic fevers, influenza, malaria, enteric fever, leptospirosis, less commonly meningococcemia and rickettsial infections. Malaria, leptospirosis, flu and enteric fever may also be coinfected with dengue. Wide spread chikungunya virus infections have occurred in various parts of India and South-East Asia. Its clinical manifestations are similar to dengue. However, fever is of shorter duration, thrombocytopenia and bleeding are less. Other clinical features that are more common in chikungunya are skin eruptions, mucosal lesions, polyarthralgia and encephalopathy. Since dengue as well as chikungunya infections are endemic in most parts of India, both infections may occur together.

The following clinical and laboratory features suggest presence of severe dengue infection:

Clinical criteria. Acute onset high-grade fever, hemorrhagic manifestations (at least a positive tourniquet test), tender hepatomegaly, effusion in body cavities and or shock.

Laboratory criteria. Thrombocytopenia (1,00,000 cells per cubic mm or less or less than 1–2 platelets per oil immersion field), rising hematocrit.

Laboratory Investigations

During the course of illness, children with severe dengue infection show increasing packed cell volume, low platelet count and decreasing leukocyte count with increasing lymphocytes. A low leukocyte count in a child with febrile illness during the endemic season suggests possible dengue infection. However, malaria and typhoid/paratyphoid may also present with low leukocyte count.

Serum chemistry may show decrease in total protein and albumin, which is more marked in patients with shock. Levels of transaminases are raised. A higher increase in SGOT than SGPT suggests a possibility of dengue infection rather than other viral infections. In severe cases there may be hyponatremia, and acidosis along with increase in urea and creatinine.

X-ray film of the chest or ultrasound examination may show varying degrees of pleural effusion, commonly on the right side, occasionally bilateral. Ultrasonography of abdomen may show ascites and enlarged gallbladder due to wall edema.

Confirmation of diagnosis of dengue may be established by following:

i. Direct methods, including (a) virus isolation by culture; (b) genome detection by PCR; (c) NS1 antigen detection
ii. Indirect methods, including (a) IgM detection; and (b) IgG detection

Virus isolation or PCR requires the sample to be obtained within the first 5 days of fever, is technically demanding, not universally available, expensive and hence of limited practical use. NS1 antigen is a highly conserved glycoprotein of dengue virus and secreted during the initial phase of illness. It disappears as the antibodies appear and hence declines as illness advances and in secondary dengue infections. The specificity is near 100% and sensitivity in the first four days of illness is 90% in primary dengue and 70% in secondary dengue infection.

Antibody determination needs careful interpretation. Following primary dengue infection, 80% of patients will have detectable IgM antibodies by day 5 and 99% by day 10. IgM antibodies peak by day 14 and are undetectable by two to three months. IgG antibodies rise later, peak to levels lower than IgM, decline slowly and remain detectable at low levels for life. Therefore, diagnosis of primary dengue infection is based on elevation of IgM.

Management

Patients with dengue infection can be classified as asymptomatic, or symptomatic as follows:

i. Undifferentiated fever
ii. Dengue without warning signs
iii. Dengue with warning signs
iv. Severe dengue infection.

Undifferentiated fever. Patients may have nonspecific symptoms. Treatments consist of paracetamol for fever and regular monitoring for development of any complications.

Dengue infection without warning signs. Patients with fever, bodyaches, rashes or minor bleeding may be treated symptomatically. Fever and bodyaches are best treated with paracetamol. Salicylates and other nonsteroidal anti-inflammatory drugs should be avoided as these may predispose to mucosal bleeds. Child should be encouraged to drink plenty of fluids. There is no specific therapy. In epidemic situations the primary care physician/health care worker should monitor the patient for warning signs (given below) along with hematocrit and platelet counts if possible.

Dengue with warning signs. Children with suspected dengue infection who have any of the following needs hospitalization: (i) abdominal pain or tenderness; (ii) persistent vomiting; (iii) clinical fluid accumulation; (iv) mucosal bleed; (v) lethargy, restlessness; (vi) liver enlargment >2 cm; and (vii) laboratory features like increase in packed cell volume (hematocrit) with concurrent with rapid decrease in platelet count.

These patients require admission to the hospital and need intravenous fluids, preferably crystalloids. All children without hypotension should be given Ringer lactate or normal saline infusion at a rate of 7 ml/kg over one hour. After one hour if the hematocrit has decreased and vital parameters are improving; fluid infusion rate should be decreased to 5 ml/kg over next hour and to 3 ml/kg/hr for 24–48 hr with frequent monitoring of hematocrit and vital parameters. When the patient is stable as indicated by normal blood pressure, good oral intake and urine output, the child can be discharged (Fig. 10.9).

If at one hour, the hematocrit is rising and vital parameters do not show improvement, fluid infusion rate is increased to 10 ml/kg over next hour. In case of no further improvement, fluid infusion rate is further increased to 15 ml/kg over next hour (third hr). If no improvement is observed in vital parameters and hematocrit at the end of 3 hr; colloids or plasma infusion in doses of 10 ml/kg is administered. Once the hematocrit and vital parameters are stable the infusion rate is gradually reduced and discontinued over 24–48 hr.

Severe dengue. Children presenting/developing any of the following are included:

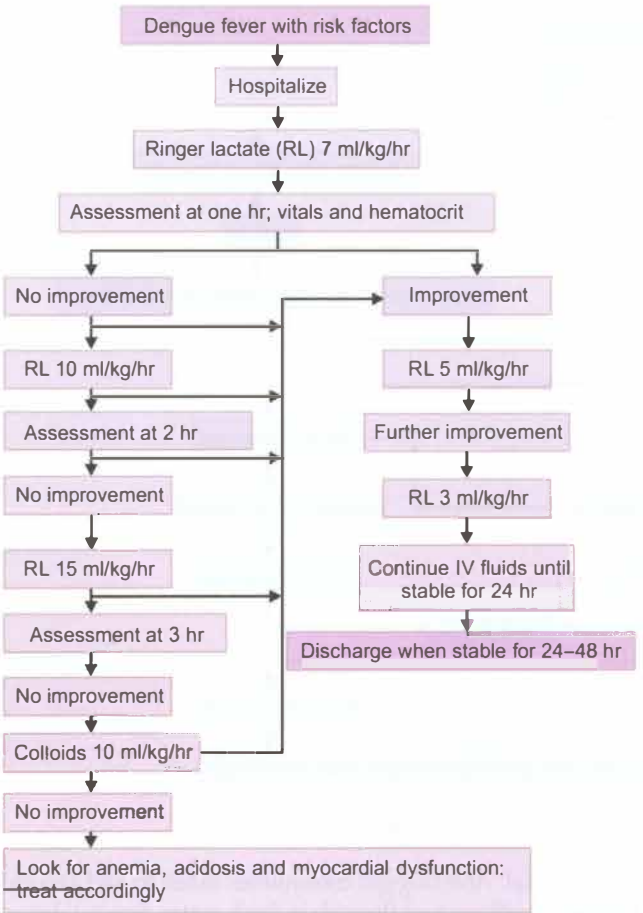

Fig. 10.9: Management algorithm for dengue fever with risk factors

- Severe plasma leakage leading to:
  - Shock
  - Fluid accumulation with respiratory distress
- Severe bleeding as evaluated by clinician
- Severe organ involvement
  - Liver: AST or ALT ≥1000 IU/l
  - CNS: Impaired consciousness
  - Heart and other organs

Children classified as severe dengue should be hospitalized (preferably in Pediatric Intensive Care Unit) and treated with normal saline or lactated Ringer solution; 10–20 ml/kg is infused over one hr or given as a bolus if blood pressure is unrecordable (earlier known as dengue shock syndrome DSS IV). In critically sick children it is preferable to establish two IV lines, one for administration of normal saline and other for infusing 5% dextrose and potassium. If there is no improvement in vital parameters and the hematocrit is rising; colloid 10 ml/kg is infused rapidly. Alternatively, if hematocrit is falling without any improvement in vital parameters; blood transfusion should be given with the presumption that lack of improvement is due to occult blood loss (Fig. 10.10). Once improvement starts then fluid infusion rate is gradually decreased. In addition to fluid management, oxygen should be administered to all patients with shock.

Management of bleeding

a. *Petechial spots or mild mucosal bleed but hemodynamically stable.* Such patients needs supportive care including bed rest, maintenance of hydration and monitoring. Avoid IM injections. There is no role of prophylactic platelet rich plasma (PRP) infusions even with severe thrombocytopenia. Avoid any procedures predisposing to mucosal trauma.

b. *Severe bleeding and hemodynamic instability, excessive mucosal bleed.* These patients should be treated with blood transfusion and monitoring. There is little evidence to support the practice of transfusing platelet concentrates and/or fresh-frozen plasma for severe bleeding. When bleeding cannot be managed with fresh whole blood or fresh-packed cells and there is possibility of DIC, fresh-frozen plasma and platelet rich plasma may be considered.

Management of fluid overload

Fluid overload with stable haemodynamic status and is out of the critical phase (more than 24–48 hr of defervescence). In such patients stop intravenous fluids but continue close monitoring. If necessary, give oral or intravenous furosemide 0.1–0.5 mg/kg/dose once or twice daily, or a continuous infusion of furosemide 0.1 mg/kg/hr. Monitor serum potassium and correct the ensuing hypokalemia.

Fluid overload with stable haemodynamic status but is still within the critical phase. Reduce the intravenous fluid accordingly. Avoid diuretics during the plasma leakage phase because they may lead to intravascular volume depletion. Patients with fluid overload and hypotension with low or normal hematocrit levels may have occult hemorrhage. Further infusion of large volumes of intravenous fluids will lead to a poor outcome. Careful fresh whole blood transfusion should be initiated as soon as possible. If the patient remains in shock and the hematocrit is elevated, repeated small boluses of a colloid solution may help.

Other supportive care Other organ dysfunction (liver, kidney) should be managed. There is no therapeutic utility of corticosteroids, intravenous immunoglobulins or recombinant activated factor VII. Broad spectrum antibiotics are only indicated in case of superadded bacterial infection. Blood transfusion (20 ml/kg) is indicated when shock persists despite declining hematocrit values (which are indicative of adequate fluid replacement) due to overt or internal hemorrhage.

All children with hypotension should receive oxygen inhalation by nasal cannula, face mask or oxygen hood.

Monitoring

In view of the dramatic course of severe dengue, monitoring of the patient is crucial in the first few hour of

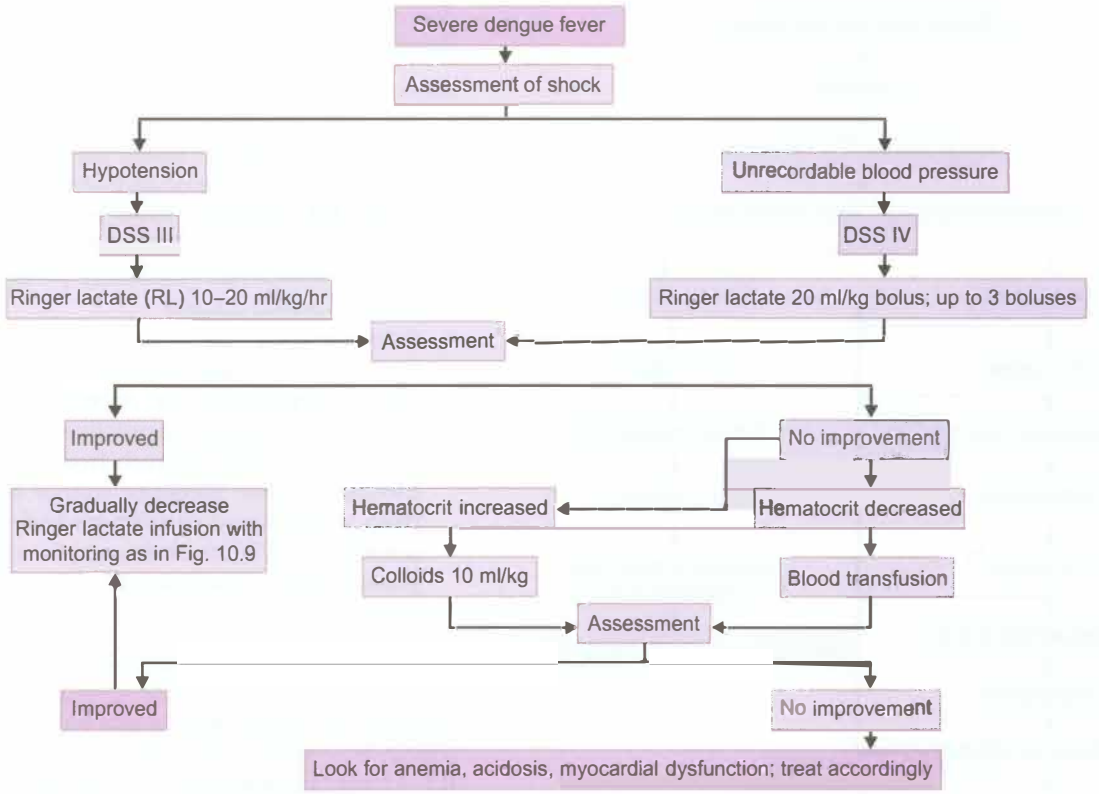

Fig. 10.10: Algorithm for management of severe dengue fever. DSS dengue shock syndrome

illness. Heart rate, respiratory rate, blood pressure and pulse pressure should be monitored every 30 min till the patient is stable, thereafter every 2–4 hr should be continued as long as the child is in the hospital. In critically ill children, central venous pressure and accurate urine output with an indwelling urinary catheter should be monitored. Absolute platelet counts should be checked once a day till it shows a rising trend.

Prognosis

Dengue fever is a self-limited disease but the mortality in severe dengue may be as high as 20–30% if left untreated. Early recognition of illness, careful monitoring and appropriate fluid therapy alone has resulted in considerable reduction of case fatality rate to less than 1 percent. Early recognition of shock is of paramount importance as the outcome of a patient with DSS depends on the duration of shock. If shock is identified when pulse pressure starts getting narrow and intravenous fluids are administered at this stage, the outcome is excellent.

Prevention

Preventive measures are directed towards elimination of adult mosquitoes and their larvae. During epidemics aerial spraying or fogging with malathion is recommended for control of adult mosquitoes. However, larval control measures by source reduction and use of larvicides are even more crucial. *Aedes aegypti* mosquitoes breed in and around human dwellings and flourish in fresh water. Special drives should be launched during and soon after the rainy season to interrupt breeding cycle of mosquitoes. There should be no opportunity for stagnation of water in the bathroom, kitchen, terrace, lawn and other open places. The stored water should be kept covered. Cooperation from every house owner and public establishment is crucial for the success of control program. Strong motivation and commitment on the part of government and its employees are fundamental prerequisites for the success of control measures.

Mesocyclops, the shellfish are credited to eat and effectively eliminate larvae of *Aedes aegypti*. The strategy has been used with success by Australian scientists working in Vietnam by growing shellfish in ponds and water traps. A live attenuated quadruple vaccine is undergoing clinical trials but there are concerns whether vaccine may predispose to development of severe dengue.

10

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Chikungunya

Chikungunya is an acute disease, which results in fever, arthritis and skin rash, caused by an enveloped virus capable of replicating in mosquitoes. Because of severe arthritic symptoms, the disease is given the Swahili name of chikungunya (that which bends up). Since an outbreak of chikungunya in Tanzania in 1952, large epidemics were reported in South Africa, India (1971), South-East Asia and Philippines. Re-emergence of chikungunya disease occurred in India during 2005–06, causing 1.3 million cases in 13 states, chiefly Andhra Pradesh and Karnataka.

Epidemiology

The rural cycle of chikungunya transmission involves *Aedes africans*, *A. fancifer* and wild primates, while the urban cycle involves *A. aegypti* and humans. In rural cycle (seen in Africa) the disease is endemic with a small number of cases occurring in most year. In urban areas, the outbreaks are sporadic and explosive with infection of a large population within weeks. In Asia, the virus may be maintained in urban cycle, with *A. aegypti*, or require reinoculation before onset of epidemic. Outbreaks typically occur during the rainy season, associated with the population density of the mosquito vector, which breeds in household containers and puddles with peak activity in mid-morning and late afternoon. After an epidemic, the disease typically vanishes for year, because a large proportion of the population is immune.

Clinical Features

The disease has a sudden onset, with an incubation period of 2–12 days. Infection is characterized by fever, headache, fatigue, nausea, vomiting, muscle pain, rash and joint pain. Fever rises abruptly to 103–104°F and is accompanied by rigors. The acute phase lasts for 2–3 days. Joint pain appears suddenly and is often very severe in intensity; the arthralgia/arthritis is polyarticular, migratory and predominantly affects the small joints of hands, wrist, ankle and feet, with less involvement of larger joints. Headache is present in 80% of cases. Photophobia and retro-orbital pain may also occur. An itchy, transient maculopapular rash appears 4–8 days later affecting the trunk and limbs. Inguinal lymph nodes may be enlarged. The joint pains may continue for many months after the illness. Fatalities are rare and associated with young age, thrombocytopenia and shock. Rarely encephalopathy may occur in infants and young children.

Diagnosis

Chikungunya should be suspected in patients who presents with the characteristic triad of fever, rash and arthritis. Viremia is present in most patients during the initial 2–4 days of disease and may be isolated in cell cultures. Polymerase chain reaction can be used to confirm the infection. Virus specific IgM antibodies may be detected by capture ELISA and hemagglutination inhibition assays by 5–7 days of illness.

Treatment

No specific treatment is available. Symptomatic treatment in the form of rest, fluids and ibuprofen, naproxen, acetaminophen, or paracetamol may relieve symptoms. Aspirin should be avoided during acute phase of illness.

Prevention and Control

Strategies for prevention and control include breaking the transmission cycle of *A. aegypti* and by holding the mosquito population at extremely low levels. A live attenuated vaccine that induces longterm production of neutralizing antibodies, is being examined.

Suggested Reading

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HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV infection has become an important contributor to childhood morbidity and mortality, especially in many developing countries. The World Health Organization (WHO) estimated that 34 million persons worldwide were living with HIV infection at the end of 2011; 2.5 million of these were children under 15 yr of age. More than 90% of HIV-infected individuals live in developing nations. Sub-Saharan Africa accounts for nearly 90% of the world's total population of HIV-infected children. India and Thailand dominate the epidemic in South-East Asia, with more recent expansion into Vietnam, China and Cambodia.

Worldwide, it is estimated that nearly 2 million require antiretroviral treatment. At present only 25% of such children have an access to the antiretroviral therapy. Without access to antiretroviral therapy, 20% of vertically infected children will progress to the acquired immunodeficiency syndrome (AIDS) or death in their first yr of life and more than half of HIV-infected children will die before their fifth birthday.

HIV-1 and HIV-2. HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus. The HIV-1 genome is single-stranded RNA that is 9.2 kb in size. The genome has three major sections: the gag region, which encodes the viral core proteins (p24, p17,

p9, p6; these are derived from the precursor p55), the pol region, which encodes the viral enzymes (reverse transcriptase [p51], protease [p10], and integrase [p32]); and the env region, which encodes the viral envelope proteins (gp120 and gp41).

The major external viral protein of HIV-1 is a heavily glycosylated gp120 protein which contains the binding site for the CD4 molecule, the most common T lymphocyte surface receptor for HIV. Most HIV strains have a specific tropism for one of the chemokines: the fusion-inducing molecule, CXCR-4, which has been shown to act as a co-receptor for HIV attachment to lymphocytes, and CCR-5, a β chemokine receptor that facilitates HIV entry into macrophages.

Following viral attachment, gp120 and the CD4 molecule undergo conformational changes, allowing gp41 to interact with the fusion receptor on the cell surface. Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity and duplication of the DNA copies produces double-stranded circular DNA. Because the HIV-1 reverse transcriptase is error-prone, many mutations arise, creating wide genetic variation in HIV-1 isolates even within an individual patient. The circular DNA is transported into the cell nucleus where it is integrated into chromosomal DNA; this is called as the provirus. The provirus can remain dormant for extended periods.

HIV-1 transcription is followed by translation. A capsid polyprotein is cleaved to produce, among other products, the virus-specific protease (p10). This enzyme is critical for HIV-1 assembly. The RNA genome is then incorporated into the newly formed viral capsid. As the new virus is formed, it buds through the cell membrane and is released.

HIV-2 is a rare cause of infection in children. It is most prevalent in Western and Southern Africa. If HIV-2 is suspected, a specific test that detects antibody to HIV-2 peptides should be used.

Transmission. Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from mother to child. The primary route of infection in the pediatric population is vertical transmission. Most large studies in the United States and Europe have documented mother-to-child transmission rates in untreated women between 12 and 30%. In contrast, transmission rates in Africa and Asia are higher, up to 50%.

Vertical transmission of HIV can occur during the intrauterine or intrapartum periods, or through breastfeeding. Up to 30% of infected newborns are infected *in utero*. The highest percentages of HIV-infected children acquire the virus intrapartum. Breastfeeding is an important route of transmission, especially in the developing countries. The risk factors for vertical transmission include preterm delivery (<34 week gestation), a low maternal antenatal CD4 count, use of illicit drugs during pregnancy, >4 hr duration of ruptured membranes and birthweight <2500 g.

Transfusions of infected blood or blood products have accounted for a variable proportion of all pediatric AIDS cases. Heat treatment of factor VIII concentrate and HIV antibody screening of donors has virtually eliminated HIV transmission to children with hemophilia. Blood donor screening has dramatically reduced, but not eliminated, the risk of transfusion-associated HIV infection. Sexual contact is a major route of transmission in the adolescent population.

Natural History

Before highly active antiretroviral therapy (HAART) was available, three distinct patterns of disease were described in children. Approximately 10–20% of HIV-infected newborns in developed countries presented with a rapid disease course, with onset of AIDS and symptoms during the first few months of life and, if untreated, death from AIDS-related complications by 4 yr of age. In resource-poor countries, >85% of the HIV-infected newborns may have such a rapidly progressing disease.

It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, it could effectively infect the majority of the body's immunocompetent cells. Most children in this group have a positive HIV-1 culture and/or detectable virus in the plasma in the first 48 hr of life. This early evidence of viral presence suggests that the newborn was infected *in utero*. In contrast to the viral load in adults, the viral load in infants stays high for at least the first 2 yr of life.

The majority of perinatally infected newborns (60–80%) present with a *second pattern*—that of a much slower progression of disease with a median survival time of 6 yr. Many patients in this group have a negative viral culture or PCR in the 1st week of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases by 2–3 months of age (median 100,000 copies/ml) and then slowly declines over a period of 24 months. This observation can be explained partially by the immaturity of the immune system in newborns and infants. The *third pattern of disease* (i.e. longterm survivors) occurs in a small percentage (<5%) of perinatally infected children who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 yr.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. Therefore, for example, a value of 1,500 CD4 cells/mm^3 in children <1 yr of age is indicative of severe CD4 depletion and is comparable to <200 CD4 cells/mm^3 in adults. Lymphopenia is relatively rare in perinatally infected children and is

usually only seen in older children or those with endstage disease.

B cell activation occurs in most children early in the infection as evidenced by hypergammaglobulinemia associated with high levels of anti-HIV-1 antibody. This response may reflect both dysregulation of T cell suppression of B-cell antibody synthesis and active CD4 enhancement of B-lymphocyte humoral responses.

CD4 depletion and inadequate antibody responses lead to increased susceptibility to various infections and the clinical manifestations vary with the severity of immunodeficiency.

Clinical Manifestations

The clinical manifestations of HIV infection vary widely among infants, children and adolescents. In most infants, physical examination at birth is normal. Initial signs and symptoms may be subtle and nonspecific, such as lymphadenopathy, hepatosplenomegaly, failure to thrive, chronic or recurrent diarrhea, interstitial pneumonia, or oral thrush and may be distinguishable from other causes only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, wasting and severe malnutrition predominate in Africa. Symptoms found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis and early onset of progressive neurologic deterioration.

The pediatric HIV disease is staged by using two parameters: clinical status (Table 10.4) and degree of immunologic impairment (Table 10.5).

Opportunistic Infections

Children with HIV infection and advanced or severe immunosuppression are susceptible to develop various opportunistic infections. The important pathogens include *Pneumocystis jiroveci*, Cryptosporidium, Cryptococcus, Isospora and CMV.

Respiratory Diseases

Pneumocystis pneumonia *Pneumocystis jiroveci* (previously *P. carinii*) pneumonia (PCP) is the opportunistic infection that led to the initial description of AIDS. PCP is one of the commonest AIDS defining illnesses in children in the US and Europe. However, data regarding the incidence of PCP in children in other parts of the world are scarce. The majority of the cases occur between 3rd and 6th months of life.

Even if a child develops PCP while on prophylaxis, therapy may be started with cotrimoxazole. This is because the prophylaxis may have failed because of poor compliance, or unusual pharmacokinetics. Untreated, PCP is universally fatal. With the use of appropriate therapy, the mortality decreases to less than 10%. The risk factors for mortality are the severity of the episode and the severity of the immunosuppression.

Recurrent bacterial infections In various studies from developing countries, up to 90% of HIV-infected children had history of recurrent pneumonias. Initial episodes of pneumonia often occur before the development of significant immunosupression. As the immunosupression increases the frequency increases.

The common pathogens for community-acquired pneumonia in these children are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*. However, in children with severe immunosuppression and in hospital-acquired infections, gram-negative organisms, such as, *Pseudomonas aeruginosa* gain importance.

The clinical features of pneumonia in HIV-infected children are similar to those in uninfected children. However, in severely immunocompromised children, the signs may be subtle. Often, the response to therapy is slow and the relapse rates are high. Bacteremia may be more common, seen in up to 50%.

Choices of appropriate antibiotics are often made based on local patterns of etiologies and susceptibilities. In many settings, an appropriate choice would be a combination of a broad spectrum cephalosporin and an aminoglycoside. In areas where a large proportion of *Staphylococcus aureus* isolates are resistant to antistaphylococcal antibiotics, then the empiric inclusion of vancomycin, clindamycin, linezolid should be considered. Children with nonsevere pneumonia can be managed as outpatients using a second or a third generation cephalosporin or a combination like amoxicillin-clauvulinic acid. Since *Pneumocystis jiroveci* pneumonia cannot be excluded at the outset in most HIV-infected children with severe respiratory infections, cotrimoxazole should be added unless another diagnosis has been definitively made.

The principles of supportive care of HIV-infected children admitted with severe pneumonia are similar to those in non-HIV-infected children.

Tuberculosis With the spread of the HIV infection, there has been resurgence in tuberculosis. Coexistent TB and HIV infections accelerate the progression of both the diseases. HIV infected children are more likely to have extrapulmonary and disseminated tuberculosis; the course is also likely to be more rapid. An HIV infected child with tubercular infection is more likely to develop the disease than a child without HIV infection. The overall risk of active TB in children infected with HIV is at least 5- to 10-fold higher than that in children not infected with HIV.

All HIV-infected children with active TB should receive longer duration of antitubercular therapy. A 9–12 month therapy is preferred. A close followup is essential to diagnose nonresponse/drug resistance early.

Viral infections Infections caused by respiratory syncytial virus, influenza and parainfluenza viruses result in

Table 10.4: WHO clinical staging of HIV/AIDS in children with confirmed infection

Clinical stage 1

Asymptomatic
Persistent generalized lymphadenopathy

Clinical stage 2

Unexplained[a] persistent hepatosplenomegaly
Papular pruritic eruptions
Fungal nail infection
Angular cheilitis
Lineal gingival erythema
Extensive wart virus infection
Extensive molluscum contagiosum
Recurrent oral ulceration
Unexplained[a] persistent parotid enlargement
Herpes zoster
Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis, tonsillitis)

Clinical stage 3

Unexplained[a] moderate malnutrition or wasting not adequately responding to standard therapy
Unexplained[a] persistent diarrhea (14 days or more)
Unexplained[a] persistent fever (above 37.5°C intermittent or constant, for longer than one month)
Persistent oral candidiasis (after the first 6–8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis/periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anemia (<8 g/dl), neutropenia ($<0.5 \times 10^9$/l) or chronic thrombocytopenia ($<50 \times 10^9$/l).

Clinical stage 4[b]

Unexplained[a] severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary/disseminated TB
Kaposi sarcoma
Cytomegalovirus infection: retinitis or CMV infection affecting another organ, with onset at age >1 mo
Central nervous system toxoplasmosis (after one month of life)
Extrapulmonary cryptococcosis (including meningitis)
HIV encephalopathy
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
Disseminated nontuberculous mycobacterial infection
Chronic cryptosporidiosis (with diarrhea)
Chronic isosporiasis
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

[a]Unexplained refers to where the condition is not explained by other causes
[b]Some additional specific conditions can also be included in regional classifications, e.g. reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in Americas region, penicilliosis in Asia and HIV-associated rectovaginal fistula in Africa

symptomatic disease more often in HIV infected children in comparison to noninfected children. Infections with other viruses such as adenovirus and measles virus are more likely to lead to serious sequelae than with the previously mentioned viruses. As RSV infection most often occurs in children in the first 2 yr of life, during which many of these may not be severely immunocompromised, the severity of illness may not be different from the non-

Table 10.5: Severity of immune suppression based on CD4 levels children

HIV-associated immunodeficiency	*Age-related CD4+ cell values*			
	≤1 mo	*12–35 mo*	*36–59 mo*	*≥5 yr*
Not significant (normal)	>35%	>30%	>25%	>500 cells/mm^3
Mild	30–35%	25–30%	20–25%	350–499 cells/mm^3
Advanced	25 –30%	20–25%	15–20%	200–349 cells/mm^3
Severe	<25% or <1500 cells/mm^3	<20% or <750 cells/mm^3	<15% or <350 cells/mm^3	<200 cells/mm^3 or <15%

HIV infected children. In children with AIDS, disseminated CMV is a known opportunistic infection, but pneumonia caused by this virus is rare. The principles of diagnosis and treatment of these infections in HIV-infected children are similar to those in non-HIV infected children.

Fungal infections Pulmonary fungal infections usually present as a part of disseminated disease in immunocompromised children. Primary pulmonary fungal infections are uncommon.

Pulmonary candidiasis should be suspected in any sick HIV-infected child with lower respiratory tract infection that does not respond to the common therapeutic modalities. A positive blood culture supports the diagnosis of invasive candidiasis.

Lymphoid interstitial pneumonitis (LIP) LIP has been recognized as a distinctive marker for pediatric HIV infection and is included as a Class B condition in the revised CDC criteria for AIDS in children. In absence of antiretroviral therapy, nearly 20% of HIV-infected children developed LIP.

The etiology and pathogenesis of LIP are not well understood. Suggested etiologies include: an exaggerated immunologic response to inhaled or circulating antigens, and/or primary infection of the lung with HIV, Epstein-Barr virus (EBV), or both.

LIP is characterized by nodule formation and diffuse infiltration of the alveolar septae by lymphocytes, plasmacytoid lymphocytes, plasma cells and immunoblasts. There is no involvement of the blood vessels or destruction of the lung tissue. Children with LIP have a relatively good prognosis compared to other children who meet the surveillance definition of AIDS.

LIP is usually diagnosed in children with perinatally acquired HIV infection when they are older than 1 yr of age, unlike PCP. Most children with LIP are asymptomatic. Tachypnea, cough, wheezing and hypoxemia may be seen when children present with more severe manifestations; crepitations are uncommon. Clubbing is often present in advanced disease. These patients can progress to chronic respiratory failure. Long standing LIP may be associated with chronic bronchiectasis. The presence of a reticulonodular pattern, with or without hilar lymphadenopathy, that persists on chest radiograph for 2 months or greater and that is unresponsive to antimicrobial therapy is considered presumptive evidence of LIP. Care should be taken to exclude other possible etiologies. A definitive diagnosis of LIP can only be made by histopathology.

Early disease is managed conservatively. The effect of antiretrovirals on LIP is probably limited. Steroids are indicated if children with LIP have symptoms and signs of chronic pulmonary disease, clubbing and/ or hypoxemia. Treatment usually includes an initial 4 to 12 week course of prednisolone (2 mg/kg/day) followed by a tapering dose, using oxygen saturation and clinical status as a guide to improvement. This is then followed by chronic low dose prednisolone.

Gastrointestinal Diseases

The pathologic changes in the gastrointestinal tract of children with AIDS are variable and can be clinically significant.

A variety of microbes can cause gastrointestinal disease, including bacteria (salmonella, campylobacter, *Mycobacterium avium* intracellulare complex), protozoa (giardia, cryptosporidium, isospora, microsporidia), viruses (CMV, HSV, rotavirus) and fungi (Candida). The protozoal infections are most severe and can be protracted in children with severe immunosuppression. Children with cryptosporidium infestation can have severe diarrhea leading to hypovolemic shock. *AIDS enteropathy*, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, is probably the result of direct HIV infection of the gut.

Chronic liver inflammation is relatively common in HIV infected children. In some children, hepatitis caused by CMV, hepatitis B or C viruses, or mycobacteria may lead to liver failure and portal hypertension. It is important to recognize that several of the antiretroviral drugs such as didanosine and protease inhibitors may also cause reversible elevation of transaminases.

Pancreatitis is uncommon in HIV infected children. This may be the result of drug therapy, e.g. didanosine, lamivudine, nevirapine, or pentamidine. Rarely, opportunistic infections such as mycobacteria or CMV may be responsible for acute pancreatitis.

The principles of management of these conditions are similar to those in non-HIV-infected children.

Neurologic Diseases

The incidence of central nervous system involvement in perinatally infected children may be more than 50% in

developing countries but lower in developed countries, with a median onset at about one and a half yr of age. The most common presentation is progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly and symmetric motor dysfunction. Meningitis due to bacterial pathogens, fungi such as Cryptococcus and a number of viruses may be responsible. Toxoplasmosis of the nervous system is exceedingly rare in young infants, but may occur in HIV-infected adolescents; the overwhelming majority of these cases have serum IgG antitoxoplasma antibodies as a marker of infection. The management of these conditions is similar to that in non-HIV-infected children; the response rates and outcomes may be poorer.

Cardiovascular Involvement

Cardiac abnormalities in HIV-infected children are common, persistent and often progressive; however, the majority of these are subclinical. Left ventricular structure and function progressively may deteriorate in the first 3 yr of life, resulting in increased ventricular mass in HIV-infected children. Children with encephalopathy or other AIDS-defining conditions have the highest rate of adverse cardiac outcomes. Resting sinus tachycardia has been reported in up to nearly two-thirds and marked sinus arrhythmia in one-fifth of HIV-infected children. Gallop rhythm with tachypnea and hepatosplenomegaly appear to be the best clinical indicators of congestive heart failure. Electrocardiography and echocardiography are helpful in assessing cardiac function before the onset of clinical symptoms.

Renal Involvement

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. Nephrotic syndrome is the most common manifestation of pediatric renal disease, with azotemia and normal blood pressure. Polyuria, oliguria and hematuria have also been observed in some patients.

Diagnosis

All infants born to HIV-infected mothers test antibody-positive at birth because of passive transfer of maternal HIV antibody across the placenta. Most uninfected infants lose maternal antibody between 6 and 12 months of age. As a small proportion of uninfected infants continue to have maternal HIV antibody in the blood up to 18 months of age, positive IgG antibody tests cannot be used to make a definitive diagnosis of HIV infection in infants younger than this age. In a child older than 18 months of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay (EIA) and confirmatory test (e.g. Western blot or immunofluorescence assay) can establish the diagnosis of HIV infection. Although serologic diagnostic tests were the most commonly used in the past, tests that allow for earlier definitive diagnosis in children have replaced antibody assays as the tests of choice for the diagnosis of HIV infection in infants.

Specific viral diagnostic assays, such as HIV DNA or RNA PCR, HIV culture, or HIV p24 antigen immune dissociated p24 (ICD-p24), are essential for diagnosis of young infants born to HIV infected mothers. By 6 months of age, the HIV culture and/or PCR identifies all infected infants, who are not having any continued exposure due to breast feeding. HIV DNA PCR is the preferred virologic assay in developed countries. Plasma HIV RNA assays may be more sensitive than DNA PCR for early diagnosis, but data are limited. HIV culture has similar sensitivity to HIV DNA PCR; however, it is more technically complex and expensive and results are often not available for 2–4 week compared to 2–3 days with PCR. The p24 antigen assay is less sensitive than the other virologic tests. Figure 10.11 shows the suggested algorithm for diagnosis of HIV infection in infants. The national program (Early Infant Diagnosis) now uses HIV DNA PCR test on dried blood spot samples; the positive tests need confirmation using a HIV DNA PCR on a whole blood sample.

Management

The management of HIV infected child includes antiretroviral therapy, prophylaxis and treatment of opportunistic infections and common infections, adequate nutrition and immunization.

Antiretroviral Therapy

Decisions about antiretroviral therapy for pediatric HIV-infected patients are based on the magnitude of viral replication (i.e. viral load), CD4 lymphocyte count or percentage and clinical condition. A child who has WHO stage 3 or 4 clinical disease should receive ART irrespective of the immunologic stage. Children who are asymptomatic or have stage 1 or 2 disease may be started on ART if they have evidence of advanced or severe immunosupression. However, current evidence shows that young children less than 2 yr of age have a higher risk of mortality without ART. *The World Health Organization now recommends initiation of ART for all HIV infected children less than 2 yr age irrespective of clinical symptoms and the immunologic stage.*

Availability of antiretroviral therapy has transformed HIV infection from a uniformly fatal condition to a chronic infection, where children can lead a near normal life. The currently available therapy does not eradicate the virus and cure the child; it rather suppresses the virus replication for extended periods of time. The 3 main groups of drugs are nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). *Highly active antiretroviral therapy (HAART) is a combination of 2 NRTIs with a PI or a NNRTI.* The national program for management of HIV infected children recommends a combination of zidovudine, lamivudine and nevirapine as the first line therapy. The

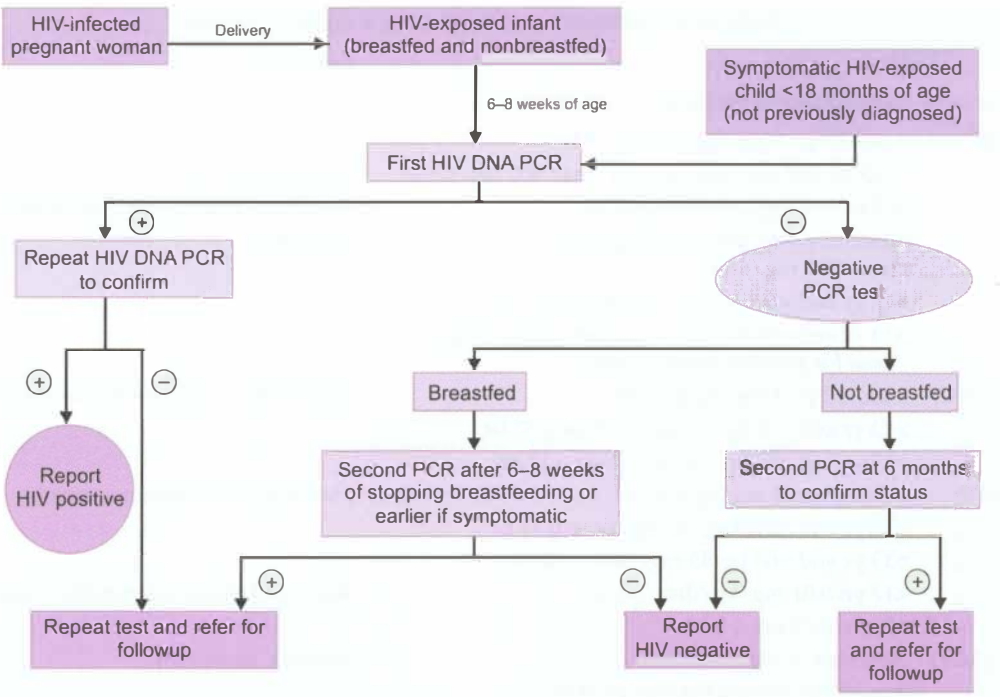

Fig. 10.11: Diagnosis of infection with HIV in children <18 months. If child is >18-month-old, adult testing strategies may be used

alternative regimen is a combination of stavudine, lamivudine and nevirapine. The details of the antiretroviral drugs are shown in Table 10.6. Pediatric fixed dose combinations have been developed, and these are administered using a weight-band based dosing system (NACO guidelines).

Cotrimoxazole Prophylaxis

In resource-limited settings, cotrimoxazole prophylaxis is recommended for all HIV exposed infants starting at 4--6 weeks of age and continued until HIV infection can be excluded. Cotrimoxazole is also recommended for HIV-exposed breastfeeding children of any age and cotrimoxazole prophylaxis should be continued until HIV infection can be excluded by HIV antibody testing (beyond 18 months of age) or virological testing (before 18 months of age) at least six weeks after complete cessation of breastfeeding.

All children younger than one yr of age documented to be living with HIV should receive cotrimoxazole prophylaxis regardless of symptoms or CD4 percentage. After one yr of age, initiation of cotrimoxazole prophylaxis is recommended for symptomatic children (WHO clinical stages 2, 3 or 4 for HIV disease) or children with CD4 <25%. All children who begin cotrimoxazole prophylaxis (irrespective of whether cotrimoxazole was initiated in the first yr of life or after that) should continue until the age of five yr, when they can be reassessed.

Nutrition

It is important to provide adequate nutrition to HIV-infected children. Many of these children have failure to thrive. These children will need nutritional rehabilitation. In addition, micronutrients like zinc may be useful.

Immunization

The vaccines that are recommended in the national schedule can be administered to HIV infected children except that symptomatic HIV infected children should not be given the oral polio and BCG vaccines.

Prevention of Mother to Child Transmission (PMTCT)

The risk of MTCT can be reduced to under 2% by interventions that include antiretroviral (ARV) prophylaxis given to women during pregnancy and labor and to the infant in the first weeks of life, obstetrical interventions including elective cesarean delivery (prior to the onset of labor and rupture of membranes) and complete avoidance of breastfeeding.

Antiretroviral drug regimens for treating pregnant women For HIV-infected pregnant women in need of ART for their own health, ART should be administered irrespective of gestational age and is continued throughout pregnancy, delivery and thereafter (recommended for all HIV-infected pregnant women with CD4 cell count <350 cells/mm^3, irrespective of WHO clinical staging; and for WHO clinical stage 3 or 4, irrespective of CD4 cell count).

Recommended regimen for pregnant women with indication for ART is combination of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) or efavirenz (EFV) during antepartum, intrapartum and postpartum

Table 10.6: Commonly used antiretroviral drugs in children

Drug	*Dose*	*Side effects*
Nucleoside reverse transcriptase inhibitors		
Abacavir (ABC)	3 mo–13 yr: 8 mg/kg/dose q 12 hr >13 yr: 300 mg/dose q 12 hr (max 300 mg/dose)	Hypersensitivity
Didanosine	0–3 mo: 50 mg/m^2/dose q 12 hr 3 mo–13 yr: 90–150 mg/m^2 q 12 hr (max 200 mg/dose) >13 yr and <60 kg: 125 mg tablets q 12 hr >13 yr and >60 kg: 200 mg tablet q 12 hr (higher dose for powder preparations)	Peripheral neuropathy, pancreatitis, abdominal pain, diarrhea
Lamivudine (3TC)	1 mo–13 yr: 4 mg/kg q 12 hr >13 yr and <50 kg: 4 mg/kg/dose q 12 hr >13 yr and >50 kg: 150 mg/dose q 12 hr	Pancreatitis, neuropathy, neutropenia
Stavudine (d4T)	1 mo–13 yr: 1 mg/kg q 12 hr >13 yr and 30–60 kg: 30 mg/dose q 12 hr >13 yr and >60 kg: 40 mg/dose q 12 hr	Headache, GI upset, neuropathy
Zalcitabine	<13 yr: 0.01 mg/kg/dose q 8 hr >13 yr: 0.75 mg q 8 hr	Rash, peripheral neuropathy, pancreatitis
Zidovudine (AZT)	Neonates: 4 mg/kg BD 3 mo-13 yr: 90–180 mg/m^2 q 6–8 hr >13 yr: 300 mg q 12 hr	Anemia, myopathy
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine (NVP)	2 mo–13 yr: 120 mg/m^2 (max 200 mg) q 24 hr for 14 days, followed by 150–200 mg/m^2 q 12 hr >13 yr: 200 mg q 24 hr for 14 days, then increase to 200 mg q 12 hr if no rash or other side effects	Skin rash, Stevens-Johnson syndrome
Efavirenz (EFV)	>3 yr: 10–14.9 kg: 200 mg q 24 hr 15–19.9 kg: 250 mg q 24 hr 20–24.9kg: 300 mg q 24 hr 25–32.4 kg: 350 mg q 24 hr 32.5–39.9 kg: 400 mg q 24 hr ≥40 kg: 600 mg q 24 hr	Skin rash, CNS symptoms, increased transaminase levels
Protease inhibitors		
Amprenavir	4–16 yr and <50 kg: 22.5 mg/kg q 12 hr (oral solution) or 20 mg/kg q 12 hr (capsules) >13 yr and >50 kg: 1200 mg q 12 hr (capsules)	
Indinavir	500 mg/m^2 q 8 hr; >13 yr: 800 mg q 8 hr	Hyperbilirubinemia, nephrolithiasis
Lopinavir/(LPV) ritonavir	6 mo–12 yr: 7–<15 kg: 12 mg/kg lopinavir/ 3 mg/kg ritonavir q 12 hr with food; 15–40 kg: 10 mg/kg lopinavir/2.5 mg/kg ritonavir q 12 hr with food >12 yr: 400 mg lopinavir/100 mg ritonavir q 12 hr with food	Diarrhea, fatigue, headache, nausea; increased cholesterol and triglycerides
Nelfinavir	<13 yr: 50–55 mg/kg q 12 hr >13 yr: 1250 mg q 12 hr (max 2000 mg)	Diarrhea, abdominal pain
Ritonavir	<13 yr: 350–400 mg/m^2 q 12 hr (starting dose: 250 mg/m^2) >13 yr: 600 mg q 12 hr (starting with 300 mg)	Bad taste, vomiting, nausea, diarrhea, rarely, hepatitis
Saquinavir	50 mg/kg q 8 hr; >13 yr: soft gel capsules-1200 mg q 8 hr	Diarrhea, headache, skin rash

period; EFV-based regimens should not be newly-initiated during the first trimester of pregnancy.

Recommended regimen for pregnant women who are not eligible for ART for their own health, but for preventing MTCT is to start ART as early as 14 weeks gestation or as soon as possible when women present late in pregnancy, in labor or at delivery.

Two options are available

Option 1. Daily AZT in antepartum period, combination of single dose of NVP at onset of labor and dose of AZT and 3TC during labor followed by combination of AZT and 3TC for 7 days in postpartum period.

Option 2. Triple antiretroviral drugs starting as early as 14 week of gestation until one week after all exposure to breast milk has ended (AZT + 3TC + LPV or AZT + 3TC + ABC or AZT + 3TC + EFV) where ABC abacavir, LPV lopinavir.

Omission of the single dose-NVP and AZT+3TC intra- and postpartum may be considered for women who received at least four week of AZT before delivery. If a woman received a three-drug regimen during pregnancy, a continued regimen of triple therapy is recommended for mother through the end of the breastfeeding period.

Regimens for Infants Born to HIV Positive Mothers

(a) If mother received only AZT during antenatal period:

For breastfeeding infants. Daily NVP from birth until one wk after all exposure to breast milk has ended. The dose of nevirapine is 10 mg/day PO for infants <2.5 kg; 15 mg/day PO for infants more than 2.5 kg.

For nonbreastfeeding infants. Daily AZT or NVP from birth until 6 wk of age. The dose of AZT is 4 mg/kg PO per dose twice a day.

(b) If mother received triple drug ART during pregnancy and entire breastfeeding: Daily AZT or NVP from birth until 6 weeks of age irrespective of feeding

Intrapartum Interventions

Avoid artificial rupture of membranes (ARMs) unless medically indicated. Delivery by elective cesarean section at 38 weeks before onset of labor and rupture of membranes should be considered. Avoid procedures increasing risk of exposure of child to maternal blood and secretions like use of scalp electrodes.

Breastfeeding

Breastfeeding is an important modality of transmission of HIV infection in developing countries. The risk of HIV infection via breastfeeding is highest in the early months of breastfeeding. Factors that increase the likelihood of transmission include detectable levels of HIV in breast milk, the presence of mastitis and low maternal CD4+ T cell count. *Exclusive breastfeeding has been reported to carry a lower risk of HIV transmission than mixed feeding.* Mothers known to be HIV-infected should only give commercial infant formula milk as a replacement feed when specific conditions are met (referred to earlier as affordable, feasible, acceptable, sustainable and safe (AFASS) in the 2006 WHO recommendations on HIV and infant feeding). Otherwise exclusive breastfeeding is recommended during the first 6 months of life. WHO recommends that the transition between exclusive breastfeeding and early cessation of breastfeeding should be gradual and not an "early and abrupt cessation". Replacement feeding should be given by katori spoon.

Conclusion

HIV infection in children is a serious problem in many developing countries. The severe manifestations of HIV infection, conditions resulting from severe immunosupression and drug toxicities may require intensive care. Development of a vaccine to prevent HIV infection is the high priority area. There is also need to find have more efficacious antiretroviral drugs that have fewer adverse effects. Making available antiretroviral therapy at an affordable cost remains a big challenge. On short-term there is a need to find effective ways to control vertical transmission from mother to child. It may help in substantial reduction in childhood HIV infection load.

Suggested Reading

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IAP, NACO. Guidelines for HIV Care and Treatment in Infants and Children. November 2006

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Influenza

The influenza virus is capable of causing disease in humans, birds and animals. In the industrialized world morbidity, absenteeism, economic burden and mortality due to influenza is well quantified and significant. Influenza has recently gained more prominence owing to the 2009 novel H1N1 pandemic.

Etiology and Epidemiology

Influenza A and B are RNA viruses that cause human disease. Influenza A is further classified into subtypes based on the two surface proteins hemagglutinin (H) and neuraminidase (N). Influenza B is classified into two distinct lineages Yamagata and Victoria but not into subtypes. Influenza has a highly segmented genome that is prone to frequent mutations and reassortment. This leads to frequent antigenic "drifts" when there is minor change in antigenicity and "shifts" where there is major change in antigenicity. These phenomena of antigenic change leads to evolution of new viruses to which there is little population immunity and causes annual outbreaks and occasionally pandemics. The novel H1N1 pandemic

occurred due to emergence of a new swine origin influenza virus H1N1 which was pathogenic to humans and capable of rapid human to human transmission and to which there was no preexisting immunity. Avian H5N1 commonly referred as bird flu is a highly pathogenic strain of influenza virus that infects and kills humans in close contact with diseased birds but has not acquired pandemic potential due to limited human to human transmissibility. The currently circulating influenza virus strains are H3N2, pandemic H1N1 and influenza B.

Influenza is transmitted from person-to-person through airborne droplet spread or through contact. The portal of entry is the respiratory tract and the virus attaches itself to the respiratory epithelium through the hemagglutinin which is the main virulence factor. The incubation period is 1–3 days and the period of infectivity is usually 7 days after illness onset and sometimes longer in those with severe disease. The attack rates are highest in children and young adults. In temperate climates there is a clear defined influenza season in fall and winters but in tropical countries like India it occurs throughout the year.

Clinical Features

In most individuals influenza is a minor illness characterized by a combination of fever, runny nose, sore throat, cough, bodyache, headache, abdominal pain, diarrhea and vomiting. The illness may have a biphasic course. Recovery usually occurs within a week. It is sometimes difficult to differentiate from common cold. Asymptomatic and subclinical infections are also very common.

A small proportion of individuals (less than 1%) can have complications and severe disease. The risk of complications is higher at extremes of age (children below 2 and the elderly), pregnant women and those who have just delivered, those with underlying comorbidities such as any chronic neurologic, metabolic, cardiac, pulmonary or renal disease, those who are immunocompromised and those with severe asthma. In the novel H1N1 epidemic the elderly were spared due to pre-existent immunity and morbid obesity emerged as an important risk factor.

The most dreaded complication of influenza is pneumonia with acute respiratory distress syndrome, respiratory failure and sometimes shock and renal failure. As many as 30% of these patients have bacterial co-infection with *S. pneumoniae* and *S. aureus*. Progression is very rapid and most patients require ventilator support over the next 24 hr. Occasionally other complications such as encephalitis, seizures, quadriparesis and myocarditis have been reported. Transplacental transmission to newborn and neonatal complications have also been reported. Complications usually set in by day 4 or 5 of illness. *The red flag symptoms are persistent high fever of more than 3 days duration, reappearance of fever after initial defervescence, breathlessness, dyspnea, tachypnea, hemoptysis in older children and adolescents, extreme weakness, poor oral intake and altered sensorium.*

It has been estimated that the novel H1N1 pandemic caused 18,000 deaths globally with case fatality rates ranging from 0.0004% to 1.5 % (0.83% in India) and one-third of those who died had no underlying risk factor.

Diagnosis

Influenza is primarily a clinical diagnosis. The complete blood count may show leukopenia and thrombocytopenia; the liver enzymes and CPK may be mildly elevated. Diagnosis may be confirmed by antigen detection or PCR on throat/nasopharyngeal swabs. Antibody tests in blood are not useful. Specific diagnostic tests such as PCR are not useful in routine clinical practice. They are expensive and have a turnaround time of 24–48 hr. Hence if specific therapy has to be administered, it has to be started before results become available. If the test is negative therapy cannot be discontinued as the sensitivity is only 60–70% and even lower if the sample is not properly collected. Thus the test does not help in the clinical decision of either starting or stopping therapy. In many instances, the report of the throat swab is received when the patient has already recovered. Henceforth molecular diagnosis of influenza should be restricted to hospitalized patients with severe disease when a definitive diagnosis helps in tracking the severity of the outbreak.

Treatment

Definitive treatment of influenza is with M2 inhibitors (amantadine/rimantidine) or neuraminidase inhibitor drugs (oseltamivir and zanamivir). These drugs reduce duration of symptoms, risk of complications and death. Though they are most effective if given within the first 48 hr of illness; therapy is useful even if given later at any time point of a severe illness. The pandemic H1N1 strain and most current seasonal flu strains are resistant to the M2 inhibitors. Hence as per current recommendations oseltamivir is the first line drug and zanamivir should be used in those with oseltamivir resistant virus. The therapeutic dose of oseltamivir is 30 mg twice daily in those with weight less than 15 kg, 45 mg twice daily for 15–24 kg, 60 mg twice daily for 25–34 kg and 75 mg twice daily for those 35 kg and above. Oseltamivir though formally not approved for infants, is generally safe and may be used in a dose of 2–3 mg/kg twice daily. The duration of therapy is 5 days. In patients with very severe disease double the recommended dose for 10 days may be used. Oseltamivir is well tolerated with occasional GI and neurological side effects.

For any patient presenting with influenza like illness (ILI), the treatment strategy depends on two factors: the severity of illness and the likelihood of complications. In patients with mild disease who are not at risk for complications, only symptomatic treatment is indicated. Antibiotics and antivirals should not be prescribed. Patients should be counseled about the red flag signs and asked to seek medical care in the event these occur. These

patients should be asked to stay at home till they are afebrile to prevent disease transmission to others.

Patients with ILI who are at high-risk for complications should be started on antiviral therapy irrespective of the severity of disease. The use of antivirals in all children below the age of 5 with flu like illness is however debatable.

For patients who present with symptoms of severe illness or who have complications, antiviral treatment with oseltamivir should be started without delay. An effort should be made to rule out other illnesses with similar symptomatology. In patients with signs of lower respiratory involvement, antibiotics like coamoxiclav or cephalosporins (cefuroxime, ceftriaxone or cefpodoxime) should also be used as bacterial coinfections are common. Supportive and intensive care is as for pneumonia or ARDS.

Prevention

Vaccination is the most effective preventive strategy and is discussed further in Chapter 9. Chemoprophylaxis with oseltamivir is also effective in preventing influenza. The dose is 30–75 mg of oseltamivir (as per weight) to be taken once daily for 10 days. It must be remembered that chemoprophylaxis is the biggest risk factor for drug resistance. Chemoprophylaxis should be considered only for very high-risk household contacts like pregnant women and the severely immunocompromised.

Household transmission can be reduced by good ventilation in the room, proper hand hygiene and adherence to cough etiquettes. Nosocomial transmission to other patients and health care workers is a concern. Vaccination for all health care workers especially during outbreaks should be considered. All patients with suspected ILI should be isolated in single rooms or cohorted in one ward. A distance of at least 1 m should be kept between patients as the droplets can travel for this distance only. Regular disinfection of all surfaces should be carried out. The staff caring for these patients should use a well fitting surgical mask that should be changed every 4 hr. They should use hand hygiene both before and after patient contact. Negative pressure rooms, N 95 masks, gowns though ideal are possible only in high resource settings.

School children show one of the highest infection rates and outbreaks are common in school. For reducing transmission, the classrooms should be well ventilated, children should be trained in hand hygiene and cough etiquettes and sick children should be prohibited from attending school till afebrile. Temporary school closure may be considered during a pandemic.

Suggested Reading

Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. NEJM 2010;362:1708–19

Emerging Viruses

This section deals briefly with some of the new emerging viral diseases seen in India.

Crimean-Congo hemorrhagic fever virus is a RNA virus of the Bunyaviridae family normally infecting cattle and occasionally transmitted to humans by infected ticks. The virus is highly contagious and human-to-human transmission in household and hospital setting is not uncommon. Outbreaks have been reported from various countries including Pakistan. It was first reported from India in 2011 from Gujarat. The presentation is that of a viral hemorrhagic fever with fever, body pain, headache, profuse bleeding, leukopenia, thrombocytopenia, altered liver functions, deranged coagulation parameters, rhabdomyolysis and renal failure. The disease mimics dengue with salient differences being early and more rapid platelet fall and rhabdomyolysis. Diagnosis is by specific PCR. Treatment is supportive; early administration of ribavarin is beneficial. Strict isolation of affected patients is crucial to prevent nosocomial transmission.

Hantaviruses cause two important clinical syndromes: hemorrhagic fever and renal syndrome (HFRS) in Europe and Asia including India and hantavirus cardiopulmonary syndrome in America. Rodents are natural hosts and humans acquire infection by inhalation of aerosols contaminated by rodent excreta or saliva. In India, HFRS and asymptomatic hantavirus infection has been reported from Tamil Nadu. The disease presents as a febrile illness with body pain, headache, thrombocytopenia, elevated liver enzymes, bleeding and renal failure. Leukocytosis with shift to left differentiates it from dengue. Diagnosis is by specific IgM antibodies. Treatment includes ribavarin and supportive care.

Nipah virus is an important cause of encephalitis increasingly reported from West Bengal, India. Its natural asymptomatic hosts are fruit bats who can transmit infection and disease to pigs and humans. Human-to-human transmission has also been reported. Clinical features in humans are fever followed by features of encephalitis and sometimes pneumonia and respiratory distress. Mortality can be as high as 70% and there are residual sequelae in survivors. Treatment is only symptomatic. Prevention centers around limiting human exposure to raw date palm juice contaminated by fruit bat excreta and infected pigs.

Chandipura virus, a rhabdovirus, is implicated as a cause of epidemic viral encephalitis in children in several states in India but not abroad. It is transmitted by bite of infected sandflies and is associated with high mortality and neurologic sequelae.

Suggested Reading

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Nipah virus. Wkly Epidemiol Rec 2011;86:451–5
Patel AK, et al. First Crimean-Congo hemorrhagic fever outbreak in India. J Assoc Physicians India 2011;59:585–9
Rao BL, et al. A arge outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus. Lancet 2004;364:869–74

COMMON BACTERIAL INFECTIONS

Staphylococcal Infections

Staphylococcus a gram-positive coccus is a very common cause of both community acquired and nosocomial disease in children.

Etiopathogenesis

Staphylococci are functionally classified on basis of production of an enzyme and virulence factor coagulase. Coagulase positive staphylococcus is termed as *S. aureus* while *S. saprophyticus* and *S. epidermidis* are important coagulase negative staphylococci (CONS). CONS usually colonize the skin of all people and *S. aureus* the nares, axilla and perineum of around 20–25% of the population. Staphylococcal infection is acquired usually by direct contact with an infected patient or carrier and sometimes contaminated objects. Airborne spread is less common. Predisposing factors for staphylococcal infections include breach in the mucocutaneous barrier, previous viral infections such as measles, depressed immunity and prosthetic material such as shunts, central venous catheters and prosthetic joints.

Clinical Features

S. aureus can cause a myriad of clinical infections involving almost all organs of the body. Infections are associated with suppuration and often require drainage and prolonged antibiotic therapy.

Commonest are infections of skin and soft tissues like furuncles, impetigo, carbuncles, abscesses and cellulitis. In some situations, the bacteria invade the fascia and muscle causing necrotizing fasciitis, an infection that is associated with very high morbidity and mortality. Staphylococcal scalded skin syndrome is another bullous infection commonly seen in infants produced by exfoliative toxin producing *S. aureus* that can lead to massive desquamation and denudation.

S. aureus is an important cause of respiratory infections such as sinusitis, otitis media, pneumonia, lung abscess and empyema. Staphylococcal pneumonia commonly occurs after antecedent viral infections, is rapidly progressive and associated with a high rate of complications such as pneumatoceles, abscess and empyema. *S. aureus* is the commonest cause of acute infective endocarditis in both patients with native and prosthetic valves and sometimes with no risk factors. It is rapidly progressive, locally destructive and is associated with significant complications. It is also the commonest cause of pyopericardium an illness with high rates of constrictive pericarditis that often requires pericardiectomy.

S. aureus is the commonest cause of musculoskeletal infections such as osteomyelitis, septic arthritis and pyomyositis. CNS infections such as meningitis usually occur following trauma or neurosurgery. *S. aureus* is also a common etiologic agent of subdural empyema, brain abscess and shunt infections. Enterotoxin producing *S. aureus* is a common cause of food poisoning that is characterized by fever and profuse vomiting.

Toxic shock syndrome (TSS) results from a locally non-invasive toxigenic strain of *S. aureus* which is characterized by fever, shock, erythematous skin rash, hepatic derangement, sensorial changes and high mortality. Disseminated staphylococcal disease is another illness usually seen in previously healthy children and most commonly reported in India. It is characterized by suppurative staphylococcal infections at multiple sites either together or serially and a prolonged course.

CONS are usually pathogens of lower virulence than *S. aureus*. Since they colonize the skin, they are often cultured as contaminants if blood cultures are not collected by aseptic techniques. They are commonly implicated in bacteremia in low birth weight babies or in those with central venous catheters, subacute infective endocarditis, CNS shunt infections, infections associated with peritoneal dialysis catheters and prosthetic joints, urinary tract infections and postoperative surgical site infections.

Treatment

The most important treatment strategies are surgical drainage and antibiotics.

Antibiotic therapy of staphylococcal infections has become complicated due to evolving resistance in staphylococci. More than 90% of the current day organisms are resistant to penicillin due to production of a beta lactamase/penicillinase that destroys the beta lactam ring of penicillin. Most of them however are sensitive to penicillinase resistant penicillins such as cloxacillin/methicillin and cephalosporins and are termed as MSSA. Some staphylococci however have acquired resistance to methicillin by production of an altered penicillin binding protein (PBP) and are termed as MRSA. MRSA were till some time back only reported as causative agents of hospital acquired infections but are now also being reported in community acquired infections.

The drug of choice for treating MSSA infections is cloxacillin. Other alternatives are first generation cephalosporins (cephalexin, cefadroxil or cefazolin), second generation cephalosporins (cefuroxime) and coamoxiclav, clindamycin. If MRSA infections are proven or suspected, drugs like vancomycin, linezolid and teicoplanin are required.

Most *S. aureus* infections need removal of any prosthetic material to ensure cure and prolonged therapy ranging

from 2 weeks for bacteremia and up to 6 weeks for osteomyelitis, septic arthritis and endocarditis.

Suggested Reading

Baranwal AK, Singhi SC, Jayashree M. A 5-yr PICU experience of disseminated staphylococcal disease, Part 1: Clinical and microbial profile. J Trop Pediatr 2007;53:245–51

Miller LG, Kaplan SL. *Staphylococcus aureus*: a community pathogen. Infect Dis Clin North Am 2009;23:35–52

Pneumococcal Infections

Pneumococcus is one of the most common bacterial causes of pediatric infections particularly pneumonia. It is currently estimated that 50% of deaths due to severe pneumonia are caused by pneumococcus. This means that of the 400,000 deaths in children below age 5 in India due to acute respiratory infections, 200,000 are perhaps due to pneumococcus.

Etiopathogenesis

Pneumococcus is a gram-positive diplococcus with a thick polysaccharide capsule. This capsule is the most important virulence factor and determines the various serotypes of the pneumococcus. Almost 90 serotypes of pneumococcus exist but only a handful cause disease. Serotypes 1, 4, 5, 6 A and 6B, 9V, 14, 18C, 19A, 19F and 23 are those that commonly cause human disease and are incorporated in the vaccines (Chapter 9). Pneumococci colonize the nasopharynx, colonization rates are highest in young children. Colonization can lead to infection in some individuals. Risk factors for pneumococcal disease include extremes of age (age less than two yr), splenic dysfunction, immunodeficiency especially HIV, any chronic disease and CSF leaks.

Clinical Features

Pneumococcal infections are distributed like a pyramid, the base of the pyramid being noninvasive disease like otitis media, sinusitis and pneumonia and the apex comprising of invasive disease like bacteremic pneumonia, bacteremia and meningitis. It is estimated that for every 1000 cases of otitis media there is 1 case of meningitis. Other less common invasive diseases due to pneumococci are osteomyelitis, septic arthritis, cellulitis and peritonitis.

Pneumococcus is responsible for 30% of all acute bacterial meningitis and is associated with high rate of complications like subdural empyema, morbidity and mortality. With increasing vaccination against *Haemophilus influenzae*, the percentage contribution of pneumococcus towards meningitis will increase further. Pneumococcal bacteremia presents as fever without focus in infants and children below age 3 and needs aggressive therapy. It is estimated that pneumococcus causes 30–50% of radiologic/severe pneumonia. Pneumococcal pneumonia has lobar distribution with necrosis and empyema being common complications.

Diagnosis

The gold standard for diagnosis of pneumococcal disease is culture. However, culture yields are poor because of several reasons. Pneumococcus, unlike Salmonella, is difficult to culture especially if antibiotics have been administered. Special media containing sheep blood are required and delays in transportation and improper storage further reduce recovery. Isolation rates from blood are low and the ideal sample of lung aspirate cannot be obtained in routine clinical practice.

Other tests useful in diagnosis are Gram stain (Fig. 10.12), latex agglutination tests and PCR in CSF and pleural fluids.

Treatment

Penicillin and its derivatives such as ampicillin and amoxicillin are the drugs of choice for treatment of pneumococcal infections. The cephalosporins particularly ceftriaxone are also satisfactory alternatives. Like many other bacteria, resistance in pneumococcus is being increasingly reported. Resistance to beta lactams is due to altered penicillin binding protein (PBP) and may be of intermediate or high level. Intermediate resistance can be overcome by using higher doses of penicillin/amoxicillin but high level resistance requires use of alternative drugs like fluoroquinolones or vancomycin.

Prevention of pneumococcal disease is discussed in Chapter 9.

Suggested Reading

WHO position paper. Weekly Epidemiologic record 2012;87:129–44

Diphtheria

Diphtheria is an acute bacterial infection caused by gram-positive bacillus, *Corynebacterium diphtheriae*.

Etiopathogenesis

The secretions and discharges from infected person or carrier are the main source of infection. The infection is transmitted by contact or via droplets of secretion. The portal of entry is commonly the respiratory tract. The

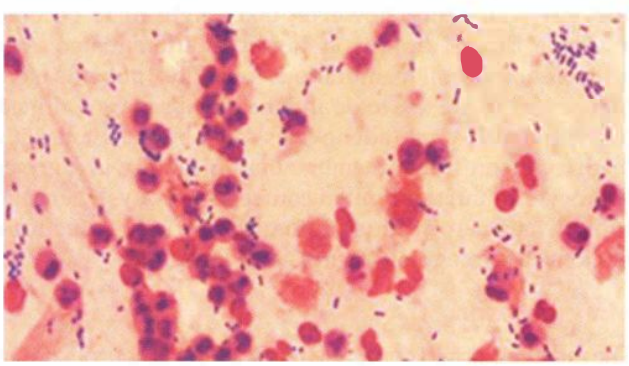

Fig. 10.12: Gram stain of pus showing abundant gram-positive diplococci suggestive of pneumococci

incubation period of the disease is 2–5 days. *C. diphtheriae* proliferate and liberate powerful exotoxin which is the principal cause of systemic and local lesions. The exotoxin causes necrosis of the epithelial cells and liberates serous and fibrinous material which forms a grayish white pseudomembrane which bleeds on being dislodged. The surrounding tissue is inflamed and edematous. The organs principally affected by the exotoxin include the heart, kidney and myocardium.

Clinical Features

The onset is generally acute with fever, malaise and headache. The child has a toxic look. The clinical features depend on the site of involvement. The commonest form is faucial/tonsillopharyngeal diphtheria in which there is redness and swelling over the fauces. The exudates coalesce to form a grayish white pseudomembrane, which extends to surrounding areas. The cervical lymph nodes are enlarged leading to a bull neck appearance. Sore throat, dysphagia and muffled voice are frequently present. In nasal diphtheria there is unilateral/bilateral sero-sanguinous discharge from the nose and excoriation of upper lip. In laryngotracheal diphtheria, the membrane over the larynx leads to brassy cough, stridor and respiratory distress. Diphtheritic lesions may occasionally also be found in skin and conjunctiva.

The commonest complication is respiratory failure due to occlusion of the airways by the membrane. Myocarditis generally occurs by second week of illness and can lead to symptoms of congestive cardiac failure, arrhythmias and sudden death.

Neurological complications include: (i) palatal palsy, which occurs in second week and is clinically manifested by nasal twang and nasal regurgitation; (ii) ocular palsy in third week; (iii) loss of accommodation, manifested by visual blurring and inability to read; and (iv) generalized polyneuritis occurs by 3rd to 6th weeks of illness. Renal complications include oliguria and proteinuria.

Diagnosis

There should be a high index of suspicion. Rapid diagnosis is enabled by Albert stain of a swab from the oropharynx and larynx. Culture, however, takes eight hr to become available. Faucial diphtheria should be differentiated from acute streptococcal membranous tonsillitis (patients have high fever but are less toxic and the membrane is confined to the tonsils), viral (adenovirus) membranous tonsillitis (high fever, sore throat, membranous tonsillitis with normal leukocyte count, self limited course of 4–8 days), herpetic tonsillitis or aphthous stomatitis, thrush, infectious mononucleosis, agranulocytosis and leukemia.

Management

The most important component of therapy is neutralization of bacterial toxin by administration of antitoxin. Diphtheria antitoxin (IV/IM) should be administered soon as infection with diphtheria bacilli is suspected even earlier than bacteriological confirmation before the bacteria have fixed to the tissues. The degree of protection offered by the diphtheria antitoxin is inversely proportional to the duration of clinical illness. Repeat doses of antitoxin may be given if clinical improvement is suboptimal.

Antibiotics such as penicillin or erythromycin should be used to terminate toxin production, limit proliferation of bacteria, to prevent spread of organism to contacts and to prevent the development of carriers. This should be followed by active immunization as *clinical disease does not confer active immunity.*

Bed rest is advocated for two to three weeks. Children should be monitored for airway obstruction and managed; tracheostomy may be required in some cases. Sudden exertion should be avoided and changes in rate and rhythm of heart should be looked for. Children with palatal palsy should be fed by nasogastric feeding. Generalized weakness due to polyneuritis is treated as for poliomyelitis or Guillain-Barré syndrome.

Prevention and Control

The patient should be isolated until two successive cultures of throat and nose are negative for diphtheria bacillus. All contaminated articles from discharges should be disinfected. All household and other contacts should be observed carefully for development of active lesions, cultured for *C. diphtheria* and given chemoprophylaxis with oral erythromycin for 7 days or single dose benzathine penicillin. Previously immunized asymptomatic patients should receive a booster dose of diphtheria toxoid. Those not fully immunized should receive immunization for their age (*see* Chapter 9).

Suggested Reading

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Pertussis (Whooping Cough)

Pertussis is an acute highly contagious respiratory tract infection, caused by *Bordetella pertussis.* It may affect any susceptible host but is more common and serious in infancy and early childhood. The disease is characterized by intense spasmodic cough. Similar illness is also caused by *B. parapertussis, B. bronchoseptica* and adenoviral infections 1, 2, 3 and 5. The worldwide prevalence of the illness has declined following widespread vaccination.

Epidemiology

Pertussis is extremely contagious with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage in humans is not known. After intense exposure as in households,

the rate of subclinical infection is as high as 80% in fully immunized and naturally immune individuals. Protection against typical disease wanes 3–5 yr after vaccination and is unmeasurable after 12 yr. Coughing adolescents and adults are the major reservoir of *B. pertussis* and are the usual sources for index cases in infants and children.

Features

The incubation period of the disease is 7–14 days. The clinical presentation can be divided into three stages.

The *catarrhal phase* lasts for 1–2 weeks and is the most infectious period. The initial manifestations are indistinguishable from upper respiratory tract infections. The child has cough, coryza with little nasopharyngeal secretions. Unlike the upper respiratory infections, the cough does not improve in a few days but becomes more severe and frequent with the passage of time. Though the cough may not be typically paroxysmal in early stages, it tends to be annoying and frequent at night. The paroxysmal nature of the cough is suspected towards the latter part of this phase.

The *paroxysmal* stage lasts for 2–6 weeks in which cough progresses to episodic paroxysms of increasing intensity ending with high-pitched inspiratory whoop. The whoop is produced by the air rushing in during inspiration through the half-open glottis. The whoop may not always be present in infants who present with apneic or cyanotic spells. The child coughs up thick tenacious mucus. The paroxysms of cough may occur frequently and terminate by vomiting. Repeated thrusting of tongue over the teeth causes ulceration of the frenulum of the tongue. Paroxysms of cough are precipitated by food, cold air and cold liquids. In infants <3 months, this stage may be considerably prolonged.

In the *convalescent phase* the intensity and paroxysms of cough decrease gradually over 1–4 weeks. The vomiting becomes less frequent. Appetite, general condition and health gradually improve.

Complications

Respiratory complications include otitis media, pneumonia, atelectasis, emphysema, bronchiectasis, pneumothorax and pneumomediastinum

- Neurological complications include seizures and encephalopathy (2–7%).
- Bleeding episodes, e.g. epistaxis, retinal or subconjunctival bleeds, intracranial hemorrhage.
- Inguinal hernia, rectal prolapse.
- Malnutrition due to persistent vomiting and disinclination to eat because of fear of paroxysms of cough with attempts at feeding.
- Flare up of tuberculosis.

Diagnosis

The diagnosis of whooping cough is based on clinical features. There may be a lymphocytic leukocytosis and low ESR. Specific diagnosis depends on isolation of the organism from nasopharyngeal swab or cough plate cultured on Bordet-Gengou medium, which is often positive in the catarrhal and paroxysmal stage. Other conditions that present with prolonged episodes of spasmodic cough include adenoviral infection, endobronchial tuberculosis, inhaled foreign body and reactive airway disease.

Management

General measures include providing adequate nutrition and hydration and avoiding factors aggravating cough. The antibiotic of choice is erythromycin (40–50 mg/kg/day in 3 divided doses) given for 14 days. It terminates the respiratory tract carriage of *B. pertussis* thus reducing the period of communicability but does not shorten the course of illness. Nebulization with salbutamol is effective in reducing bronchospasm and controlling bouts of cough. If nebulization is not possible, salbutamol may be given orally. Cough suppressants and antihistaminic agents should be avoided.

Prevention

Chemoprophylaxis with erythromycin is recommended for close family contacts especially children <2-yr-old. Children under 7 yr of age should be vaccinated (Chapter 9).

Suggested Reading

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Zouari A, Smaoui H, Kechrid A. The diagnosis of pertussis: which method to choose? Crit Rev Microbiol 2012;38(2):112–21

Enteric Fever

The term enteric fever includes typhoid fever caused by *Salmonella enterica* var *typhi* and paratyphoid fever caused by *S. enterica* var *paratyphi* A, B or C. Paratyphoid infections constitute about 20% of all cases of enteric fever worldwide. As enteric fever is a disease transmitted by the feco-oral route, its greatest burden is in resource-limited countries where water supply and sanitary conditions are poor. In a community-based study in urban slums of Delhi the incidence was estimated to be 980/100,000 population. Enteric fever is the most common cause of fever lasting for more than 7 days in clinical practice in India.

Etiopathogenesis

S. enterica serotype *typhi/paratyphi* is a gram-negative, non-lactose fermenting, flagellate bacterium. The somatic or O antigen is shared among various salmonellae; the flagellar or H antigen is specific to the serovar. *S. enterica* var *typhi* also possesses a Vi polysaccharide capsule.

The infective dose of typhoid/paratyphoid bacillus varies from 10^3 to 10^6 organisms. The organism must

survive the gastric barrier to reach the small intestine; hence, conditions which reduce gastric acidity, such as use of antacids, H2 receptor blockers and proton pump inhibitors, reduce the infective dose. On reaching the small intestine, the organism penetrates the mucosa and infects the lymphoid follicles and subsequently the draining mesenteric lymph nodes and the liver and spleen. It multiplies in the reticuloendothelial system and after incubation period varying from 7 to 14 days spills into the bloodstream and is widely disseminated, especially to liver, spleen, bone marrow, gallbladder and the Peyers patches of the terminal ileum. This spill marks the onset of clinical manifestations of enteric fever. Infection leads to both local and systemic immune responses, which are, however, inadequate to prevent relapse or reinfection.

Clinical Features

There is no appreciable difference between the manifestations of typhoid and paratyphoid fever. The hallmark of enteric fever is fever which starts as a low grade fever and then shows stepwise increase peaking to as high as 103–104°C by the end of the first week. This pattern differentiates it from viral fever where the peak is usually at the onset of fever. With fever, there is associated malaise, dull headache, anorexia, nausea, poorly localized abdominal discomfort, mild cough and malaise. There may be diarrhea; constipation in children is rare. Physical findings are unremarkable with the exception of a coated tongue, tumid abdomen and sometimes hepatosplenomegaly. The rash described in Western textbooks is seldom or never seen in Indian subjects. Infants and young children with enteric fever may have diarrhea as a predominant manifestation or a short-lasting undifferentiated febrile illness. In the absence of treatment fever may continue for 3–4 weeks followed by natural remission or by development of complications.

Complications

The commonest intestinal complications are bleeding or perforation seen in the 2nd or 3rd week of illness in 10–15% adult patients, but less frequently in children. Bleeding is due to erosion of a necrotic Peyers patch through the wall of a vessel and is usually mild but can, sometimes, be life-threatening. Perforation is a dreaded complication manifesting as acute abdomen, with high mortality unless appropriately treated.

The term severe or complicated enteric fever is used for patients presenting with neurological complications such as delirium, coma, obtundation, stupor and/or shock and is associated with mortality rates as high as 50%. Other complications of enteric fever include splenic abscesses, hepatitis, cholecystitis, pneumonia, disseminated intravascular coagulation and other manifestations such as psychosis, ataxia or meningitis. The case fatality rate is less than 1% in appropriately treated cases but may be 10–20% in inadequately treated or complicated cases.

Relapse Relapse may occur in 5–15% of treated cases, usually due to the organism with the same susceptibility as the original attack and is relatively a milder illness. Rate of relapse is dependent on choice of drug therapy. It is higher with beta lactams such as cefixime or ceftriaxone as compared to quinolones and azithromycin.

Carrier state Although 5–10% adult patients may shed salmonella in stool following an acute attack for up to 3 months, only 1–4% excrete bacilli for more than 1 yr. These individuals are potential sources of infection for family members and contacts and for the community if they are in occupations that involve food-processing. There is no data on carrier prevalence in children and routine culture of stool following recovery from enteric fever is not recommended.

Diagnosis

Leukocyte counts may be normal to low with absolute eosinopenia and neutrophilic predominance. Anemia and thrombocytopenia may occur in advanced illness. There may be mild elevation of transaminases to 2–3 times normal (SGOT higher than SGPT). A high C reactive protein (CRP) helps to differentiate enteric from viral fevers especially dengue.

The gold standard for diagnosis is blood culture. The sensitivity is greatest in the first week at around 90% but drops to 40% in the 4th week. Salmonella is an easy organism to culture and use of bile broth media and automated culture systems such as BACTEC improve recovery. Sufficient blood should be collected (10 ml in adults and 5 ml in children) and a blood: media ratio of 1:5 should be maintained. Bone marrow cultures have higher yield as compared to peripheral blood cultures as Salmonella is a pathogen of the reticuloendothelial system and should be done when patients present in later stages of the illness. Stool and urine cultures are not recommended. Antimicrobial susceptibility testing of the isolate is important.

The Widal test detects presence of IgG and IgM antibodies to H (flagellar antigen) of *S. enterica* var *typhi* and *paratyphi* A and B, and O (somatic antigen) common to typhi and paratyphi A and B. Anti O titers are both IgG and IgM that rise and decline early, while anti H are primarily IgG that rise and decline late in course of the disease. The conventional method of interpretation of the Widal test has been to demonstrate four-fold rise in antibody titers in two samples. A single titer of at least 1:160 for both O and H is also considered positive. The sensitivity of the test is low in the first week of illness and in patients treated with prior antibiotics. Specificity is low owing to anamnestic reactions, prior vaccination, cross reactivity with other Enterobacteriaceae and subclinical infections in endemic areas. Other tests such as Tubex and Typhidot that detect IgM antibodies against typhoid have not proven superior to the Widal test.

Treatment

Indications for inpatient treatment Most cases of enteric fever can be managed at home with oral antibiotics and advice to seek medical followup in case of failure to respond to therapy or development of complications. Children with persistent vomiting, inability to take orally, severe diarrhea or abdominal distension usually require intravenous antibiotics therapy and intravenous fluids, necessitating admission to hospital.

Antimicrobial susceptibility Though resistance to chloramphenicol was first noted soon after its first use in the 1940s, it was not until 1972 that chloramphenicol-resistant typhoid fever became a major problem. Multi drug resistant typhoid fever (MDRTF) became a common occurrence by the end of 1990s, with emergence of *S. typhi* simultaneously resistant to all the drugs that were used as first-line treatment (chloramphenicol, trimethoprim, sulfamethoxazole and ampicillin). Fluoroquinolones, introduced in the late 1980s and early 1990s, produced very good results initially, but the past decade has seen a progressive increase in the minimum inhibitory concentrations of ciprofloxacin in *S. typhi* and *paratyphi*. Since minimum inhibitory concentrations are below the standard susceptibility breakpoint, laboratories report bacteria as sensitive to fluoroquinolones; but the use of fluoroquinolones is associated with a high incidence of clinical failure because drug levels needed to kill organisms are not achieved with standard doses, and often, even with highest tolerated doses. Now that the susceptibility breakpoints have been revised downwards, this discordance between *in vitro* and *in vivo* susceptibility will be resort. *Resistance to nalidixic acid* has been suggested as a marker of fluoroquinolone failure.

Currently, third-generation cephalosporins such as ceftriaxone and cefixime are the first-line agents for therapy of enteric fever. Azithromycin is a new drug that is being used as an alternative agent.

Choice for empirical therapy For uncomplicated enteric fever, oral cefixime at a dose of 20 mg/kg/day is the drug of choice, both for sensitive and multidrug resistant *S. typhi*. In areas where quinolone resistance is infrequent (rare at the moment in India), fluoroquinolones may still be considered the drugs of choice; however, if both quinolone resistance and resistance to other drugs (like amoxicillin, chloramphenicol, cotrimoxazole) are widespread, the only options are oral cefixime or azithromycin.

Azithromycin (10–20 mg/kg/day) is a good second choice agent; chloramphenicol (50 mg/kg/day), amoxicillin and cotrimoxazole are other second-line agents. The choice of medication depends on individual preference, experience and level of comfort and cost considerations. Once culture results are available, therapy can be modified. There is no data at present to support use of combination therapy in enteric fever.

For severe illness and where complications are present, intravenous ceftriaxone and cefotaxime are used at a dose of 100 mg/kg/day. In patients with history of penicillin or cephalosporin allergy, aztreonam, chloramphenicol (in higher than usual doses) or cotrimoxazole (in higher than usual doses) are used as second-line agents. Parenteral treatment is continued until defervescence has occurred, oral intake has improved and complications resolved. Thereafter, therapy can be switched to oral cefixime to complete a total duration of 14 days. Other oral drugs that may be used for switch over therapy include cefpodoxime, azithromycin, cotrimoxazole and amoxicillin. However, the experience with cefpodoxime is limited and the other agents require switch to a different class of antimicrobials than cephalosporins.

If cultures are positive and show quinolone sensitivity, therapy should be changed to ciprofloxacin at a dose of 20 mg/kg/day as quinolones are associated with faster defervescence and lower relapse rates as compared to ceftriaxone. If cultures are positive and show quinolone resistance as well as sensitivity to other drugs ampicillin, chloramphenicol and cotrimoxazole), it is prudent to continue with ceftriaxone alone rather than change because the older drugs do not offer any advantage over ceftriaxone. If cultures are negative and defervescence has not occurred by day 7, a thorough search for alternative etiology for fever should be made and ceftriaxone continued. There is no role for changing the antimicrobial agent or adding another drug, since ceftriaxone resistance is still anecdotal.

Therapy of relapses Relapse rates vary with the type of drug and are most common with beta lactams (ceftriaxone, cefixime) especially if shorter duration of therapy is used. Usually relapses may be satisfactorily treated with the same drug as used for primary therapy but at appropriate dose and duration. However, if the isolate is quinolone sensitive and fluoroquinolones were not used for primary therapy, they should be used for treatment of the relapse.

Therapy of carriers The carrier state is uncommon in children and testing for chronic carriage 3 months after an episode of enteric fever is not recommended. However, if chronic carriage is demonstrated, treatment with amoxicillin (100 mg/kg/day) with probenecid (30 mg/kg/day) or cotrimoxazole (10 mg/kg/day) for 6–12 weeks is recommended. If the strain is nalidixic acid sensitive, quinolones for 28 days is a better option.

Prevention

The most effective and desirable method for preventing enteric fever is by improving hygiene and sanitation. This will yield additional dividends of reduction in the burden of other water-borne illnesses as well. Vaccination is a major preventive strategy.

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Leptospirosis

Leptospirosis is a zoonotic disease of worldwide distribution, caused by spirochetes. Most cases occur in tropical and subtropical countries. While rats are the principal source of human infection, dogs, cats, livestock and wild animals are other reservoirs. Infected animals may excrete spirochete in urine for several weeks. The survival of excreted organisms depends on the moisture content and temperature of the soil. Humans acquire infection after getting exposure to water or soil contaminated with rat urine. Agricultural workers, veterinarians, meat handlers, rodent control workers and laboratory personnel are at risk of getting infected because of occupational exposure. Infection is common in the monsoons and during flooding.

Pathogenesis

Leptospira enter the body through abrasions and cuts in skin or through mucous membranes and spread to all organs hematogenously. The organisms damage the endothelial lining of small blood vessels, with leakage and extravasation of blood cells, hemorrhage and ischemic damage to various organs including liver, kidneys, meninges and muscles.

Clinical Features

Human infection ranges from asymptomatic infection to a severe multiorgan involvement which is often fatal. Symptomatic infection is a relatively mild as an anicteric febrile illness in over 70% of patients; about 20% present as aseptic meningitis, while severe leptospirosis with hepatorenal dysfunction (Weil disease) develops in 5–10% of individuals. The incubation period is usually 1–2 weeks.

The illness is often biphasic. In the initial or septicemic phase lasting 2–7 days, the onset is abrupt with high grade fever with rigors and chills, lethargy, severe myalgia, headache, nausea, vomiting. There may be conjunctival suffusion with photophobia and orbital pain, generalized lymphadenopathy and hepatosplenomegaly. Transient maculopapular rash may be seen in <10% cases. Hypotension with bradycardia and circulatory collapse is rare. Some patients develop acute respiratory distress syndrome with respiratory failure. Most patients are asymptomatic within one week.

In some patients, after a brief asymptomatic phase, the second phase, called the immune or leptospiruric phase, becomes manifest where *Leptospira* localize to tissues to cause specific signs and symptoms. In this phase, circulating autoantibodies to *Leptospira* are present; organisms can no more be isolated from blood or CSF but persist in tissues like kidneys and aqueous humor. During the immune phase, some children develop aseptic meningitis or uveitis with recurrence of fever. Encephalitis, cranial nerve palsies, paralysis and papilledema are rare. Central nervous system abnormalities usually normalize within 1 week; mortality is rare.

In *icteric leptospirosis* (Weil syndrome) after the initial phase of fever patients develop severe hepatic and renal dysfunction. Jaundice and hepatomegaly are usually detected; splenomegaly is found in 20%. Renal failure may develop, often during the second week of illness. All patients have abnormal urinary finding on urinalysis in the form of hematuria, proteinuria and casts. Azotemia is common, often associated with oliguria or anuria. Hemorrhagic manifestations are rare but when present, may include epistaxis, hemoptysis and gastrointestinal and adrenal hemorrhage. Transient thrombocytopenia may occur, and mortality is 5–15%.

Diagnosis

Complete blood count shows anemia, leukocytosis with polymorph predominance and thrombocytopenia. The CRP is elevated and liver enzymes are mildly elevated with SGOT more than SGPT. The CPK is high. In patients with Weil disease there is elevated serum creatinine, deranged coagulation parameters and direct hyperbilirubinemia with raised transaminases.

Specific diagnosis is established by serologic testing, microscopic demonstration of the organism or culture. The gold standard for serologic diagnosis is the microscopic agglutination test (MAT), which is only available in reference centers. Commercial kits for serologic diagnosis include rapid tests and IgM ELISA. These tests are positive after 5 days of illness. Cross reactivity and false positivity is seen with other infections like enteric fever and malaria. Demonstration of organism in tissues or urine by dark field microscopy or immunoflorescence and cultures are not routinely available.

Leptospirosis should be differentiated from other febrile illnesses commonly seen in the monsoon season like malaria, dengue, enteric fever, acute viral hepatitis and hantavirus infections.

Treatment

Treatment should be initiated as early as possible. For a severe case of leptospirosis, parenteral penicillin G (6–8 million U/m^2/24 hr q 4 hr IV) for 7 days is the drug of choice. Ceftriaxone and IV tetracycline are also acceptable alternatives. For oral treatment amoxicillin and doxycycline (in children above 8 yr) are the drugs of choice.

Prevention

Prevention entails avoidance of exposure to contaminated water. Single dose doxycyline or amoxicillin following

exposure can prevent illness but is not routinely recommended.

Suggested Reading

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Tetanus

Tetanus is caused by the bacterium *Clostridium tetani*, a spore forming, anerobic, gram-positive motile bacillus, found in human and animal feces. Its spores are widespread in the environment. Tetanus commonly occurs in areas where soil is cultivated, in rural areas, in warm climates and during summer months. According to WHO estimates, it contributes to 8% of vaccine preventable deaths.

Pathogenesis

C. tetani is a noninvasive organism. The spores of the organism remain nonpathogenic in soil or contaminated tissues until conditions are favorable for transformation into vegetative form. Transformation occurs in the presence of locally decreased oxygen reduction potential, typically in devitalized tissue, in the presence of a foreign body, trauma and crush injury and suppurative infections. Two types of toxins are produced by the organism, *tetanolysin* and *tetanospasmin*. Tetanospasmin, is the main toxin responsible for the manifestations of the disease. It binds to the neuromuscular junction at the site of injury, and undergoes retrograde axonal transport to reach the presynaptic nerve terminal where it prevents the release of inhibitory neurotransmitters glycine and GABA leading to uncontrolled contraction of muscles.

Clinical Features

Tetanus mainly affects the unimmunized and partly immunized individuals. The disease may occur in various forms: neonatal, generalized, localized and cephalic. The most common forms are generalized and neonatal tetanus.

Generalized tetanus has an incubation period of approximately 8 days (range 2–14 days). However, the disease may occur months after the initial injury. The incubation period depends on the distance of the site of injury from the central nervous system. The faster is the onset of symptoms, the poorer is the prognosis. Characteristically, there is descending paralysis, with initial involvement of the jaw muscles. There is spasm of the masseters leading to trismus or lockjaw. Subsequent involvement of the neck, back and abdominal muscles occurs, soon involving the whole body. As the disease progresses, minimal stimuli may lead to generalized spasms, which are the hallmark of the disease and contribute to serious complications and death. Typically, the sensorium of the patient is preserved. There is difficulty in swallowing. Autonomic instability may occur, with blood pressure fluctuations in the form of hypertension or hypotension, diaphoresis and arrhythmias. Recovery usually begins after 3 weeks and approximately takes four weeks. Recovery from tetanus occurs by sprouting new nerve terminals in the spinal cord leading to relaxation of the contracted muscles.

Neonatal tetanus is a major cause of mortality in developing countries. Pregnant women who are not immunized against tetanus do not pass on protective antibodies to their babies. Infection results of unhygienic birth practices, most commonly when the umbilical cord is contaminated at the time of cutting after delivery. Symptoms usually appear by the third day afterbirth, never in the first two days of life and rarely after the age of two weeks. Excessive unexplained crying followed by refusal of feeds and apathy are the common initial symptoms. The baby develops progressive feeding difficulty, becomes rigid, develops paralysis and may develop opisthotonic posturing and experience painful spasms. The mouth is kept slightly open due to pull and spasm of the neck (Fig. 10.13). Reflex spasm of the masseter makes feeding painful. Pharyngeal muscles go into spasm and cause dysphagia and choking, lockjaw or reflex trismus followed by spasms of limbs. There is generalized rigidity and opisthotonus in extension. Spasm of larynx and respiratory muscles are characteristically induced by stimuli such as touch, noise and bright light, resulting in episodes of apnea and cyanosis. Constipation persists until the spasms are relieved. Intercurrent infections, dehydration and acidosis may complicate the clinical picture. It has a very high case fatality rate of 70 to 100%.

Localized tetanus is less severe in comparison and is characterized by rigidity and pain confined to the muscles adjacent to the wound. It may lead to generalized tetanus later. In patients with isolated localized tetanus, the mortality is less than 1%. *Cephalic tetanus* is a form of local tetanus, which occurs due to injury of the bulbar muscles. It has a poor prognosis.

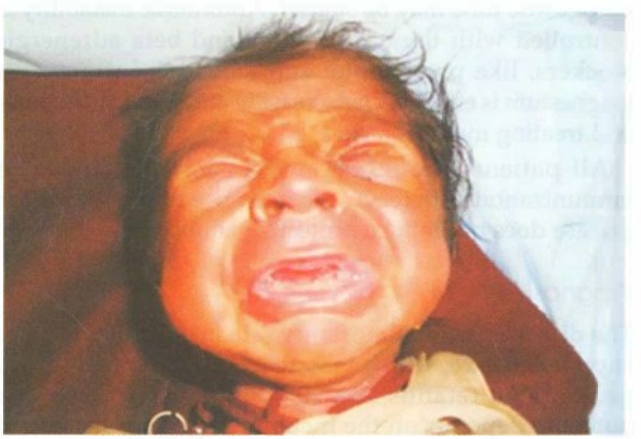

Fig. 10.13: Neonatal tetanus. *Courtesy:* Dr Amarjeet Mehta, Jaipur

Treatment

Most patients require intensive care management and good supportive care. The aims of treatment are airway maintenance, prevention of further toxin absorption, relieving clinical features, e.g. spasms, controlling autonomic instability and antibiotics. Airway management may require intubation and mechanical ventilation, especially in severe cases and if the infant gets frequent episodes of largyngeal spasms, apneic attacks with cyanosis or central respiratory failure. Neutralization of free toxin is done by administering human tetanus immunoglobulin (TIG); however, antitoxin cannot dislodge the toxin already fixed to the nerve roots. The route of administration is intramuscular or intrathecal. The usual dose is 500 to 1000 IU. Antibiotic therapy is needed to abolish the bacteria from the wound site. The commonly used antibiotics are crystalline penicillin or metronidazole.

Spasms are precipitated by minimal stimuli, therefore, efforts should be made to avoid noxious stimuli including bright lights, pain and loud noises. Patient should be kept in a dark, quiet and isolated room, which should be lighted well to permit observation of the child; handling should be minimum. Intramuscular injections must be avoided. Temperature should be maintained within normal limits. Relief of spasms is done by using benzodiazepines. The most commonly used agent is diazepam, either as an intermittent IV bolus or as continuous infusion. Diazepam prevents further spasms by causing GABA-mediated central inhibition. It also helps by reducing anxiety and promoting muscle relaxation. Other agents used for severe spasms include pancuronium bromide.

Supportive care includes adequate hydration, early detection of myoglobinuria and prevention of renal shutdown. Oropharyngeal secretions should be sucked periodically. Maintenance of oxygen is important. Oral feeding should be stopped and an IV line should be established for providing adequate fluids, calories and electrolytes and for administration of medications. After three to four days of treatment, milk feeding through nasogastric tube may be started. Autonomic instability is controlled with the use of alpha and beta adrenergic blockers, like propranolol and labetalol. Intravenous magnesium is effective in decreasing autonomic instability and treating muscle spasms.

All patients should receive a complete course of immunization with tetanus toxoid once recovered, as the disease does not induce protective antibodies.

Prognosis

The disease has high mortality rate in spite of adequate supportive care, which may reach up to 50% in severe generalized tetanus and 90% in neonatal form. The outcome depends on the incubation period, the site of injury, the rate of progression of illness and presence of autonomic instability. Survivors do not manifest any neurological sequelae, except when apneic episodes are unduly prolonged and unattended. The prognosis in neonatal tetanus is worse if the (i) onset of symptoms occurs within the first weeks of life, (ii) interval between lockjaw and onset of spasms is less than 48 hr, (iii) high fever and tachycardia are present, and (iv) spasms, especially of larynx resulting in apnea are severe and frequent.

Prevention

Immunization with tetanus toxoid leads to induction of protective antibodies (Chapter 9). Maternal and neonatal tetanus can be effectively prevented by immunizing the mother during pregnancy, and ensuring clean delivery and cord care.

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Rickettsial Infections

Rickettsial diseases are a group of febrile illnesses caused by obligate intracellular gram-negative bacilli and transmitted to man by arthropod vectors.

Etiopathogenesis and Epidemiology

Rickettsia are a group of motile, gram-negative, nonspore forming highly pleomorphic bacteria that present as cocci, rods or thread like obligate, intracellular parasites. Scrub typhus caused by *R.tsutsugamushi*, Indian spotted fever caused by *R.conorii* and Q fever caused by *C. burnetti* are the rickettsial infections prevalent in India. Cases have been reported from all states chiefly from rural and forested areas and occasionally also from urban areas.

Scrub typhus is transmitted by bite of the trombiculid mite and Indian spotted fever by ticks. Rickettsial disease is due to invasion of the endothelial region of the vasculature and subsequent microvasculitis. This process especially affects the brain, cardiac and skeletal muscle, skin, liver, lungs and kidneys.

Clinical Manifestations

Incubation period in children varies from 2 to 14 days. A history of exposure to tick, history of origin from an endemic area or a similar illness in family members may be forthcoming. Severity of manifestations varies from a mild, self limiting illness to a life-threatening disease.

Initially the illness appears to be nonspecific and patients present with unrelenting headache, very high fever, anorexia, myalgias, restlessness, calf muscle pain and tenderness. Gastrointestinal symptoms include abdominal pain, nausea, vomiting and diarrhea. Skin rash

is usually not present until after 2-4 days of illness. The triad of fever, headache and rash is observed in only half of the patients. In spotted fever, rash is initially discrete pale rose red blanching macules or maculopapules on the extremities. Later, the rash spreads rapidly to involve the entire body including palms and soles and becomes more petechial sometimes with palpable purpura (Fig. 10.14). In severe form of the disease, petechiae may enlarge into ecchymosis, which can become necrotic. Severe vaso-occlusive disease secondary to rickettsial vasculitis and thrombosis is infrequent but can result in gangrene of the digits, toes, earlobes, scrotum, nose or entire limbs (Fig. 10.15). In scrub typhus, rash is seen initially on trunk or may not be present at all. Painless eschar, may be seen at the initial site of tick attachment and regional lymphadenopathy and is seen in scrub typhus.

Complications may involve any organ system and include encephalopathy, pulmonary edema, myocarditis, acute renal failure and vascular collapse.

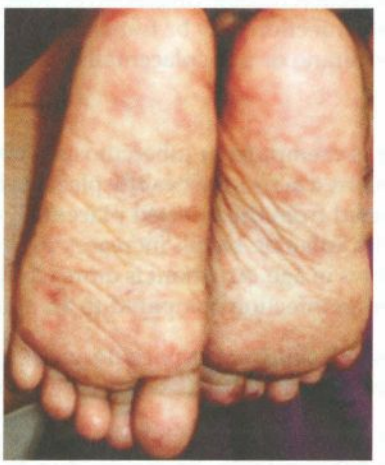

Fig. 10.14: Maculopapular rash on the soles. *Courtesy:* Dr Atul Kulkarni, Sholapur

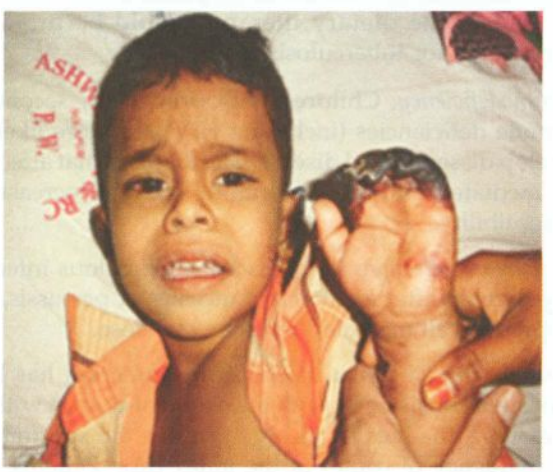

Fig. 10.15: Necrotic rash in spotted fever. Note the gangrene of ear lobes and fingers. *Courtesy:* Dr Atul Kulkarni, Sholapur

In Q fever no vector is involved. Transmission is by inhalation of infected dust from soil previously contaminated by urine or feces of diseased animals. This fever is rarely reported in children. This presents in acute as well as chronic forms. Rash which is typical of variants of rickettsial fever is not seen in Q fever. Pneumonia, hepatitis and meningitis are other features. Endocarditis is seen in chronic variety.

Diagnosis

Laboratory findings are nonspecific. Total leukocyte count may be initially normal or low but leukocytosis develops as the disease progresses. Anemia, thrombocytopenia, hyponatremia and elevated serum aminotransferases are some other features.

Specific diagnosis of a rickettsial illness is confirmed by serological testing. Serological evidence of infection occurs not earlier than the second week of illness in any of the rickettsial diseases and hence a specific diagnosis may not be available until after the patient has fully recovered or worsened. Serodiagnosis of rickettsial disease is possible using the immunoflourescence assay for detection of IgG and IgM. However, it is expensive and not widely available. ELISA is specific and sensitive allowing detection of IgG and IgM antibodies.

Detection of IgM antibodies to scrub typhus and Indian spotted fever is available in India. The Weil-Felix test depends on detection of antibodies to various *Proteus* species containing antigen with cross reacting epitopes to antigens from members of the genus *Rickettsia*. It is widely available but unacceptable for accurate diagnosis because of low sensitivity and specificity. Weil-Felix test can be used in developing countries where other tests are not available for diagnosis of rickettsia infection but the test should be interpreted in conjunction with history and clinical presentation.

If clinical suspicion for rickettsia is high, then empirical therapy should be started without waiting for any confirmatory test.

Differential Diagnosis

Spotted fever can mimic a great number of febrile illnesses. Most important of these are meningococcemia, measles and enteroviral exanthemas. Other diseases included in differential diagnosis are typhoid fever, secondary syphilis, leptospirosis, toxic shock syndrome, scarlet fever, rubella, Kawasaki disease, parvoviral infection, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, Henoch-Schönlein purpura, hepatitis, dengue fever, infectious mononucleosis and malaria.

Treatment

Doxycycline is the drug of choice for all age groups. Chloramphenicol is reserved for patients with doxycycline allergy and for pregnant women. Doxycycline can be used

safely in young children because tooth discoloration is dose dependent and children are unlikely to require multiple courses. Furthermore, the increased mortality with chloramphenicol compared with tetracycline, when other factors such as severity are considered, have led to preference for doxycycline even in young children. The therapy should be continued for a minimum of 5–7 days and for at least 3 days until the patient is afebrile in order to avoid relapse. Patients treated with one of these regimens usually become afebrile within 48 hr and thus the entire therapy lasts for less than 10 days. In patients with severe disease, admission to an intensive care unit and appropriate supportive therapy may be required.

Prevention

Known tick infested areas should be avoided. Daily inspection of body for ticks is particularly important. Disinfection of dogs will minimize the tick population. Health education of people about mode of transmission by ticks and means of personal protection is equally important. Prophylactic antimicrobial therapy is not recommended.

TUBERCULOSIS

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis still is one of the deadliest diseases in the world killing nearly 2 million people every yr. More than ninety percent of all tuberculosis cases occur in the developing countries, where limited resources are available for optimal treatment. Tuberculosis continues to be an important cause of morbidity and mortality for children worldwide.

Magnitude

Most children acquire the organism from adults in their surroundings. Several estimates make use of an arbitrary calculation assigning 10% of the tuberculosis burden to children. Tuberculosis infection and disease among children are much more prevalent in developing countries, where resources for control are scarce. The annual risk of tuberculosis infection in developing countries in children is 2–5%. The estimated lifetime risk of developing tuberculosis disease for a young child infected with *M. tuberculosis* as indicated by positive tuberculin test is about 10%. About 5% of those infected are likely to develop disease in the first yr after infection and the remaining 5% during their lifetime. These rates increase about six-fold in HIV infected individuals. Nearly 8–20% of the deaths caused by tuberculosis occur in children. The age of the child at acquisition of infection has a great effect on the occurrence of tuberculosis disease. Approximately 40% of infected children less than 1 yr of age if left untreated develop radiologically significant lymphadenopathy or segmental lesions compared with 24% of children between 1 and 10 yr and 16% of children 11 and 15 yr of age. In India, over 100,000 children die from tuberculosis every yr.

Epidemiology and Pathogenesis

Agent. All patients of pulmonary tuberculosis and most cases of extrapulmonary disease are caused by human type strain of *Mycobacterium tuberculosis*. A few cases of extrapulmonary illness particularly the tubercular lymphadenitis may be due to the bovine strain.

Reservoir of infection. The infection is spread by the tuberculous patient, who discharges tubercle bacilli in his sputum or nasopharyngeal secretions during bouts of coughing or sneezing, etc. Such patients are open or infective cases. In the pediatric age groups, few infections may also occur by the transplacental route (congenital tuberculosis).

Mode of infection. The usual mode of infection is through inhalation of droplets of infected secretions. The infected sputum spitted carelessly by open cases of tuberculosis dries up and the tubercle bacilli are resuspended in the dust and air. This may be a source of infection through breathing. Infection through ingestion of infected material is rare. Rarely infection may be transmitted through skin, mucous membrane or transplacentally.

Host Factors

Age. No age is exempt from tuberculosis. Tubercle bacilli are not transferred across the healthy placenta but the fetus may be infected from the infected placenta. Frequency of infection with tubercle bacilli increases progressively as the child grows in age. An infant is more likely to develop disease after an infection compared to an older child.

Sex. Adolescent children, especially girls, are prone to develop active tuberculosis disease during puberty.

Malnutrition. Undernourished children are more susceptible to develop tuberculosis, probably due to depressed immunological defenses. Tuberculosis may precipitate kwashiorkor or marasmus in an infant with borderline undernutrition. A malnourished patient, who does not respond to the dietary therapy should be promptly investigated for tuberculosis.

Immunodeficiency. Children with primary or secondary immune deficiencies (including HIV) are more likely to develop disseminated disease. The diseases that affect the cell mediated immunity are more likely to increase the susceptibility.

Intercurrent infections. A quiescent tuberculous infection may flare up after an attack of measles or pertussis, that suppresses cell mediated immune response.

Environment. The risk of acquiring infection has been associated consistently with the extent of contact with the index case, the burden of organisms in the sputum and the frequency of cough in the index case. Patients with smear positive pulmonary tuberculosis are more likely to transmit infection. An increased risk of developing

infection has been seen in institutional settings, including nursing homes, correctional institutions and homeless shelters.

Pathology

The inhaled tubercle bacilli may lodge in the pulmonary alveoli and cause inflammation with hyperemia and congestion. Initially, the polymorphonuclear leukocytes infiltrate at the site of lesion. The phagocytic ability of these cells is poor and they are soon eliminated.

Further course of the infection depends on the immune response of the host. If the host resistance is good, the inflammatory exudate around the primary focus is absorbed and the caseous area inspissated. Healing occurs by fibrosis and calcification. When the cell mediated immune response is weak, the bacilli continue to multiply and the inflammatory process extends to the contiguous areas. Progressive primary disease is a serious complication of the pulmonary primary complex (PPC) in which the PPC, instead of resolving/calcifying, enlarges steadily and develops large caseous center. The center then liquefies; this may empty into an adjacent bronchus leading to formation of a cavity. This is associated with large numbers of tubercle bacilli. From this stage, the bacilli may spread to other parts of the lobe or the entire lung. This may lead to consolidation of area of lung or bronchopneumonia. Cavitary disease is uncommon in children. The enlarged lymph nodes may compress the neighboring airway. Ball-valve effect due to incomplete obstruction may lead to trapping of air distal to obstruction (emphysema). Enlarged paratracheal nodes may cause stridor and respiratory distress. Subcarinal nodes may impinge on the esophagus and may cause dysphagia. If the obstruction of bronchus is complete, atelectasis occurs.

Outcome of bronchial obstruction may include: (i) complete expansion and resolution of chest X-ray findings; (ii) disappearance of the segmental lesions; and (iii) Scarring and progressive compression of the lobe or segment leading to bronchiectasis. A caseated lymph node may erode through the wall of the bronchus, leading to tuberculous bronchitis/endobronchial tuberculosis. Fibrosis and bronchiectatic changes may supervene. Discharge of the bacteria into the lumen may lead to its bronchial dissemination.

Hematogenous dissemination of *M. tuberculosis* occurs early in the course of the disease; this results when the bacilli find their way into bloodstream through lymph nodes. This may result in foci of infection in various organs. If the host immune system is good, then these foci are contained and disease does not occur. Seeding of apex of lungs leads to development of Simon focus. Lowering of host immunity may lead to activation of these metastatic foci and development of disease. This is especially seen in young infants, severely malnourished children and children with immunodeficiency. Massive seeding of bloodstream with *M. tuberculosis* leads to miliary tuberculosis, where all lesions are of similar size. This usually occurs within 3–6 months after initial infection.

Pulmonary tuberculosis resulting from endogenous reactivation of foci of infection is uncommon in children; but may be seen in adolescents. The commonest site for this type of disease is the apex of the lung (Puhl lesion), because the blood flow is sluggish at apex. Regional lymph nodes are usually not involved. Miliary and meningeal tuberculosis usually occur within a yr of the primary lesion.

Clinical Features

The incubation period varies between 4 and 8 weeks.

Intrathoracic Tuberculosis

The onset of symptoms is generally insidious, but may be relatively acute in miliary tuberculosis.

Primary infection usually passes off unrecognized. Asymptomatic infection is defined as infection associated with tuberculin hypersensitivity and a positive tuberculin test but with no striking clinical or roentgenographic manifestations.

Most symptoms in children with pulmonary primary complex (PPC) are constitutional in the form of mild fever, anorexia, weight loss, decreased activity. Cough is an inconsistent symptom and may be absent even in advanced disease. Irritating dry cough can be a symptom of bronchial and tracheal compression due to enlarged lymph nodes. In some children, the lymph nodes continue to enlarge even after resolution of parenchymal infiltrate. This may lead to compression of neighboring regional bronchus. The PPC may be picked-up accidentally during evaluation of intercurrent infections.

Progressive primary disease (PPD) is the result of the progression of primary disease. Children with PPD may present with high-grade fever and cough. Expectoration of sputum and hemoptysis are usually associated with advanced disease and development of cavity or ulceration of the bronchus. Abnormal chest signs consist mainly of dullness, decreased air entry and crepitations. Cavitating pulmonary tuberculosis is uncommon in children.

Children with *endobronchial tuberculosis* may present with fever and troublesome cough (with or without expectoration). Dyspnea, wheezing and cyanosis may be present. Occasionally, the child not responding to bronchodilators may be misdiagnosed as asthma. In a wheezing child not responding to bronchodilators less than 2-yr-old, the possibility of endobronchial tuberculosis should always be considered. Partial compression of the airway can lead to emphysema. Features of collapse may be present if a large airway is completely compressed.

Miliary tuberculosis is characterized by hematogenous spread and progressive development of innumerable small foci throughout the body. The disease is most common in infants and young children. The onset of illness is often sudden. The clinical manifestations depend on the

numbers of disseminated organisms and the involved organs. The child may have high-grade fever, which is quite unlike other forms of tuberculosis. The child may also have dyspnea and cyanosis. There are hardly any pulmonary findings but fine crepitations and rhonchi may be present. These findings may occasionally be confused with other acute respiratory infections of childhood. The illness may be severe, with the child having high fever, rigors and alteration of sensorium. In addition, these children may have lymphadenopathy and hepatosplenomegaly. The other presentation of miliary tuberculosis may be insidious with the child appearing unwell, febrile and losing weight. Choroid tubercles may be seen in about 50% patients. Meningitis may occur in 20–30% cases.

Pleural effusion follows the rupture of a subpleural focus into the pleural cavity. The pleura may also be infected by hematogenous spread from the primary focus. The effusion usually occurs because of hypersensitivity to tubercular proteins. If the sensitivity is high, there is significant pleural effusion along with fever and chest pain on affected side. Minor effusions associated with the rupture of primary foci are usually not detected. Tuberculous effusion is uncommon in children younger than 5 yr of age and is rarely associated with segmental lesion and miliary tuberculosis. The onset may be insidious or acute with rise in temperature, cough, dyspnea and pleuritic pain on the affected side. There is usually no expectoration. Pain in chest may disappear once the fluid separates the inflamed pleural surfaces; this may be replaced by some discomfort. Increase in effusion may make breathing shallow and difficult. The clinical findings depend on the amount of fluid in the pleural cavity. In early stages, a pleural rub may be present. Early signs include decreased chest wall movement, impairment of percussion note and diminished air entry on the affected side. As the fluid collection increases, the signs of pleural effusion become more definite.

Extrathoracic Tuberculosis

The most common forms of extrathoracic disease in children include tuberculosis of the superficial lymph nodes (scrofula) and the central nervous system. Other rare forms of extrathoracic disease in children include osteoarticular, abdominal, gastrointestinal, genitourinary, cutaneous and congenital disease.

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TB of the superficial lymph nodes can be associated with drinking unpasteurized cow's milk or can be caused by extension of primary lesions of the upper lung fields or abdomen leading to involvement of the supraclavicular, anterior cervical, tonsillar and submandibular nodes. Although lymph nodes may become fixed to surrounding tissues, low grade fever may be the only systemic symptom. A primary focus is visible radiologically only 30 to 70% of the time. Tuberculin skin test results are usually reactive. Although spontaneous resolution may occur, untreated lymphadenitis frequently progresses to caseating necrosis, capsular rupture and spread to adjacent nodes and overlying skin, resulting in a draining sinus tract that may require surgical removal.

Central nervous system disease is the most serious complication of tuberculosis in children and arises from the formation of a caseous lesion in the cerebral cortex or meninges that results from occult lymphohematogenous spread. Infants and young children are likely to experience a rapid progression to hydrocephalus, seizures and raised intracranial pressure. In older children, signs and symptoms progress over the course of several weeks, beginning with fever, headache, irritability and drowsiness. The disease advances with symptoms of lethargy, vomiting, nuchal rigidity, seizures, hypertonia and focal signs. The final stage of disease is marked by coma, hypertension, decerebrate and decorticate posturing and death. Rapid confirmation of tuberculous meningitis can be difficult because of the wide variability in cerebrospinal characteristics, nonreactive tuberculin skin tests in 40% and normal chest radiographs in 50%. Because improved outcomes are associated with early institution of antituberculous therapy, the diagnosis should be considered for any patient with basilar meningitis, hydrocephalus or cranial nerve involvement that has no other apparent cause.

Tuberculosis of abdomen is often due to hematogenous spread from the primary focus in the lungs. It may, however, be secondary to swallowing of the infected sputum by a patient with pulmonary lesions. Primary tuberculosis of the intestines due to ingestion of the food contaminated by tubercle bacilli is relatively less common in India as the milk is generally boiled before use. Patients with abdominal tuberculosis may remain asymptomatic initially. Symptomatic patients show evidence of tuberculous toxemia and may present with colicky abdominal pain, vomiting and constipation. The abdomen feels characteristically doughy. The abdominal wall is not rigid but appears tense, so that the abdominal viscera cannot be palpated satisfactorily. The rolled up omentum and enlarged lymph nodes may appear as irregular nodular masses with ascites. The liver and spleen are often enlarged. Histological examination of the liver may show granulomatous hepatitis and fatty change.

Diagnosis

The diagnosis of tuberculosis in children is usually based on clinical signs and symptoms, chest roentgenogram, tuberculin testing and history of contact with adult patients. Clinical features may be nonspecific and chest radiograph and Mantoux test are difficult to interpret. In addition, these do not give conclusive evidence for the disease. Although demonstration of mycobacterium in various clinical specimens remains gold standard, this is often not possible in children due to the paucibacillary nature of the illness.

A history of contact with an infective case. Contact is defined as any child who lives in a household with an adult taking antitubercular therapy or has taken such therapy in past 2 yr. A history of contact is available in less than one-third of the patients. Tracing of contact is important not only for confirming the diagnosis but also for protection of other vulnerable children from the disease.

Various scoring systems have been developed for diagnosis of tuberculosis. In these scoring system more weightage is given to laboratory tests, i.e. demonstration of acid-fast bacilli, tubercles on histology, suggestive radiology and tuberculin test >10 mm induration. These scoring systems may be used as screening tools but not for starting treatment.

Laboratory Tests

The diagnostic tests for pulmonary tuberculosis can be divided into 2 categories: (i) demonstration or isolation of *M. tuberculosis* or one of its components and and (ii) demonstration of host's response to exposure to *M. tuberculosis.*

Demonstration of M. tuberculosis or its components. The organism can be demonstrated by (i) Ziehl Neelson (ZN) staining, (ii) special stains, (iii) cultures, (iv) polymerase chain reaction, and (v) other methods. The above methods can be used on sputum, induced sputum, gastric lavage, bronchoscopic lavage fluid, or pleural fluid. The best specimen for demonstration of *M. tuberculosis* in children is the early morning gastric aspirate obtained by using a nasogastric tube before the child arises. The yield on ZN stain is less than 20% and depends on extent of pulmonary disease. For better results at least 2 consecutive specimen of gastric aspiration are recommended.

Young children are not able to provide sputum. In them, sputum can be induced. Following an overnight fast, the patient receives salbutamol by nebulizer followed by hypertonic saline (3% or 5%) inhalation by nebulizer. Older children may provide expectoration at end of procedure. In young children including infants, a nasopharyngeal aspirate is collected and processed like sputum for smear and culture to identify *M. tuberculosis.* Gastric aspirates may similarly be collected.

Culture. Lowenstein-Jensen (LJ) medium is the most widely used medium for determination of characteristic features of colonial morphology, growth rate and pigment production. Though the culture technique is simple, 7–10 weeks of incubation may be necessary for detection of organisms. Microscopic examination of thin layer culture plate may lead to detection of microcolonies of *M. tuberculosis* as early as after 7 days. The yield of culture of gastric aspirate varies from 30 to 50% in children with tuberculosis. Excessively long period required for isolation of *M. tuberculosis* by conventional culture techniques has led to the development of other techniques for culture such as BACTEC radiometric assay, Septichek AFB system and mycobacterial growth indicator tube (MGIT) system.

Polymerase chain reaction (PCR). PCR is the most commonly used technique of nucleic acid amplification, for diagnosis of tuberculosis. The PCR may be used to (i) diagnose tuberculosis rapidly by identifying DNA from *M. tuberculosis* in clinical samples that are negative by microscopic examination; (ii) determine rapidly whether acid-fast organisms identified by microscopic examination in clinical specimens are *M. tuberculosis* or atypical mycobacteria; and (iii) identify the presence of genetic modifications known to be associated with resistance of some antimycobacterial agents. The most commonly used target for detection of *M. tuberculosis* is the insertion sequence IS6110. The sensitivity ranges from 4–80% and the specificity 80–100%. PCR gives rapid results and has a greater sensitivity compared with traditional microbiological methods. This makes PCR a suitable technique in childhood tuberculosis, especially when diagnosis is difficult or needed urgently. However, the possibility of false positive results must be considered, especially when the clinical symptoms and history of exposure of the child make the diagnosis improbable.

A new test based on real time PCR technique that is fully automated (GenXpert) has been developed for identification of *M. tuberculosis* in sputum in adult patient. This method gives results within 2 hr, in addition it provides result about sensitivity to rifampicin. This test is under evaluation for diagnosis of tuberculosis in children.

Serodiagnosis. In absence of a satisfactory diagnostic method for childhood tuberculosis, interest has been generated in serodiagnosis. ELISA has been used in children to detect antibodies to various purified or complex antigens of *M. tuberculosis.* Despite a large number of studies, serology has limited role in the diagnosis of tuberculosis in children. Sensitivity and specificity depend on the antigen used, gold standard for the diagnosis and the type of tubercular infection. At present, serodiagnosis does not have any role in diagnosis of childhood pulmonary tuberculosis and recently these tests have been banned by the Government of India.

Methods to diagnose latent tuberculosis infection. Till date, tuberculin skin test was the only method to diagnose latent tuberculosis infection. Recently, a new test QuantiFERON®-gold TB test (QFT) was approved by the Food and Drug Administration for latent *M. tuberculosis* infection. This *in vitro* diagnostic aid measures cell mediated immune reactivity to *M. tuberculosis* and is based on the quantitation of interferon-gamma released from sensitized lymphocytes in whole blood incubated overnight with specific antigens. Another *in vitro* test-ELISPOT is also available for diagnosis of latent infection. These tests are currently not recommended in endemic countries like India.

Tuberculin skin test. The tuberculin skin test (Mantoux test) is most commonly used for establishing the diagnosis of tuberculosis in children. Although currently available tuberculin skin test antigens are neither 100 percent sensitive nor specific, no better diagnostic test is widely available. The positive and negative predictive values of the tuberculin skin test are affected significantly by a number of factors. Infection with *M. tuberculosis* produces a delayed-type hypersensitivity reaction to specific antigenic components of the bacilli. All PPD lots are bioassayed to demonstrate equal potency. Thus, the standard test dose of a commercially available preparation is defined as the dose of that product that is biologically equivalent to 5 TU of PPD-S or 2 TU of tuberculin PPD RT23. The reaction to tuberculin typically begins 5 to 6 hr after the patient receives the injection and reaches maximal induration at 48 to 72 hr. Rarely, vesiculation and necrosis may occur. Variability of the tuberculin skin test may be reduced by giving careful attention to details of administration and reading. A one-quarter to one-half inch, 26-gauge needle and tuberculin syringe are used to inject 0.1 ml of PPD intradermally into the volar aspect of the forearm. Forty eight to seventy-two hr after the injection is given, the diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters. A nonreactive tuberculin skin test does not exclude latent or active tuberculosis. Numerous factors can diminish tuberculin reactivity, resulting in a false-negative reaction. Numerous factors also have been associated with false positive tuberculin reactions and decreased tuberculin test specificity (Table 10.7). Because some antigens in PPD are shared with other mycobacteria and Bacille Calmette-Guérin (BCG), false-positive reactions can occur in children infected with other mycobacterium or have received BCG vaccination. No reliable method for distinguishing BCG-induced cross reactivity from reactivity secondary to mycobacterial infection exists. Although BCG vaccination of older children or adults results in greater initial and more persistent cross-reactivity, most of these individuals lose cross-reactivity within 10 yr of receiving the vaccination. Interpretation of tuberculin skin test reactions is based on risk of infection and progression to disease (Table 10.8).

Table 10.8: Interpretation of Mantoux test

Size of induration	*Interpretation*
<5 mm	Negative; no active disease
5–10 mm	Borderline; consider positive in immunocompromised host; contact with adult patient with sputum AFB positive tuberculosis
≥10 mm	Positive; suggests disease in presence of clinical features

BCG test. An accelerated response after injection of the vaccine is observed in individuals suffering from tuberculosis. An induration of more than 5–6 mm after 3 days of BCG vaccine is considered a positive reaction. The Indian Academy of Pediatrics does not recommend BCG test for diagnosis of tuberculosis.

Radiology. Chest radiograph has an important role in diagnosis of childhood tuberculosis, especially pulmonary

Table 10.7: Causes of false-positive and false-negative Mantoux test

False-positive results

Infections due to atypical mycobacteria
BCG vaccination
Infection at the site of test

False-negative results

Infections
Viral (measles, mumps, chickenpox, HIV)
Bacterial (typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming tuberculosis)
Live virus vaccinations (measles, mumps, polio, varicella)
Metabolic derangements
Chronic renal failure, liver failure, severe malnutrition
Diseases affecting lymphoid organs
Hodgkin disease, lymphoma, chronic leukemia, sarcoidosis
Drugs: Corticosteroids, immunosuppressive agents
Age: Newborns, elderly patients
Stress: Surgery, burns, mental illness, graft-versus-host reactions
Factors related to the tuberculin
Improper storage (exposure to light and heat)
Improper dilutions
Chemical denaturation
Contamination
Adsorption (partially controlled by adding Tween 80)
Factors related to the method of administration
Injection of too little antigen
Subcutaneous injection
Delayed administration after drawing into syringe
Factors related to reading the test and recording results
Inexperienced reader
Error in recording

tuberculosis. In extrapulmonary tuberculosis, presence of lesions on chest radiograph supports diagnosis.

The typical chest X-ray appearance of a pulmonary primary complex is that of an airspace consolidation of variable size, usually unifocal and homogeneous (Fig. 10.16). Enlarged lymph nodes are usually seen in the hila, right paratracheal region. Adenopathy alone may be the sole manifestation of primary tuberculosis. There is no consensus regarding the most common site of involvement. Consolidation in progressive primary disease (PPD) is usually heterogeneous, poorly marginated predilection of involvement of apical or posterior segments of upper lobe or superior segment of lower lobe (Fig. 10.17).

There may be features of collapse (Fig. 10.18). Bronchiectasis may occur in PPD because of (i) destruction and fibrosis of lung parenchymal resulting in retraction and irreversible bronchial dilatation, and (ii) cicatricial bronchostenosis secondary to localized endobronchial infection resulting in obstructive pneumonitis and distal bronchiectasis. In children, cavitary disease is uncommon.

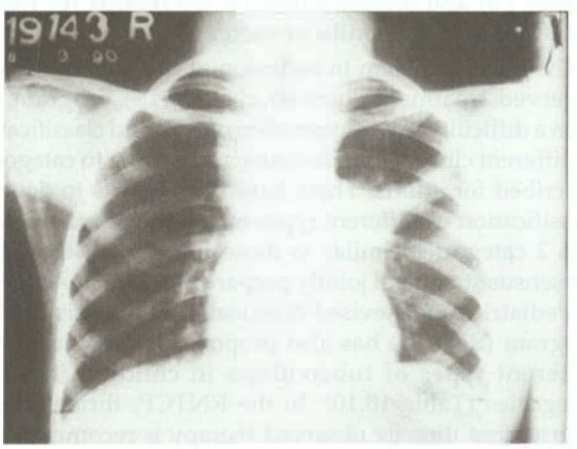

Fig. 10.16: X-ray film of primary pulmonary complex showing left hilar adenopathy and ill-defined parenchymal lesion

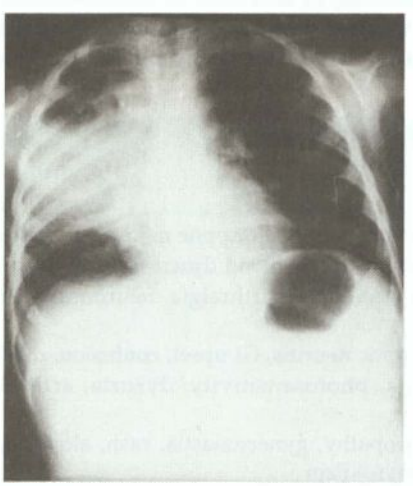

Fig. 10.17: Progressive pulmonary disease showing consolidation

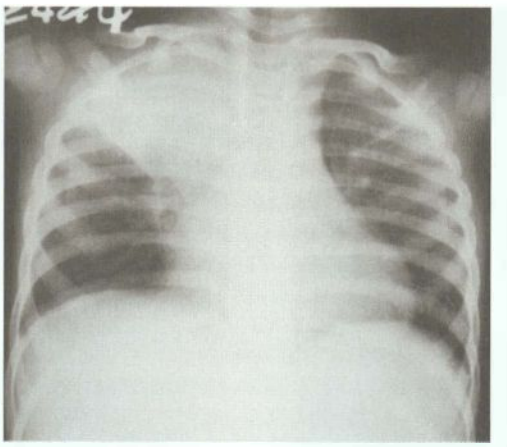

Fig. 10.18: Collapse consolidation of right upper lobe

Pleural effusion may occur with or without lung lesion (Fig. 10.19). In miliary tuberculosis, there are multiple lesions of size 2–5 mm (Fig. 10.20). Occasionally, the chest radiograph may be normal and lymphadenopathy may be detected on computed tomography (CT). In addition, CT features such as low attenuation lymph nodes with peripheral enhancement, lymph node calcification, branching centrilobular nodules and miliary nodules are helpful in suggesting the diagnosis in cases where the radiograph is normal or equivocal. Other features such as segmental or lobar consolidation and atelectasis are nonspecific. Contrast enhanced MRI is emerging as a very useful technique for diagnosing CNS tuberculosis, as it demonstrates the localized lesions, meningeal enhancement and the brainstem lesions.

Histopathology. Lymph nodes, liver and other tissues may be examined for histological evidence of tuberculosis by fine needle aspiration cytology.

Diagnostic Algorithm

The diagnosis of tuberculosis disease in children continues to be challenging. Even in advanced nations, the diagnosis

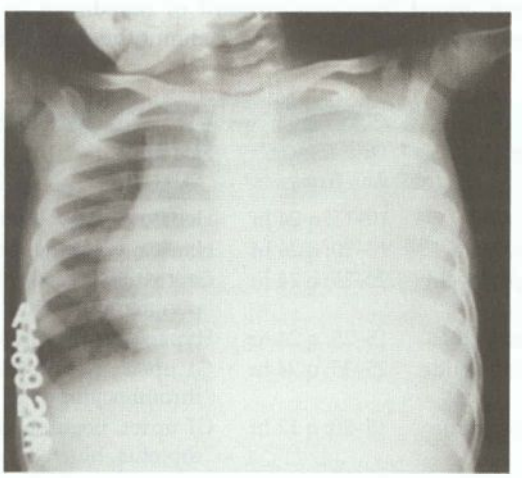

Fig. 10.19: Massive pleural effusion on left side

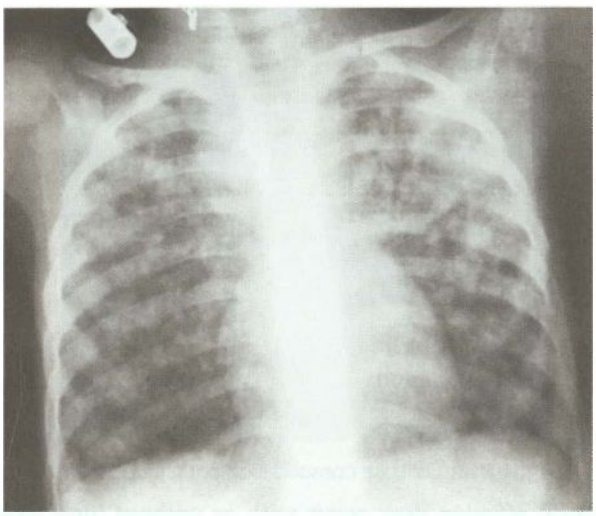

Fig. 10.20: Miliary shadows with right paratracheal adenopathy

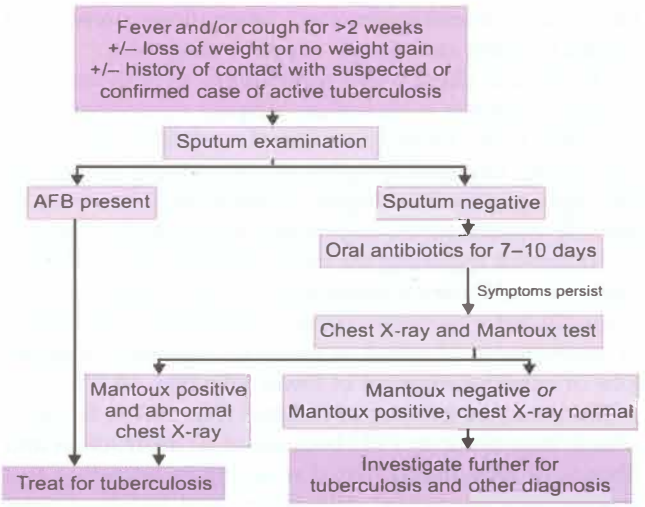

Fig. 10.21: Proposed diagnostic algorithm for pulmonary tuberculosis

is most often made by combination of a positive tuberculin skin test, chest radiograph, physical examination and history of contact with adult patient with tuberculosis. Newer diagnostic methods such as PCR and serodiagnosis have not given encouraging results. Newer staining and culture methods have found their place in the management of tuberculosis. There is a need to develop better techniques for diagnosis of tuberculosis in children. A suggested algorithm for diagnosis of pulmonary tuberculosis is given in Fig. 10.21.

Treatment

The principles of therapy in children with tuberculosis are similar to that of adults. The drugs used for treatment of tuberculosis in children are given in Table 10.9.

Drug Regimens

During the last few yr, changes have occurred in the therapeutic approach to childhood tuberculosis as a result of large number of treatment trials for children and concern about the development of resistance to antituberculosis drugs. Short-course chemotherapy, with the treatment duration of 6 months, has become the standard practice. Extrapulmonary TB (osteoarticular TB, neurological TB) and disseminated TB are treated for longer durations of 9–12 months or more.

The major problem in inclusion of children in directly observed treatment short-course (DOTS) program has been a difficulty in demonstration of AFB and classification of different clinical manifestations according to categories described for adults. There have been efforts to develop classification of different types of childhood tuberculosis into 2 categories similar to those for adults. Recently a consensus statement jointly prepared by Indian Academy of Pediatrics and Revised National Tuberculosis Control Program (RNTCP) has also proposed a classification of different types of tuberculosis in children into two categories (Table 10.10). In the RNTCP, thrice weekly intermittent directly observed therapy is recommended.

Corticosteroids

Corticosteroids, in addition to antitubercular drugs, are useful in treatment of patients with CNS tuberculosis and occasionally pulmonary tuberculosis. These are useful in

Table 10.9: Doses and side effects of antitubercular drugs

Drug	*Dose (mg/kg/day; frequency)*	*Side effects*
Isoniazid	10–15; q 24 hr	Hepatotoxicity, hypersensitivity rash, fever, peripheral or optic neuritis, psychosis, seizures
Rifampicin	10–20; q 24 hr	Nausea, vomiting, hepatotoxicity, flu-like syndrome, blood dyscrasia, arthralgia, wheezing
Streptomycin	20–25; q 24 hr	Ototoxicity (vestibular or hearing loss), rash, fever, arthralgia, neuromuscular blockade, peripheral neuritis, anaphylaxis
Ethambutol	15–25; q 24 hr	Hypersensitivity (rash, fever), joint pain, optic neuritis, GI upset, confusion, dizziness
Pyrazinamide	25–35; q 24 hr	GI upset, hepatotoxicity, hyperuricemia, photosensitivity, dysuria, arthralgia, fever, thrombocytopenia
Ethionamide	15–20; q 12 hr	GI upset, hepatotoxicity, peripheral neuropathy, gynecomastia, rash, alopecia, headache, diplopia, blurred vision, tremors, hypothyroidism
Cycloserine	15–20; q 12 hr	Seizures, psychosis, peripheral neuritis

Table 10.10: Standardized clinical categories and clinical conditions

WHO categories	*Conditions in adults*	*Suggested conditions in children*	*Daily regimen#*	*Intermittent (DOTS)# regimen*	
				Intensive phase	*Continuation phase*
Category I	Sputum positive pulmonary TB *Serious extrapulmonary disease* Abdominal TB Osteoarticular TB Genitourinary TB Neurological TB Pericardial TB	Pulmonary primary complex Progressive primary disease Tubercular lymphadenitis Pleural effusion	2 HRZE + 4 HR	$2\ H_3R_3Z_3E_3$	$4\ H_3R_3$
Category II	Relapse Treatment failure Return after default (interrupted treatment)	Relapse Treatment failure Interrupted treatment	2 SHRZE + 1 HRZE + 5 HRE	$2\ S_3H_3R_3Z_3E_3$ + $1\ H_3R_3Z_3E_3$	$5\ H_3R_3E_3$

It is mandatory to screen all children in the household of an adult patient with sputum positive tuberculosis for evidence of tuberculosis. H isoniazid; E ethambutol; R rifampicin; S streptomycin; Z pyrazinamide

#The numerical before the letters denotes number of months for which the drug is to be given, e.g. 4 HR means 4 months of INH and rifampicin; the subscript after the letters refers to the number of doses per week. Thrice weekly regimens are used in Revised National Tuberculosis Control Program using directly observed treatment short-course (DOTS). The duration of therapy is longer in osteoarticular and neurological tuberculosis

settings where the host inflammatory reaction contributes significantly to tissue damage. Short-courses of corticosteroids are indicated in children with endobronchial tuberculosis that causes localized emphysema, segmental pulmonary lesions or respiratory distress. Some children with severe miliary tuberculosis may show dramatic improvement with corticosteroids if alveolocapillary block is present. While significant improvement in symptoms can occur in children with pericardial effusion, steroids do not alter outcome of pleural effusion. The most commonly used medication is prednisolone, at doses of 1–2 mg/kg/day for 4–6 weeks.

Management of an Infant Born to Mother with Tuberculosis

Congenital tuberculosis is rare. The fetus may be infected either by hematogenously through umbilical vessels or through ingestion of infected amniotic fluid. In the former situation, there will be primary focus in liver and in latter it will be in lungs. It is difficult to find the route of transmission in a newborn with multiple focus of infection. It is difficult to differentiate between congenital and postnatally acquired tuberculosis. Infants born to mothers with active tuberculosis should be screened for evidence of disease by physical examination, tuberculin test and X-ray film of chest. If physical examination and investigations are negative for disease, the infant should receive isoniazid prophylaxis at doses of 10 mg/kg/day for 6 months. After three months, the patients should be examined for evidence of infection and a repeat tuberculin test is done. If tuberculin test is negative, the infant can be immunized with BCG and INH can be stopped. If tuberculin test is positive but the infant is asymptomatic, INH prophylaxis is continued for another 3 months. Infants with congenital tuberculosis should be treated with four drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) in the intensive phase followed by two drugs (isoniazid, rifampicin) during maintenance phase for next 4 months.

Management of a Child in Contact with an Adult with Tuberculosis

Nearly one-third of children (aged less than 5 yr) in contact with adults with active tuberculosis disease may have evidence of tuberculosis infection. The infection is more commonly associated with younger age, severe malnutrition, absence of BCG vaccination, contact with an adult who is sputum positive and exposure to environmental tobacco smoke. Children below 5 yr of age in contact with adult patients with pulmonary tuberculosis should be treated with INH prophylaxis at a dose of 10 mg/kg/day for 6 months.

Monitoring of Therapy

Response to treatment can be judged using the following criteria: clinical, radiological, bacteriological, and laboratory test.

Clinical Criteria

Clinical improvement assesses the response of therapy. The child should be seen every 2–4 weeks initially, then every 4–8 weeks. On each visit, improvement in fever, cough, appetite and subjective wellbeing is assessed. The child is examined for weight gain and improvement in chest findings. Compliance is assessed by talking to parents and checking medications on each visit. Majority of children show improvement in symptoms within a few weeks.

In the presence of poor response or worsening of symptoms or signs, the initial basis of diagnosis is reviewed, especially, if there are no problems with compliance. Assessment for possibility of drug resistant tuberculosis should be made. After the treatment is over, followup every 3–6 months for next 2 yr is desirable.

Radiological Criteria

Clinical improvement precedes radiological clearance of lesion on chest X-ray films. The first chest X-ray during therapy should be done after 8 weeks, i.e. at the end of intensive phase. In patients who show increase or little change in radiological features coupled with delayed clinical response, prolongation of intensive phase by one month is suggested. Further films are taken after 4 weeks and child, if better, should be shifted to continuation phase; else the child is investigated for failure of treatment and drug resistance. The degree of radiological clearance can be graded as (i) complete clearance, (ii) moderate to significant clearance ($\frac{1}{2}-\frac{2}{3}$ clearance), and (iii) mild clearance (decrease in size) or (iv) no clearance or appearance of new lesion. One should not attempt to treat till complete radiological clearance, improvement in the X-ray may continue to occur even after stoppage of therapy.

Microbiological Criteria

Most childhood pulmonary tuberculosis is paucibacillary. In children, where isolation of *M. tuberculosis* was possible at the time of diagnosis, every effort should be made to document disappearance of bacilli during therapy.

Drug Resistant Tuberculosis

Children in the following categories are at risk of drug resistant tuberculosis: Contact with adult patients who have proven drug resistant tuberculosis; unsatisfactory response to antituberculosis drugs and children who initially respond to antituberculosis drugs and then show deterioration. Appearance of new lymph nodes on treatment, persistence of shadow or isolated non-clearance of X-ray film of the chest should not be considered an indicator of drug resistant tuberculosis.

It is important that clinicians should neither miss nor make over diagnosis of drug resistant tuberculosis. Problems with over diagnosis and its treatment are many fold as second line drugs are less effective, have more side effects and are expensive. A physician can suspect drug resistant tuberculosis on basis of criteria given above, but before making a diagnosis all attempts should be made to demonstrate AFB from appropriate samples and get its culture and sensitivity.

Suggested Reading

Chauhan LS, Arora VK. Management of pediatric tuberculosis under the Revised National Tuberculosis Control Program (RNTCP). Indian Pediatrics 2004;41:901–5

Kumar A, Gupta D, Nagaraja SB, et al. Updated National guidelines for pediatric tuberculosis in India, 2012. Indian Pediatr 2013;50:301–06.

Seth V, Kabra SK (Eds). Essentials of Tuberculosis in Children, 3rd edn. New Delhi; Jaypee Publishers, 2010

Mycobacteria Other than Tuberculosis

Atypical mycobacteria or nontuberculous mycobacteria or mycobacteria other than tuberculosis (MOTT) are environmental pathogens that are being increasingly recognized as cause of human disease. More than 125 NTM species have been recognized till date and new species are being identified constantly. NTM are classified depending on the rapidity of growth in media as rapid growers which grow within 7 days and slow growers as those which take longer to grow. Acquisition of NTM is through contact with the environment and human to human or animal to human transmission almost never occurs. Though asymptomatic infection can occur, there is no recognized latent infection or reactivation disease. NTM infections may occur in previously healthy or those with underlying immunodeficiency like HIV. The main clinical syndromes recognized with NTM infection are pulmonary, disseminated, lymph node disease and skin and soft tissue infections.

Lymphatic disease is the most common manifestation of NTM disease in children. It usually presents as painless cervical adenitis in children aged 1–5 yr with no systemic symptoms. The main differential is tuberculous lymphadenitis. The definitive diagnosis is by culture; the usual causative organisms are MAC (*Mycobacterium avium intracellulare*), *M. scrofulaceum* and *M. haemophilum*. Treatment is complete excision of the lymph nodes. Pulmonary disease due to NTM usually occurs in adults with underlying pulmonary problems and is usually due to MAC, *M. kansasii* and *M. abscessus*. Disseminated NTM disease is seen mainly in adults and less commonly children with advanced HIV infection is usually due to MAC and presents as fever, weight loss, night sweats, abdominal pain, diarrhea and anemia. Blood cultures are positive. Skin and soft tissue infections are usually a consequence of trauma or health care procedures. These are usually due to *M. abscessus*, *M. chelonae*, *M. fortuitum*, *M. ulcerans* and *M. marinum*. They have been implicated in infections following injections, central lines, peritoneal dialysis catheters, laparoscopy, liposuction, cosmetic procedures, implants and prosthesis, LASIK and surgery. These mycobacteria species are usually hardy, resist the commonly used disinfectants and hence occur when surgical equipment is rinsed with tap water and inadequately disinfected. Usually these infections present as indolent abscesses that do not respond to the usual antibiotics.

Microbiologic diagnosis of NTM infections is possible in specialized laboratories where identification and speciation is done by advanced biochemical/molecular methods. Treatment of NTM disease depends on the causative organism and its sensitivity. MAC is usually treated with combination therapy consisting of a macrolide (clarithromycin/azithromycin), rifampicin, ethambutol and an aminoglycoside (only in initial stages) for around 12–18 months. Treatment of rapidly growing mycobacteria group of organisms depends on the antimicrobial sensitivity and generally includes a combination of clarithromycin, quinolones, aminoglycosides (tobramycin/amikacin), cefoxitin, imipenem, minocycline and clofazimine.

Suggested Reading

An Official ATS/IDSA Statement: Diagnosis, Treatment and Prevention of Nontuberculous Mycobacterial Diseases. Am J Respir Crit Care Med 2007;175:367–416

Brucellosis

Brucellosis though a relatively uncommon chronic granulomatous infection is discussed here as it is often missed or misdiagnosed as tuberculosis. It occurs worldwide especially in the Middle Eastern countries and has been reported from India.

Etiopathogenesis

Brucella species are intracellular gram-negative coccobacilli. The classification of brucella species is based on its preferred hosts namely *B. melitensis* (sheep and goats), *B. abortus* (cattle), *B. suis* (pigs), *B. canis* (dogs). Brucellosis is a zoonosis and transmission to humans can occur through the consumption of infected unpasteurized milk and animal products, through direct contact with infected animal parts such as placenta, by inoculation of skin and mucous membranes, and by inhalation of infected aerosolized particles. The vast majority of cases worldwide are attributed to *B. melitensis*.

Clinical Features

Human brucellosis can be an acute illness (<2 months), subacute illness (2–12 months) or chronic illness (>1 yr). The incubation period is usually between 7 days and 3 months. A history of exposure to animals especially drinking unpasteurized milk without proper boiling is present. Fever can be continuous or intermittent and persist for several months due to partial response to antibiotics. Fever is usually accompanied by profuse sweating, joint pains (particularly knee) and hepatosplenomegaly and less common lymphadenopathy. In untreated cases complications such as spondylitis, osteoarthritis, meningoencephalitis, brain abscess, pneumonia and endocarditis can occur.

Diagnosis

Blood count usually reveals anemia, leukopenia and thrombocytopenia. The liver enzymes are mildly elevated (SAP and GGT more than transaminases).

The gold standard for diagnosis is blood culture, which has good sensitivity if done prior to antibiotic therapy and specimen incubated for 4 weeks. The sensitivity of bone marrow cultures is higher since organisms are present in large amounts in the reticuloendothelial system. Serologic diagnosis can be established by the serum agglutination test where titers above 1:160 or 1: 320 may be considered diagnostic or by IgG and IgM antibodies by ELISA.

The common differentials for brucellosis include tuberculosis, enteric fever, chronic malaria, HIV, sarcoidosis and lymphoproliferative disorders.

Treatment

Treatment of human brucellosis (adult or pediatric) is always with a combination of antibiotics for 6 weeks as all monotherapies and short treatments are characterized by unacceptably high relapse rates. Brucella is sensitive to many antibiotics but the regimens designed for the treatment of brucella infection should have one or more drugs that can penetrate macrophages and act in the acidic intracellular environment. The standard regime is a combination of doxycycline with streptomycin for 3 weeks followed by doxycycline and rifampicin to complete 3 more weeks. For children less than 8 yr of age combinations containing rifampicin and TMP-SMZ with or without aminoglycosides are recommended. Regimes containing macrolides and quinolones are also being evaluated. Treatment is prolonged for endocarditis and neurobrucellosis.

Prevention

Preventive strategies includes control of disease in livestock and preventing human exposure particularly boiling milk before use.

Suggested Reading

Pappas G, Akritidis N, Bosilkovski M, et al. Brucellosis: Review. N Engl J Med 2005;352:2325–36

FUNGAL INFECTIONS

Fungi have become increasingly common cause of disease in humans. Superficial fungal infections are detailed in the chapter on skin.

Invasive Candidiasis

Candida is a yeast like fungus with major species being *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*. It commonly causes superficial infections such as thrush, vaginitis, paronychia, etc. Colonization with candida at mucosal sites in patients on antibiotic therapy is also common. More serious are invasive infections that happen in hospitalized individuals with impaired defenses. Common risk factors for invasive candidiasis include prolonged intensive care stay, broad spectrum antibiotic therapy, renal failure, very low birthweight, corticosteroid and other immunosuppressive therapy, use of total parenteral nutrition especially intralipids, neutropenia and central venous catheters. The commonest form of invasive candidiasis is bloodstream infection and less commonly meningitis, endocarditis, osteomyelitis and septic arthritis. Clinical features are similar as bacterial sepsis and outcomes are poor if therapy is not initiated early.

Diagnosis is by fungal cultures and occasionally by PCR. It is important to differentiate colonization from true infection to avoid overtreatment. At the same time it is important to have a high index of suspicion so that therapy

is started early in patients with likelihood of infection. Fluconazole is the drug of choice especially because of ease of administration and availability of oral switchover. Fluconazole resistant candida are treated by amphotericin B , echinocandins and newer azoles like voriconazole.

Aspergillosis

Aspergillus is a ubiquitously distributed filamented fungus; the two common species causing human infection are *A. fumigatus* and *A. niger*. Aspergillus causes certain non-invasive infections like otomycosis, sinusitis. aspergilloma and allergic bronchopulmonary aspergillosis. More sinister is invasive aspergillosis which can have mortality as high as 50%. Invasive aspergillosis occurs in the immunocompromised; common predisposing factors include patients with cancer undergoing chemotherapy and resultant neutropenia, stem cell transplant recipients and patients on other immunosuppressive drugs. Common sites of involvement are the lungs and sinuses. Diagnosis is primarily by radiology (Fig. 10.22) and histopathologic demonstration of the invasive hyphae in biopsy samples and culture. Serial estimation of galactomannan in serum samples has emerged as a noninvasive diagnostic test. Treatment should be aggressive. The drug of choice is voriconazole. Other options are amphotericin B and caspofungin. Fluconazole has no activity against aspergillus. Surgical resection may be required in nonresponding cases.

Mucormycosis

Mucormycosis or more appropriately termed as zygomycosis refers to infection with the filamented fungi of the genus *Mucor* and *Rhizopus*. The hyphae are broad and aseptate unlike those of Aspergillus that are narrow and septate. Zygomycosis is an invasive infection that primarily occurs in patients with risk factors such as diabetic ketoacidosis, cancer chemotherapy, transplant recipients, iron overload and receipt of immunosuppressive drugs. Sites of involvement are mainly the nasal sinuses and less commonly pulmonary, gastrointestinal and skin/soft tissue. Infection can sometimes occur due to direct inoculation in traumatic/surgical wounds and injection sites. Clinical features depend on the site involved; in the nasal form pain, swelling, bloody discharge and presence of blackish eschars on nasal examination are common. Confirmation of diagnosis is by demonstration of the characteristic hyphae on histopathology and fungal cultures. Treatment includes radical surgical debridement, antifungal therapy with amphotericin B and correction of underlying predisposing factors.

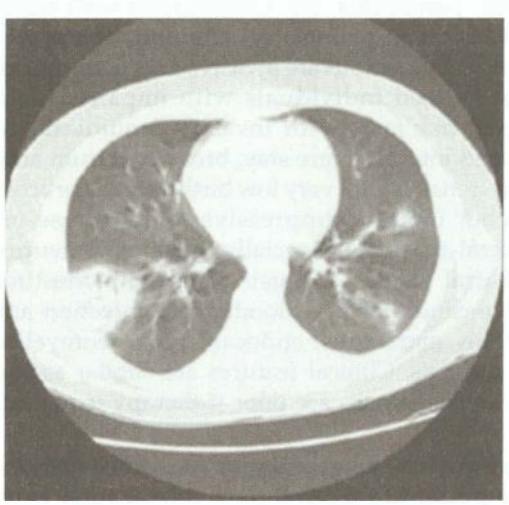

Fig. 10.22: Multiple air space opacities with irregular borders and internal cavitation suggesting invasive aspergillosis

Cryptococcosis

Infection with *Cryptococcus neoformans* is commonly seen in HIV infected individuals with advanced immunosuppression. The disease often affects the central nervous system; pulmonary and disseminated forms are less common. Clinical symptoms include headache, vomiting, altered sensorium, signs of meningism and less commonly neurologic deficits. The diagnosis is confirmed by demonstrating cryptococci in the CSF by India ink, cryptococcal antigen testing and finally culture. CSF is usually under increased pressure and has high protein with pleocytosis. Treatment includes antifungal therapy with amphotericin B and flucytosine for 2 weeks followed by fluconazole for prolonged periods. Reduction of elevated pressure by serial lumbar punctures is also crucial.

Suggested Reading

Smith PB, Steinbach WJ, Benjamin DK. Neonatal candidiasis. Infect Dis Clin N Am 2005;19:603–15

Steinbach WJ. Antifungal agents in children. Pediatr Clin North Am 2005;52:895–915

PROTOZOAL INFECTIONS

Malaria

Malaria, the most important protozoal disease in humans, is caused by the genus *Plasmodium*. Four species are pathogenic, *P. vivax*, *P. falciparum*, *P. malariae* and *P. ovale*, of which the first two occur in India.

Epidemiology

Malaria afflicts 200–300 million patients each yr globally, causing about 650,000 deaths, chiefly in young children. While 70% cases are reported from sub-Saharan Africa, malaria is an important cause of morbidity and mortality in South Asia. In India, malaria causes about 2 million cases and 1000 deaths annually, the majority of which occur in association with infection with *P. falciparum*. Endemic regions include Orissa, Chhattisgarh, West Bengal, Karnataka, Jharkhand, Madhya Pradesh, Uttar Pradesh, Assam, Gujarat and Rajasthan. Malaria is also common in urban areas, particularly due to construction activities, population migration and inappropriate water storage and disposal. The sixth Millennium Development

Goal aims for reduction in malaria mortality by 75% by 2015.

Transmission

The infectious stage of the parasite, the sporozoite, is transmitted to the host by the bite of the female mosquito. Six species of anopheline mosquitoes are important in the transmission of the disease, namely *Anopheles culicifacies* (rural), *A. fluvitalis*, *A. stephensi* (urban), *A. minimus*, *A. philippinesis* and *A. sundaicus*. The parasites develop in the vector's body and make it infectious if the mosquito is susceptible, feeds on human blood and lives for at least 10–12 days after an infective blood meal. Mosquitoes usually breed in edges of streams, water tanks, pits, cisterns and overhead tanks. *A. stephensi* breed in wells, cisterns, fountains and overhead tanks, *A. fluviatilis* in moving water and *A. sundaicus* in brackish water. Breeding sites such as burrowed pits, pools, ponds, marshy areas and unregulated irrigation channels are conducive to mosquito breeding and spread of malaria. Mosquitoes thrive best in temperature between 20 and 30°C, relative humidity 60% and in areas with good rainfall. The peak transmission season of malaria is between July and November.

Life Cycle of the Parasite

Hepatic or tissue phase in human host (Exoerythrocytic schizogony). The trophozoites injected by an infectious mosquito invade hepatocytes and reticuloendothelial tissues. In the hepatocyte, each parasite replicates to form 2000 to 15000 merozoites in case of *P. vivax* infection and 40000 merozoites for *P. falciparum*. Merozoites released from hepatocytes invade red cells. This first hepatic phase is asymptomatic and constitutes the incubation period, lasting about 10 days.

Erythrocytic schizogony. In erythrocytes, parasites develop into ring forms, mature trophozoites and then multinucleated schizonts, which rupture and release more merozoites. Repeated cycles of erythrocyte invasion and rupture lead to chills, fever, headache, fatigue, nonspecific symptoms and with severe malaria, signs of organ dysfunction.

Manifestations of severe malaria, including cerebral malaria, noncardiogenic pulmonary edema and renal failure are caused by high concentrations of *P. falciparum* infected erythrocytes in the microvasculature. Since mature *P. falciparum* organisms in the erythrocytes adhere to endothelial cells, only ring forms circulate (except in severe infections) and levels of peripheral parasitemia may be low despite substantial infection.

Gametocytic phase. After several stages of schizogony, some merozoites are converted to gametocytes which are taken up by mosquitoes. These do not cause symptoms but are responsible for transmission of malaria.

Exoerythrocytic phase. Merozoites of *P. vivax*, but not those of *P. falciparum*, may go into a dormant stage (hypnozoite) in the liver and cause relapses by invading the bloodstream weeks or even yr later. This intermittent release of schizonts in case of *P. vivax* and *P. ovale* may last for 2–3 yr and for *P. malariae* for 10–20 yr.

Mosquito. The gametocytes ingested by the mosquito multiply in the stomach (sporogonic cycle). Fertilization of female gametes generates motile and elongated zygotes (ookinetes) that invade the midgut to develop into oocysts (resting stage), which later grow and rupture to release sporozoites. These reach the mosquito salivary glands and may be inoculated in a new human host.

Immunity Against Malaria

Epidemiologic observations suggest that patients with sickle cell trait, thalassemia and glucose-6-phosphate dehydrogenase deficiency are relatively immune to malaria. Homozygotes of sickle cell disease are not protected from malaria but heterozygotes are immune. Variations in HLA frequency may also determine the prevalence of malaria.

Clinical Patterns of Malaria

The clinical manifestations and severity of malaria depend on the species of the parasite and endemicity of disease. Most cases of severe or complicated malaria are due to *P. falciparum*; recently there is an increasing number of reports due to severe disease by *P. vivax*. In highly endemic areas with "stable malaria" such as sub-Saharan Africa, children below 5 yr are most affected with severe anemia and cerebral malaria being prominent manifestations. In areas of lower endemicity all ages including children and young adults are affected.

The incubation period of malaria varies between 9 and 30 days, the least for *P. falciparum* and longest for *P. malariae* infections. The onset of the disease is not as characteristic as is believed, especially in infections with *P. falciparum*. The onset of the disease is sudden with fever, headache, loss of appetite, lassitude and pain in the limbs. The fever may be continuous or remittent for several days before it becomes classically intermittent. The illness, then, is characterized by a *cold stage* (chills and rigors with headache, nausea, malaise and anorexia); *hot stage* (dry flushed skin, rapid respiration and marked thirst); and *sweating stage* (temperature falls by crisis). The classic intermittent fever is not usually seen in children.

On basis of severity malaria is classified as 'complicated or severe' and uncomplicated malaria which has treatment and prognostic implications. Severe malaria can affect virtually every organ system and has a mortality rate of approximately 20%. The criteria for severe malaria are listed below. Any of the criteria if present with asexual parasitemia with *P. falciparum* or *P. vivax* classifies malaria as severe and should be treated as such.

Features of Severe Malaria

- Impaired consciousness or unrousable coma
- Prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
- Failure to feed
- Multiple convulsions —more than two episodes in 24 hr
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse or shock, systolic blood pressure <70 mm Hg in adults and <50 mm Hg in children
- Clinical jaundice plus evidence of other vital organ dysfunction
- Hemoglobinuria
- Abnormal spontaneous bleeding
- Pulmonary edema (radiological)

Laboratory findings of severe malaria

- Hypoglycemia (blood glucose <2.2 mmol/l or <40 mg/dl)
- Metabolic acidosis (plasma bicarbonate <15 mEq/l)
- Severe normocytic anemia (Hb <5 g/dl, packed cell volume <15%)
- Hemoglobinuria
- Hyperparasitemia (>2% or 100 000/µl in low intensity transmission areas or >5% or 250 000/µl in areas of high stable malaria transmission intensity)
- Hyperlactatemia (lactate >5 mmol/l)
- Renal impairment (serum creatinine >265 µmol/l).

Diagnosis

Peripheral smear The gold standard for diagnosis of malaria is careful examination of a properly prepared thick film. Thick smears have as sensitivity of detecting 5–10 parasites/µl. Thin smears have a lower sensitivity of 200 parasites/µl but enable species identification. Microscopy also provides information about the parasite load (number of infected RBC/total RBC), prognosis (mature schizonts and pigmented neutrophils indicating a poor prognosis) and tracks response to therapy (Fig. 10.23). The main drawback is need for expertise and that they are time consuming (a careful examination of 100 fields needs 20 min). Sometimes peripheral smears may be negative due to partial antimalarial treatment or sequestration of parasitized cells in deep vascular beds. Repeating smears every 6–8 hourly at least three times is recommended if the clinical suspicion for malaria is high and the initial smear is negative.

Quantitative buffy coat (QBC) test is a new method for identifying the malarial parasite in the peripheral blood. It involves staining of the centrifuged and compressed red cell layer with acridine orange and its examination under UV light source. It is fast, easy and claimed to be more sensitive than the traditional thick smear examination. Disadvantages include need for special equipment, cost, false positives due to staining artefacts and inability to speciate the parasite. QBC has been largely supplanted by the rapid diagnostic tests detailed below.

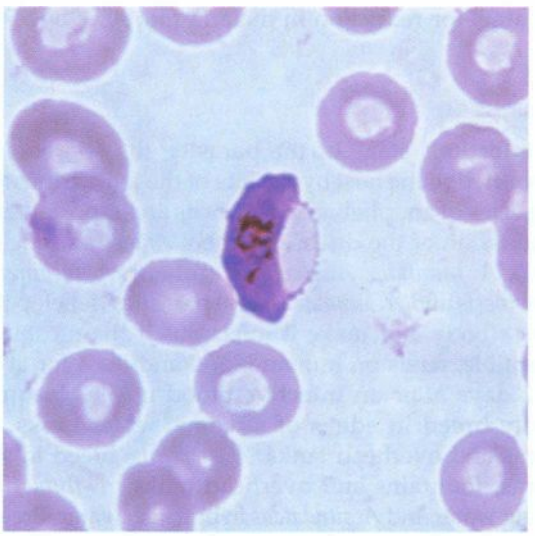

Fig. 10.23: Gametocyte of *Plasmodium falciparum*

Rapid diagnostic tests detect malaria antigens (PfHRP2/PMA/pLDH) from asexual and/or sexual forms of the parasite as color changes on antibody coated lines on the strips. In general, these are quick and simple to use, distinguish between the major forms of human malaria, and are useful when reliable microscopy is not available. Disadvantages include cost, lower sensitivity than microscopy (detect 100–200 parasites/µl), variation in quality from batch to batch and need for rigorous storage conditions. In addition they do not give any information about the parasite load and cannot be used to monitor response to therapy. The OptiMAL test based on detection of parasite LDH (Fig. 10.24) and tests based on plasmodium aldolase are superior to the Parasight F test which is based on detection of HRP 2 antigen of *P. falciparum* as the latter is positive even in past infection and cannot be used to diagnose *P. vivax* malaria.

Polymerase chain reaction (PCR) has been found to be highly sensitive and specific for detecting all species of malaria, particularly in cases of low level parasitemia but is not available commercially and hence of limited practical utility.

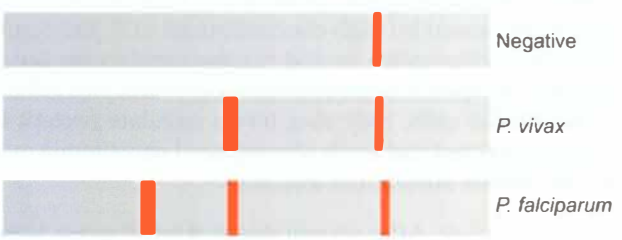

Fig. 10.24: OptiMAL test for rapid diagnosis of malaria. Expected reaction patterns on the OptiMAL test strip for a negative patient, a patient with *P. vivax* malaria, and a patient with *P. falciparum* malaria

Tests for disease management and assessing severity

These include blood counts and culture, PT, PTT, blood glucose, electrolytes, pH, bicarbonate, chloride and lactate; chest X-ray for respiratory distress syndrome; serum bilirubin, transaminases and creatinine; and urine hemoglobin. The WHO consensus statement recommends that a lumbar puncture should be done in a patient presenting with acute febrile encephalopathy. However, in the Indian scenario, CSF examination is not required if the smear diagnosis of faciparum malaria is unequivocal.

Differential Diagnosis

Common clinical differentials for malaria include other tropical and monsoon infections like typhoid fever, leptospirosis, dengue, viral hepatitis. Cerebral malaria should be differentiated from other causes of acute febrile encephalopathy like meningitis and encephalitis. Patients with algid malaria (those in shock) mimic meningococcemia and gram-negative shock.

Treatment of Uncomplicated Malaria

In a setting of suspected uncomplicated malaria, establishing a lab diagnosis is a must before giving empirical therapy. This is to prevent irrational therapy and consequent drug resistance and also to avoid missing other causes of febrile illness.

Vivax malaria The drug of choice for managing vivax malaria is still chloroquine. Resistance to chloroquine has been rarely reported in India. The total dose is 25 mg/kg; first dose given as 10 mg/kg and then 5 mg/kg at 0, 6, 24 and 48 hr respectively. Fever should be brought down before giving chloroquine to reduce the risk of vomiting. Radical therapy with primaquine is indicated for vivax malaria to eliminate the exoerythrocytic stages in liver and reduce risk of relapses. Primaquine also has schizonticidal effect and due to this effect functions as combination therapy for vivax malaria along with chloroquine. The G6PD level should be checked prior to administering primaquine. The dose of primaquine is 0.25–0.3 mg/kg/day for 14 days. The risk of relapse is reduced by two-thirds with primaquine. For patients who relapse despite primaquine, higher doses of 0.5–0.75 mg/kg may be used. Primaquine is contraindicated in infants, pregnant and breastfeeding women. For patients who cannot be given primaquine, relapses may be prevented by administering chloroquine as suppressive therapy in a dose of 10 mg/kg weekly.

Quinine and pyrimethamine sulfadoxine do not have adequate activity against vivax malaria and should not be used for treatment.

Uncomplicated falciparum malaria Falciparum malaria should always be treated with combination therapy. Both drugs should have independent mode of action and should be effective in the area where they are used. Hence pyrimethamine–sulfadoxine is not combination therapy as both partner drugs have similar mechanism of action. Similarly if an area has resistance to pyrimethamine–sulfadoxine and mefloquine then these should not be used as part of combination therapy.

Artemisinin based combination therapy (ACT) is the treatment of choice for falciparum malaria (Table 10.13). Artemisinin (qinghaosu) is the antimalarial extract isolated from *Artemisia annua*. Artemisinin and its derivatives (artemether, artesunate, arteether) are the most rapidly acting of all antimalarials; they also have a broad time window of antimalarial effect from ring forms to mature trophozoites (like chloroquine and unlike quinine that acts only on mature forms). Artemether lumefantrine is the most commonly used oral ACT at this time. Other drugs such as mefloquine and pyrimethamine–sulfadoxine may be used in combination with artesunate in those areas where resistance to these drugs is uncommon. Artesunate amodiaquine is not available in India at present and dihydroartemisinin piperaquine is a new combination drug that may be introduced soon.

Oral quinine with clindamycin or doxycycline (in children aged more than 8 yr) is alternative treatment for but is associated with disadvantages such as poor tolerability of oral quinine and prolonged therapy.

Chloroquine should not be used for treatment for falciparum malaria unless there is demonstrable sensitivity to the drug in a particular area; similarly mefloquine and pyrimethamine sulfadoxine monotherapy is not recommended. At the end of therapy a single gametocidal dose of primaquine 0.75 mg/kg is recommended to reduce community transmission of malaria.

Uncomplicated mixed malaria It should be treated as *P. falciparum* malaria with ACT. The preferred ACT for mixed malaria is dihydroartemisinin piperaquine, which is not available. Use of artemether lumefantrine may be associated with higher rates of recrudescence of vivax malaria. Primaquine should also be used as mentioned earlier.

Treatment of Complicated or Severe Malaria

The treatment of severe malaria is a medical emergency as it is associated with high mortality rates of up to 20%. If the suspicion of malaria is strong then treatment should be initiated without waiting for confirmation of diagnosis. Severe malaria whether due to falciparum or vivax should be treated similarly. Supportive care and treatment of complications are as important as antimalarial therapy.

Antimalarial therapy Treatment should be parenteral as most patients are not able to take orally and the bioavailability of oral drugs is unpredictable. The choice is between use of artemisinin based combination therapy or quinine. Results of meta analysis indicate that at present, in children in the Indian subcontinent the two drugs have equal efficacy. ACT is much easier to

administer with fewer side effects than quinine; it is however more expensive.

Artemisinin based therapy Parenteral formulations of artesunate, artemether and arteether are commercially available; artesunate is the agent for which most safety and efficacy data is available. Artesunate is available as a dry powder which is reconstituted with sodium bicarbonate and given as a bolus injection. Artemether and arteether are given by the intramuscular route. The dose of artesunate is 2.4 mg/kg and that of artemether 3.2 mg/kg given stat and then repeated after 12 hr and 24 hr and then daily. Parasite counts start declining 5–6 hr after institution of therapy with artemisinin derivatives, unlike quinine. Asexual parasitemia generally disappears after a mean time of 72 hr. Once the patient is better, treatment can be shifted to oral and a full course of oral ACT given earlier.

Artemisinin derivatives have a good safety profile. Local reactions after intramuscular administration are rare and much less frequent as compared to IM quinine. Cardiotoxic effects in the form of prolongation of the QT interval in patients being administered high dose artemether have been reported. No clinical significance of this has been noted except that artemisinins should not be combined with other cardiotoxic drugs such as quinine/halofantrine. In two human trials, use of artemether was associated with more frequent convulsions and longer recovery time from coma as compared to quinine, longterm sequelae being comparable in both the groups.

Quinine based therapy Quinine acts principally on the mature trophozoite stage of parasite development; it does not prevent sequestration or further development of formed schizonts and does not kill the pre-erythrocytic or sexual stage of *Plasmodium falciparum*.

Parenteral quinine is available as dihydrochloride salt in concentrations of 300 mg/ml. It is readily photodegraded and should be stored in brown glass ampoules in the dark. Photodegradation is insignificant over short periods (<24 hr) when quinine is dissolved in 0.9% saline or dextrose. Quinine must always be given by rate controlled intravenous infusion and never by bolus or push injection. It is recommended to administer a loading dose of quinine i.e. 20 mg salt/kg diluted in 10 ml/kg of normal saline or dextrose over a period of 4 hr at treatment onset. The objective of loading dose is to provide therapeutic levels as early as possible in the course of treatment without overshoot to toxic levels. The loading dose should be avoided if there is reliable evidence that the patient has received quinine/halofantrine/mefloquine in the past 24 hr (both halofantrine and mefloquine produce additive cardiac toxicity). After the loading dose, quinine should be continued at a dose of 10 mg salt/kg as infusion over 2 hr every 8 hr. Intramuscular quinine is another alternative for initial therapy if facilities for controlled IV quinine administration are not available. Quinine should not be given subcutaneously as this may cause skin necrosis.

The parasite counts start declining only after 24 hr, slower than artemisinin derivatives and may even increase in the first 24 hr. The patient should be switched to oral quinine as soon as possible. If parenteral quinine has to be continued beyond 48 hr or if renal failure supervenes, the maintenance dose should be reduced to 5–7 mg salt/kg to avoid quinine toxicity. Total duration of therapy is 7 days. A second drug such as doxycycline or clindamycin should be added. A single dose of primaquine 0.75 mg/kg is recommended on completion of quinine therapy to eradicate gametocytes and prevent transmission.

The only contraindication to use of quinine is reliable evidence of severe quinine allergy and G6PD deficiency. Thrombocytopenia, jaundice, renal failure, hypotension are not contraindications for quinine administration. Minor side effects including tinnitus, deafness, headache, nausea and visual disturbances termed as "cinchonism" are common with quinine therapy in conscious patients but do not warrant dose reduction. They however reduce compliance with the 7-day treatment regimen. Serious side effects with parenteral quinine are rare if it is administered properly. Quinine produces prolongation of the QTc interval in the ECG. Routine ECG monitoring during quinine infusion is not required if there is no evidence of preexisting heart disease. Quinine is known to produce hypoglycemia through stimulatory action on the pancreatic beta cells. Quinine can cause marked intravascular hemolysis or black water fever and in this setting change of therapy to artemisinin derivatives may be required. Quinine can rarely cause immune mediated thrombocytopenia and this must be suspected if platelet counts fail to recover with clinical improvement.

Supportive Therapy in Severe Malaria

- Admit to intensive care if available
- Rapid clinical assessment with respect to level of consciousness, blood pressure, pallor, rate and depth of respiration, hydration status. Fundus should be examined. The patient should be weighed
- Relevant investigations are sent
- Parenteral antimalarial therapy should be started empirically awaiting confirmation of diagnosis. Doses should be calculated as mg/kg body weight. Doses of salt and base should not be confused (quinine is prescribed as salt)
- If blood glucose cannot be determined or if hypoglycemia documented, glucose should be given
- Good nursing care especially if patient is unconscious
- Oxygen therapy and other respiratory support if required
- Appropriate fluid therapy to avoid under/overhydration. One of the most important points is not to ascribe deep/rapid breathing in a child with severe malaria and anemia to congestive heart failure. In most of these children it has been demonstrated that rapid breathing

is due to metabolic acidosis and respond well to fluid expansion/blood transfusion and not diuretic therapy

- Assessment of pulse rate, blood pressure, respiratory rate, core body temperature, pallor, level of consciousness at least 4 hourly to enable early detection of complications. Monitoring of urine output by indwelling catheter and watch for hemoglobinuria. If facilities are available and clinical conditions warrant central venous pressure and arterial blood pressure should be monitored. Blood glucose in children with coma should be ideally monitored initially every hour; then 2–4 hr, or if clinical deterioration occurs. Blood counts, electrolytes and creatinine should be monitored on a regular basis. Monitor parasite count 6 hourly for the first 48 hr
- Broad spectrum antibiotics (3rd generation cephalosporins and aminoglycoside, beta lactam-beta lactamase inhibitor combinations) should be given in (i) any child with localized signs suggesting bacterial infection; (ii) any child in shock; and (iii) any child with severe respiratory distress in whom deep breathing does not rapidly improve with correction of dehydration or anemia.
- Avoidance of harmful treatments such as corticosteroids, osmotic diuretics.

Treatment of complications is outlined in Table 10.12.

Response to Therapy, Treatment Failures, Recrudescence and Relapse

An optimal response to therapy is defined as a count which on day 1 is less than day 0, a count on day 3 which is less than 25% of count on day 0, no parasites in peripheral blood 72 hr after starting therapy and up to 28 days and no fever after 72 hr.

Patients with parasitologically confirmed malaria who continue to have fever 72 hr after starting antimalarials are occasionally encountered in clinical practice. If they are smear negative, causes could be IV thrombophlebitis, secondary bacterial infections, coinfections such as typhoid or rarely immune phenomena. If the smear is positive then this is early treatment failure; causes are choice of wrong drug, substandard drug, wrong dose, poor compliance or drug resistance. If drug resistance is suspected than treatment should be changed to alternative artemisinin based combination or quinine.

Reappearance of asexual parasites within 28 days of treatment is defined as recrudescence/late treatment failure. Causes again are choice of wrong drug, wrong dose, poor compliance or drug resistance. Recrudescence is fairly common if artemisinin monotherapy is used. Treatment of recrudescence includes optimizing drug therapy or change to an alternative regime.

Control and Prevention of Malaria

Control and prevention of malaria is based on elimination of the vector by strategies like insecticide spraying, use of insecticide treated bed nets and elimination of breeding places. Vaccines against malaria have been under development for a long time but are yet not commercially available nor very effective. In holoendemic areas like Africa chemoprophylaxis with pyrimethamine sulfadoxine administered twice during pregnancy reduces the prevalence of maternal anemia and low birth weight.

Chemoprophylaxis against malaria is recommended for travelers from nonendemic areas to endemic areas. Drugs commonly used are chloroquine (for areas known to be fully chloroquine sensitive), mefloquine, chloroquine-proguanil, doxycycline and atovaquone-proguanil (expensive but safest). Prophylaxis should be started at least 1–2 weeks before departure and continued for 4 weeks after return (except atovaquone-proguanil where it can be started on the day of departure).

National Vectorborne Disease Control Program

These strategies are two-fold: early case detection and prompt treatment and vector control. It has laid out guidelines for detection and management of malaria and are more or less similar to what has been discussed earlier. The program recommends treatment of uncomplicated vivax malaria with chloroquine and falciparum malaria

Table 10.11: Drug doses for oral antimalarial drugs

Drug	*Oral dose*
Chloroquine (tablet 250 mg contains 150 mg of base; syrup 50 mg of base/5 ml)	10 mg/kg of base loading; then 5 mg/kg after 6 hr, 24 hr and 48 hr
Primaquine (tablet 7.5 mg, 15 mg)	0.25–0.75 mg/kg
Artemether lumefantrine (tablet 20 mg artemether and 120 mg lumefantrine; syrup 40 mg artemether per 5 ml)	Administer one dose each at 0, 8, 24, 36, 48 and 60 hr as follows: 5–14 kg: 1 tablet; 5–24 kg: 2 tablet; 25–34 kg: 3 tablet; >35 kg: 4 tablet Alternatively, give 1.7 mg/kg of artemether component q 12 hr for 3 days
Artemether	4 mg/kg single dose
Mefloquine (250 mg tablets)	Two doses, 15 mg/kg and 10 mg/kg, given 8 hr apart
Pyrimethamine sulfadoxine	1.25 mg/kg of pyrimethamine (max 75 mg) single dose
Doxycycline	3.5 mg/kg/day
Clindamycin	10 mg/kg twice daily
Quinine (tablet 300 mg of salt)	10 mg/kg of salt thrice daily

Table 10.12: Treatment of complications of severe malaria

Hyperpyrexia	Use tepid sponging, fanning, paracetamol to induce defervescence Avoid aspirin and other NSAIDs due to risk of gastrointestinal bleeding
Cerebral malaria	Nurse in lateral position; turn every 2 hr; continuous NG aspiration; maintain airway; irrigate and patch eyes If convulsions occur: Exclude hypoglycemia, hyperthermia; manage seizure with slow IV push of diazepam, midazolam or lorazepam; if seizure recurs, load with phenytoin 15–20 mg/kg Consider CT scan for intracerebral bleed, cerebral edema or herniation if consciousness deteriorates or new neurological abnormalities appear For raised intracranial pressure, nurse with head propped up and in midline position; control seizures; hypoglycemia; use hyperventilation; use of mannitol is controversial; corticosteroids do not have a role
Anemia	Transfuse packed cells if hemoglobin is <5 g/dl or in presence of impaired consciousness, hyperparasitemia, respiratory distress or metabolic acidosis; use diuretics and slow transfusion if fluid overload present; perform exchange transfusion in patients with overt congestive cardiac failure
Hypoglycemia	1 ml/kg of 50% glucose given slowly IV; followed by infusion of 10% dextrose; frequent monitoring of blood sugar; may use octreotide and glucagon if IV fluids restricted
Metabolic acidosis	Correct hypovolemia, hypoglycemia and anemia; administer oxygen; administer sodium bicarbonate slowly if pH <7
DIC	Vitamin K, fresh frozen plasma and/or cryoprecipitate; exchange transfusion in presence of fluid overload
Renal failure	Careful fluid challenge with 20 ml/kg of normal saline, followed by furosemide 1 mg/kg (max 5 mg/kg) if no response noted; restrict fluid intake; dialysis indicated in presence of refractory hyperkalemia or metabolic acidosis, fluid overload and rapid rise of serum creatinine
Hemolysis	May prefer artemisinin derivatives as antimalarial drug; transfusion with packed cells to maintain hematocrit; monitor urine output and renal function for need of dialytic support
Acute respiratory distress syndrome	Occurs due to pulmonary capillary leak and, less commonly, from fluid overload; administer oxygen; nurse in propped up position; restrict fluid intake; loop diuretics may help; severe cases need mechanical ventilation with high peak end expiratory pressure
Shock	Send blood culture and administer broad spectrum antibiotics (e.g. cefotaxime and amikacin); monitor central venous pressure; replace fluids; administer vasopressors and respiratory support as required
Hyperparasitemia	Consider exchange transfusion

with artemisinin combination therapy. For severe malaria, artemisinin derivatives or quinine may be used. Strategies for vector control include source control, elimination of breeding places, biologic control with use of larvivorous fish in water bodies and finally chemical vector control by indoor residual spray, space fogging and use of chemical larvicides like abate in water bodies.

Suggested Reading

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10

Leishmaniasis

Leishmaniasis is caused by parasites of the genus *Leishmania* transmitted by the bites of female sandflies. Three major clinical forms are described: visceral leishmaniasis (VL), cutaneous leishmaniasis, and mucocutaneous leishmaniasis (espundia). In India, the visceral and cutaneous forms are caused by *Leishmania donovani*. The term kala-azar (*kala* black; *azar* sickness), refers to the hyperpigmented skin of patients with visceral leishmaniasis. About 100,000–300,000 cases are reported annually in India, chiefly from Bihar and Eastern UP.

Transmission and Etiopathogenesis

The parasite exists in two forms; as nonflagellated, round or oval shaped amastigotes (Leishman-Donovan bodies) in the human or animal reservoir and as flagellated promastigotes in the sandfly and culture media. In India, humans are the chief reservoir (anthroponotic cycle) and female sandfly of the genus *Phlebotomus* are the vectors of the parasite. When feeding on an infected animal or human, the sandfly may ingest an amastigote which develop into a promastigote in the digestive tract, migrates to the proboscis (salivary glands) and is injected into a susceptible host when the sandfly takes its next feed. Within the new host, promastigotes infect macrophages where they develop into amastigotes. These amastigotes multiply in the cells of the mononuclear phagocyte system.

Although all ages are affected, children aged 1–4 yr are more susceptible. The protective immune response in visceral leishmaniasis is primarily cell mediated immunity which results in subclinical infection and spontaneous

cure in majority of cases. Failure of this immunity leads to leishmaniasis. Malnutrition and HIV predispose to clinical disease.

Clinical Features of Visceral Leishmaniasis

The incubation period is 3 to 8 months (range 10 days–34 months). Features include high grade fever, weight loss, hepatosplenomegaly, abdominal discomfort, lymphadenopathy and pallor. Fever may be high or low grade, remittent, intermittent or continuous; the '*double-rise*' of temperature in a day (*double quotidian*), is uncommon. Splenohepatomegaly, with the spleen much larger than the liver, is usual. Spleen is usually huge, firm, smooth and nontender and is palpable by the end of first month of illness. Unlike African leishmaniasis, lymphadenopathy is infrequent in Indian patients (<5%). Hyperpigmentation of skin is a characteristic feature and occurs in about two-thirds of patients in late stages of disease, affecting the face, hands and upper trunk. Progressive emaciation occurs in all cases, though appetite is preserved. Cough and diarrhea are common. Bleeding manifestations in the form of petechial hemorrhages, epistaxis and gum bleeding may be seen. Pedal edema may occur due to hypoalbuminemia. Jaundice is uncommon. Diminished cell mediated immunity may account for the high incidence of secondary infections. Pancytopenia and hypergammaglobulinemia are characteristic.

The disease may begin insidiously and be asymptomatic initially, but usually runs a chronic course that may be fatal without or despite treatment. Death usually occurs within 2 yr in 75–95% cases, because of severe secondary bacterial infections or gastrointestinal bleeding.

Post Kala-azar Dermal Leishmaniasis

Post kala-azar dermal leishmaniasis (PKDL) develops after resolution of visceral leishmaniasis and is seen in a small percentage of patients in Africa and India. This is usually due to infection by the *L. donovani* cluster. The interval to development of PKDL is variable; it usually occurs 1–10 yr after successful treatment of visceral leishmaniasis. Hypopigmented macular, maculopapular or nodular skin lesions are seen first in the perioral area, chin and lips and later appear over the neck, extensor surfaces of the arms, trunk and legs. Lepromatous leprosy is a close differential, but peripheral nerves are spared. Skin lesions may persist for up to 20 yr. These patients may act as chronic reservoir of infection.

Diagnosis

Visceral leishmaniasis should be suspected in a patient from an endemic area presenting with prolonged pyrexia and splenomegaly. Cases in nonendemic areas have been reported but are rare. Clinical differentials include chronic malaria, storage disorders, leukemia, lymphoma, chronic liver disease with portal hypertension and HIV. Preliminary tests show pancytopenia, mild elevation of liver enzymes and hypergammaglobulinemia with reversal of albumin globulin ratio. The aldehyde test has poor sensitivity and specificity.

Diagnosis of visceral leishmaniasis is based on microscopic detection of amastigotes in smears of tissue aspirates or biopsy samples. Bone marrow aspirate or biopsy is frequently the tissue of choice with sensitivity between 55 and 97%. Lymph node aspirate smears (sensitivity 60%), liver biopsy (sensitivity 85%) and splenic aspirates (sensitivity 97%) may be used for diagnosis. Though splenic aspirate has the highest sensitivity, the procedure may result in life-threatening hemorrhage; the procedure is contraindicated if the prothrombin time exceeds control value by 5 seconds or platelet count is below 40,000/mm^3.

Immunochromatographic strip (dipstick ELISA) testing of blood from a finger prick for leishmanial anti-K39 antibody has been used successfully in field serodiagnosis with a sensitivity of 90–100% and high specificity (90%) in symptomatic patients. Titers to rK39 decrease following successful therapy and tend to rise in cases of relapse, thus making it useful to recognize treatment failures. This test is useful in clinical management in resource-poor areas. Newer methods with high sensitivity and specificity include the detection of Leishmania antigen and antibody in the urine.

Treatment

Drug therapy Treatment of leishmaniasis is based on pentavalent antimonials; however, increasing resistance to antimonials is a major problem, most evident in North Bihar, where the failure rate for this treatment is more than 50%. Pentavalent antimony [Sb (V)] can be given in the form of sodium stibogluconate [Sb (V) 100 mg/ml] or meglumine antimonate [Sb (V) 85 mg/ml]; both may be given intravenously or intramuscularly with equal efficacy (Table 10.13). The dose of Sb (V) is 20 mg/kg for 28 days. IM injections are painful and better avoided. IV injections should be diluted 1:10 with 5% dextrose and infused slowly over 20 min. Adverse effects include vomiting, fatigue, arthralgia, myalgia, abdominal pain, elevated serum transaminases, lipase and amylase levels, bone marrow depression, and ECG abnormalilties, including

Table 10.13: Treatment of visceral leishmaniasis

Drug	*Dose*	*Duration*
Pentavalent antimony	20 mg/kg/day IM or IV	28 days
Amphotericin B	1 mg/kg IV alternate day	28 days
Liposomal amphotericin B	2 mg/kg/day IV	5 days
Miltefosine	2.5 mg/kg/day oral	28 days
Pentamidine	4 mg/kg thrice weekly IV/IM	8 weeks
Paramomycin (Aminosidine)	16–20 mg/kg/day IV/IM	21 days

nonspecific ST and T-wave changes and T-wave flattening or inversion. Weekly ECG monitoring is recommended during therapy. In some resistant cases, addition of IFNγ to Sb (V) has been successful in inducing remission.

Amphotericin B is an effective treatment used in Sb (V) resistant cases. It is toxic and requires admission to the hospital for a prolonged period. The main side effects include fever, chills, thrombophlebitis, hypokalemia and renal failure. The alternative is to use the liposomal form, which is highly effective and less toxic, but continues to be very expensive. Liposomal amphotericin B is currently the drug of choice for resistant leishmaniasis. Compared to conventional amphotericin, its concentration in reticuloendothelial cells is ten-fold more and is ten times less toxic. Recent studies using lower doses of this agent show that it may be cost-effective even in resource poor areas with high antimonial resistance.

Miltefosine is the first effective orally active drug against leishmaniasis. Studies of treatment with this drug for 3 or 4 weeks have shown a cure rate of 95–100%; cure rates at 6 months' followup are also comparable to amphotericin B. It has the added benefit of a very good safety profile; gastrontestinal side effects are frequent but mild.

Other drugs used in treating leishmaniasis include pentamidine and paromomycin. Pentamidine is used in treatment-resistant cases of visceral leishmaniasis. Its use is limited by its substantial toxicity, including hypotension, hypoglycemia, renal damage, injection abscess, and diabetes, necessitating close inpatient monitoring. Though paromomycin is inexpensive, nephrotoxicity and ototoxicity are concerns with its use. Sitamaquine, another oral agent, is associated with a 50–67% cure rate.

Supportive care Severe anemia and thrombocytopenia may necessitate packed cell and platelet transfusion. The child should receive a nutritious diet and coexisting nutritional deficiencies should be corrected. Concurrent infections should be treated using appropriate antimicrobial agents.

Response to treatment Fever, spleen size, hemoglobin, blood cell counts, serum albumin and body weight are monitored for response to therapy. In most patients, the fever subsides within 7 days, blood counts and hemoglobin levels rise, the patient feels better and spleen becomes smaller within 2 weeks. Parasitological cure should be documented at the end of therapy by splenic or bone marrow aspiration. As relapses are common in this disease, patient should be followed for at least 6 months before a longterm definite cure is pronounced. The spleen may take 6 months to 1 yr to regress completely. Relapse is suggested by an increase of spleen size, a fall in hemoglobin levels and is confirmed by the demonstration of parasites.

Treatment of PKDL Treatment is indicated only for those who have severe and prolonged disease. Pentavalent antimonials (2 month course) and liposomal amphotericin B are both effective.

Leishmania–HIV Coinfection

Leishmaniasis may occur in HIV infected persons, either as an opportunistic infection or as a result of reactivation of subclinical infection. A high index of suspicion is required in patients with HIV with the typical presentations of visceral leishmaniasis such as pyrexia, pancytopenia and hepatosplenomegaly. However, the presentation may be atypical with prominent gastrointestinal or upper respiratory tract involvement and absence of hepatosplenomegaly. The Leishmania antibody test (direct agglutination test) is frequently negative. The main risk group is intravenous drug users where an anthroponotic cycle is involved, with leishmania organisms present in used syringes being inoculated intravenously.

In leishmania–HIV coinfection, leishmaniasis is often intractable and is associated with a high relapse rate. Visceral leishmaniasis in HIV infection is being proposed for inclusion in the Centers for Disease Control clinical category C for the definition of AIDS as an indicator disease. Although treatment of coinfection has not been adequately studied, pentavalent antimonials are commonly used. Meglumine antimonite, liposomal amphotericin and oral miltefosine have been used in small studies. Secondary prophylaxis, using pentavalent antimonials administered once every 28 days or liposomal amphotericin B every 21 days, prevents relapse and improves survival. Secondary prophylaxis should be continued at CD4 counts below 200/mm^3.

Prevention and Control

Control of leishmaniasis involves controlling the source of infection and eradicating the vector and depends on local epidemiology. Where sand flies are mostly endophilic (rest mostly indoors after feeding), spraying houses with insecticide is effective, while use of treated and untreated bed nets is effective where sand flies are endophagic (feed mainly indoors). Insecticide treatment of dogs and dog collars is useful where canines are important reservoirs. In India, where anthroponotic transmission is important, effective treatment of patients, especially those with PKDL (who may act as longterm reservoirs), has been found to be effective in controlling transmission when combined with vector control.

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Amebiasis

Amebiasis is defined as infection with *Entamoeba histolytica*. Clinical features of amebiasis range from

asymptomatic colonization to amebic dysentery and invasive extraintestinal amebiasis, occurring most commonly as liver abscess.

Epidemiology

E. histolytica is thought to infect 10% of the world's population and 2–55% Indians. However, these may be overestimates, because two morphologically identical, genetically distinct but apparently nonpathogenic Entamoeba species, namely *E. dispar* and *E. moshkovskii*, cause most asymptomatic cases.

Amebic dysentery and extraintestinal amebiasis is associated with a high rates of morbidity and mortality. It is less common in children, accounting for less than 3% of diarrhea in children below 5 yr.

Etiopathogenesis

An ingested cyst divides in the small intestine to form 8 trophozoites that colonize the mucosa of the large intestine. Trophozoites cause tissue invasion and destruction with little or no local inflammation, resulting in characteristic flask shaped ulcers in cecum, transverse colon and sigmoid colon. Extraintestinal complications occur when trophozoites invade the bloodstream and migrate through the portal circulation to lodge, most commonly, in the liver. *Amebic liver abscess* is usually single (95%) and more frequently involves the posterosuperior part of right lobe of the liver. The abscess may regress, rupture or disseminate; transdiaphragmatic rupture may cause amebic empyema and pulmonary amebiasis. Rare complications include amebic involvement of peritoneum, pericardium, pleura, lungs, brain, genitourinary system and skin.

Clinical Features

Asymptomatic cyst passage is the most common manifestation of *E. histolytica*. In most cases the infection resolves spontaneously; uncommonly, amebic dysentery and other invasive manifestations may occur later.

After an incubation period varying from weeks to months, about 10% individuals colonized with *E. histolytica* develop symptomatic disease. Amebic colitis presents as abdominal pain or tenderness (in 80%), with watery, bloody or mucous diarrhea. Some may have only intermittent diarrhea alternating with constipation. Fever is unusual. Occasionally, fulminant amebic colitis may occur, with profuse bloody diarrhea, fever, widespread abdominal pain, diffuse tenderness and pronounced leukocytosis. Toxic megacolon, ameboma, cutaneous amebiasis and rectovaginal fistulae can occur as complications of intestinal amebiasis.

Amebic liver abscess, seen in about 1% of infected individuals, may occur months to yr after infection. While some individuals may have concurrent amebic colitis, more commonly, there are no bowel symptoms. The child usually presents with fever with chills and rigors and right upper quadrant pain of acute onset (<10 days). Examination reveals toxic appearance, right upper quadrant tenderness and hepatomegaly; jaundice is unusual (10–15%). Cough along with dullness or crepitations in the right lung base may be present. Complications include rupture into the pleura pericardium and superinfection with bacteria.

Diagnosis

Diagnosis of amebic colitis is established by demonstration of motile trophozoites by direct microscopic examination of fresh fecal sample. At least 3 stool specimens taken on consecutive days should be examined because the test has poor sensitivity (<60%; ~90% with 3 fresh samples). Stool contains plenty of erythrocytes but few leukocytes, unlike bacillary dysentery, where leukocytes are plentiful. Presence of ingested erythrocytes within trophozoites is pathognomonic for *E. histolytica*. Presence of cysts of *E. histolytica* in stool samples is of no clinical significance and should not be treated.

Serological tests are routinely employed for diagnosis of extraintestinal disease with *E. histolytica* especially for differentiating amebic from pyogenic liver abscess. They are positive in 70–80% patients with invasive disease at presentation and in >90% cases beyond first week of symptoms. IgG antibodies persist for yr after *E. histolytica* infection, whereas the IgM antibodies indicate present or current infection. Commonly used serologic tests in clinical practice are ELISA, IHA and IFA. Serological response as detected by ELISA becomes negative 6–12 months after infection. The IHA test is simple to perform and has been shown to be highly specific (~99%) and sensitive. The test may stay positive for as long as 10 yr following complete recovery, limiting its utility in endemic areas. The IFA test is rapid, reliable, reproducible and helps to differentiate amebic liver abscess from other nonamebic etiologies.

In case of a liver abscess chest radiograph shows elevated diaphragm and pleural reaction on the right side. Ultrasound, CT, MRI, or isotope scan can localize the abscess in most cases. Leukocytosis without eosinophilia, mild anemia, raised alkaline phosphatase, and a high erythrocyte sedimentation rate (ESR) are common laboratory findings in these patients.

Treatment

The practice of giving antiamebic drugs for all children presenting with diarrhea should be strongly discouraged since amebiasis is relatively uncommon in young children.

Metronidazole is the drug of choice for treating amebic colitis (Table 10.14). Alternatives include tinidazole, orindazole and secnidazole. Since metronidazole does not destroy the cysts, a luminal agent (paromomycin, iodoquinol, or diloxanide furoate) should be used to eradicate colonization. When possible, fulminant amebic

Table 10.14: Treatment of amebiasis

Medication		*Pediatric dose*		*Adult dose*
Invasive disease		**Colitis**	**Liver abscess**	
Tissue amebicide	Metronidazole	35–50 mg/kg/day for 7–10 days (in 3 divided doses)	35–50 mg/kg/day for 7–10 days (in 3 divided doses)	750 mg 8 hourly
	or			
	Tinidazole	50 mg/kg/day for 3 days (once daily)	50 mg/kg/day for 3–5 days (once daily)	2 g once a day
Followed by				
Luminal amebicide	Paromomycin	25–35 mg/kg/day for 7 days (in 3 divided doses)	25–35 mg/kg/day for 7 days (in 3 divided doses)	25–35 mg/kg/day (in 3 divided doses)
	or			
	Diloxanide furoate *or*	20 mg/kg/day for 7 days (in 3 divided doses)	20 mg/kg/day for 7 days (in 3 divided doses)	500 mg 8 hourly
	Iodoquinol	30–40 mg/kg/day for 20 days (in 3 divided doses)	30–40 mg/kg/day for 20 days (in 3 divided doses)	650 mg 8 hourly
Asymptomatic intestinal colonization				
	Paromomycin *or*	As above		
	Diloxanide furoate *or*	As above		
	Iodoquinone	As above		

colitis, even with perforation, is managed conservatively, with the addition of antibiotics to deal with bowel flora.

Most amebic liver-abscesses, even large ones, can be cured without drainage. Most patients show a response to treatment (reduced fever and abdominal pain) within 72–96 hr. Individuals with amebic liver abscess should also receive a luminal agent to eliminate intestinal colonization. Therapeutic aspiration guided by CT in the treatment of uncomplicated amebic liver abscess is controversial. Large amebic liver abscesses (>300 ml) may benefit from aspiration with decrease in duration of hospital stay and faster clinical improvement recovery when compared to those managed medically alone. Abscess cavity resolves slowly over a period of several months.

Aspiration is reserved for individuals in whom diagnosis is uncertain (where pyogenic abscess or bacterial superinfection is a concern), those who have not responded to metronidazole therapy (persistent fever or abdominal pain after 4 days of treatment), individuals with large left lobe abscesses (because of the risk of rupture into the pericardium), size more than 8–10 cm (suggesting impending rupture) and severely ill patients with an accelerated clinical course and large abscesses. Aspiration, percutaneous catheter drainage, or both, improve outcomes in the treatment of amebic empyema after liver abscess rupture, and in treatment of amebic pericarditis or peritonitis.

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Giardiasis

Giardiasis, caused by *Giardia lamblia* (also known as *G. intestinalis* or *G. duodenalis*), is a major cause of diarrhea in children and in travelers.

Epidemiology

The infection is endemic in developing countries with poor sanitation. Individuals with malnutrition, humoral immunodeficiencies and cystic fibrosis are particularly susceptible. Children appear to be more severely affected than adults.

Etiopathogenesis

Giardia exists in two stages, cysts and trophozoites. Outside the human body it exists in the form of cysts. Cysts are hardy, capable of surviving in cool, moist environments for up to 2 months and in water that has been routinely chlorinated, but are destroyed by boiling for 10 min. Transmission of infection is through cysts, which may be ingested in contaminated water or food or spread by direct person-to-person contact. Ingestion of 10–100 cysts is sufficient for causing infection. Low pH of the duodenum facilitates excystation and release of trophozoites. Trophozoites colonize the duodenum and proximal jejunum of the host, where they attach to the intestinal brush border. It is believed that the infection causes diarrhea via a combination of intestinal malabsorption and hypersecretion. These effects cause malabsorption and maldigestion and in addition, may facilitate the development of chronic enteric disorders, including inflammatory bowel disease and irritable bowel syndrome.

Clinical Features

The incubation period after ingestion of cysts is 1–2 weeks. Most infections in both children and adults are *asymptomatic*. *Symptomatic* infections are more common in children than in adults and usually take the form of acute diarrhea with sudden onset of explosive, watery, foul smelling stools, along with nausea and anorexia; others may also have abdominal distension, flatulence, epigastric cramps and mild fever. There is no blood or mucus in stools. The illness may last 3–4 days and is usually self limiting in normal immunocompetent children. Variable degree of malabsorption may occur. Some patients may have a protracted course, with persistent or recurrent mild to moderate symptoms such as brief episodes of loose foul smelling stools alternating with constipation. Persistent diarrhea may be seen in 30–50% cases. A few children may develop chronic diarrhea, lactose and fat malabsorption and failure to thrive.

Diagnosis

Diagnosis of giardiasis is established by microscopic examination of at least 3 fresh specimens of stools collected on alternate days. There is no blood or leukocytes in stools. Enzyme immunoassay (EIA) and direct fluorescent antibody test for *Giardia* antigens in stools have been reported to have better sensitivity and require less expertise than traditional microscopy. Where diagnosis is strongly suspected, duodenal aspirate or biopsy may yield high concentration of *Giardia* when fresh wet mount is examined for trophozoites. Where duodenal aspirate is negative, intestinal biopsy may be considered in presence of features like lactose malabsorption or abnormal radiographic findings (edema or segmentation in small intestine), or a suggestive setting like absent secretory IgA or hypogammaglobulinemia.

Treatment

All symptomatic cases—acute and persistent diarrhea, failure to thrive and malabsorption syndrome—require drug treatment. Asymptomatic cyst carriers are not treated except in specific situations like for outbreak control or for prevention of spread from toddlers to immunocompromised family members. Treatment options are listed in Table 10.15.

Table 10.15: Agents for treatment of giardiasis

Drug	*Dosage*
Drugs of choice	
Tinidazole	50 mg/kg (maximum 2 g) orally, single dose
Metronidazole	5–10 mg/kg (maximum 250 mg) orally q 8 hr for 7 days
Nitazoxanide	Age 1–3 yr: 100 mg orally q 12 hr for 3 days Age 4–11 yr: 200 mg orally q 12 hr for 3 days Age >11 yr: 500 mg orally q 12 hr for 3 days
Alternative agents	
Albendazole	10–15 mg/kg (maximum 400 mg) orally once daily for 5 days
Mebendazole	200 mg orally q 8 hr for 5 days
Paromomycin*	10 mg/kg orally q 8 hr for 5–10 days
Furazolidone^	1.5 mg/kg (maximum 100 mg) orally q 6 hr for 7–10 days
Quinacrine	2 mg/kg (maximum 100 mg) orally q 8 hr for 5 days

*Has poor intestinal absorption; useful in treating giardiasis during pregnancy

^Monoamine oxidase inhibitor; significant food and drug interactions if used for >5 days

Suggested Reading

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Amebic Meningoencephalitis

The term amebic meningoencephalitis refers to infection of the central nervous system by free living amebae. The disease occurs in two clinical forms: primary amebic meningoencephalitis caused by *Naegleria fowleri* and granulomatous amebic encephalitis induced by amebae of *Acanthamoeba* and *Balamuthia* genera.

Primary Amebic Meningoencephalitis

N. fowleri causes fulminating meningoencephalitis, infecting mostly children and healthy young adults. History of swimming in fresh water lakes, pools and ponds, usually during hot summer months, is common. The amebae enter the nose through contaminated water (rarely, air), penetrate the nasal mucosa and the cribriform plate and travel along the olfactory nerves to the brain leading to a diffuse hemorrhagic necrotizing meningoencephalitis. Microscopic demonstration of motile amebae in fresh cerebrospinal fluid is required for diagnosis. CSF evaluation shows a high WBC count (usually in thousands per mm^3) with a polymorphonuclear predominance and elevated protein.

Disease progression is usually rapid, and might lead to death within 5–10 days. A combination of high dose amphotericin B, both intravenous and intrathecal, along with rifampicin and chloramphenicol, has been employed successfully.

Granulomatous Amebic Encephalitis (GAE)

This is an infection with *Acanthamoeba* species and, rarely, *Balamuthia* species, that is acquired through lung or skin and spreads hematogenously. The infection is usually seen in immunocompromised children, e.g. those with AIDS, SLE or postrenal transplantation. Clinically, the disease has a subacute or chronic course similar to tubercular meningitis. Untreated, the condition is fatal. CSF

examination reveals motile trophozoites or cysts of *Acanthamoeba* in addition to elevated proteins and lymphocytic leukocytosis. A triplex real time PCR assay for simultaneous identification of *Acanthamoeba* spp., *B. mandriallaris* and *N. fowleri* has been developed. CT scan of brain may reveal granulomatous lesions and ventricular dilatation. Treatment has been attempted with fluconazole, ketoconazole, sulfonamides and cotrimoxazole, but prognosis is poor.

Suggested Reading

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CONGENITAL AND PERINATAL INFECTIONS

Congenital and perinatal infections are often referred to by the acronym TORCH. This refers to toxoplasmosis (T), rubella (R), cytomegalovirus (C) and herpes simplex virus (H or HSV). The 'Others' group (O) is ever expanding and includes several infections like syphilis, malaria, tuberculosis, HIV, HCV, HBV, varicella, enterovirus and parvovirus infections. This section will focus on toxoplasmosis, rubella, cytomegalovirus, herpes simplex and syphilis as they are not discussed elsewhere and share common features.

General Principles

Fetal and neonatal infections occur only with primary infection in the mother. Latent infection or reactivation affects the baby very infrequently, with the exception of syphilis. Not all infections in mother are transmitted to the baby due to the placental barrier and not all infected babies are affected. The transmissibility and severity of fetal affection depends on the timing of gestation. Generally, *infection during the first trimester has the most devastating consequences*. Congenital and perinatal infections can manifest during pregnancy as ultrasonographic findings, soon after birth or later in life. The common manifestations of intrauterine infections are abortions (recurrent only with syphilis), intrauterine growth retardation, intrauterine death, prematurity, deafness, chorioretinitis, aseptic meningitis, microcephaly and mental retardation, lymphadenopathy, hepatosplenomegaly, neonatal hepatitis, anemia, thrombocytopenia and skeletal abnormalities.

Tests that are useful in diagnosis include a complete blood count, liver and renal functions, skeletal survey, fundus examination, hearing evaluation and imaging of the central nervous system. Specific diagnosis is generally by serology and the TORCH screen is often ordered for. However, it must be remembered that serologic diagnosis by IgM and IgG estimation is tricky, should be done in both baby and mother and is interpreted with caution. Treatment is possible and rewarding for toxoplasmosis, syphilis and herpes simplex, only partly successful for CMV and not available for rubella.

Congenital Toxoplasmosis

The maternal primary infection is generally subclinical. In HIV infected or immunocompromised women, reactivation of latent infection may also affect the fetus. The transmissibility increases but the risk of fetal disease decreases with advancing pregnancy. The clinical manifestations are similar to those mentioned earlier. The classical triad of toxoplasmosis includes intracranial calcification, hydrocephalus and chorioretinitis. Infants asymptomatic at birth may later present with mental retardation and deafness. Diagnosis is confirmed by demonstrating a positive toxoplasma IgM in serum of the affected child. Treatment is recommended for all affected babies even if they are asymptomatic. Therapy is with pyrimethamine, sulfadiazine and folinic acid for a period of 1 yr. Since maternal infection results from ingestion of food or water contaminated with oocysts or tachyzoites in infected meat, prevention centers around advising pregnant women to wash fruits and vegetables carefully, limit contact with soil and refrain from eating undercooked meat.

Congenital Rubella

Transmissibility is highest in the first trimester and so is the rate of fetal disease (90% at <11 weeks). The fetus is completely spared if infection occurs beyond 16 weeks. Clinical manifestations are as mentioned earlier; the classical triad of congenital rubella syndrome consists of deafness, cataract and congenital heart disease. Delayed manifestations such as diabetes mellitus and renal disease have also been described. Diagnosis is by demonstration of positive rubella IgM in cord or neonatal blood. No treatment exists. A unequivocal diagnosis of rubella in the first trimester of pregnancy is an indication for maternal termination of pregnancy. Vaccinating all children and particularly all adolescent girls against rubella is strongly recommended to reduce the burden of congenital rubella.

Congenital Cytomegalovirus (CMV) Infection

Congenital CMV is reported to be the commonest congenital infection in developed countries. Data from developing countries is lacking. Most fetal infections occur with primary infection in the mother; transmission and fetal disease occur throughout pregnancy. The overall transmission rate with primary infection is 30% and 10% of all infected babies are symptomatic. CMV remains latent in the body and can reactivate any time; similarly reinfections can also occur. The transmission risk with reactivation or reinfection is only 1% and only 5–10% of infected babies are symptomatic.

Congenital infection can affect all organ systems; periventricular calcification is characteristic of CMV (Fig. 10.25). CMV transmission can also occur during delivery and breastfeeding and is of consequence only in the preterm and very low birthweight babies. In this

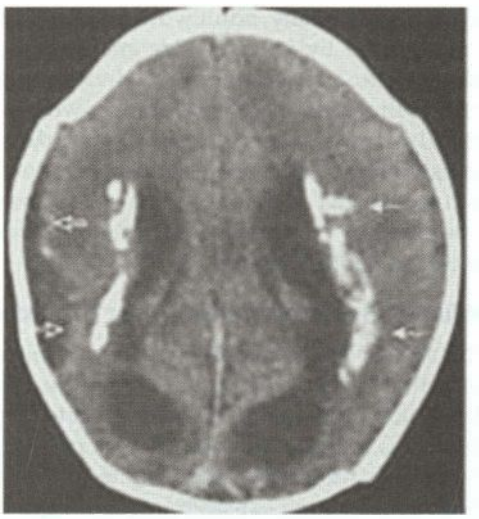

Fig. 10.25: Classical periventricular calcification of CMV

setting it presents as a sepsis like illness with pneumonia and respiratory distress. CMV transmission due to blood and blood products can also cause anemia, thrombocytopenia and hepatosplenomegaly in preterm infants. The diagnosis of congenital CMV can be confirmed by a positive IgM in cord blood or in the first two weeks of life. The sensitivity is low and a negative IgM does not rule out CMV. A positive CMV IgM after the first 2 weeks of life can also occur due to postnatal transmission and is not an accurate method for diagnosis. In babies older than 2 weeks, a positive quantitative CMV PCR is the method of choice. Antiviral treatment with ganciclovir or valganciclovir is available but is indicated only in patients with progressive disease and deafness.

Perinatal Herpes Simplex Virus (HSV)

Transmission of HSV to babies usually occurs in mothers who develop primary genital herpes at the time of delivery. Reactivation of genital herpes is associated with very low rates of transmission and fetal affection. Infected babies may be asymptomatic or have fulminant disease. Three forms of disease have been described; a vesicular eruption limited to skin, eyes and mouth, CNS disease presenting as meningitis with seizures and altered sensorium and disseminated disease presenting as sepsis-like illness with high mortality. The latter two may not have associated skin eruptions, which further complicates diagnosis. Diagnosis is by Tzanck smear of the skin lesions, culture or PCR for the virus from lesions or from CSF. HSV serology has no role in making diagnosis. Treatment with intravenous acyclovir should be started promptly in neonates with suspected or confirmed infection. Babies born to mothers with active herpetic lesions during delivery should be watched carefully for disease. Elective cesarean section should be considered in mothers with active primary genital herpes and unruptured membranes.

Congenital Syphilis

Syphilis is the only maternal infection that is associated with recurrent abortions; hence, the TORCH screen should include VDRL. Maternal syphilis can be transmitted throughout pregnancy, more commonly during later pregnancy as the placenta thins down. Apart from the clinical features mentioned earlier, infected babies have other pathognomonic features like skeletal lesions, snuffles, pneumonia alba and bullous skin lesions. Some babies manifest delayed features like depressed nasal bridge, notched central incisors, keratitis, saber shins and frontal bossing. Diagnosis is by quantitative VDRL estimation. Treatment is with procaine penicillin; ceftriaxone should be used if procaine penicillin is not available.

Suggested Reading

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HELMINTHIC INFESTATIONS

General Considerations

Helminthiasis is caused by three groups of worms, i.e. nematodes (roundworms), trematodes (flukes), and cestodes (tapeworms). These organisms differ markedly in their life cycles, mode of infections and pathogenesis.

Nematodes (roundworms). Intestinal nematodes are the most common type of helminthiasis. These include *Ascaris lumbricoides, Strongyloides stercoralis, Ancylostoma duodenale and Necator americanus* (all residing in the small intestine). *Trichuris trichiura* (located in the large intestine) and *Enterobius vermicularis* (lodged in cecum). Transmission occurs directly by ingestion of eggs in case of Enterobius, trichuris, and *Ascaris* or indirectly by larval penetration of the skin, i.e. in *Ancylostoma* and *Strongyloides*. Adult stages inhabit the human intestinal lumen but do not multiply there, with the exception of *Strongyloides*.

Nonintestinal nematodes include microfilariae such as *Brugia malayi, B. timori* or *Wuchereria bancrofti*. These result in filariasis characterized by lymphangitis and lymphadenitis. *Onchocerca volvulus* and *Loa loa* are other nonintestinal nematodes or public health importance. Filariasis is transmitted to man by larvae during mosquito bite, while black fly transmits the larvae in onchocerciasis.

Other tissue dwelling nematodes include *Toxocara canis, Trichinella spiralis* and *Dracunculus medinensis*. All tissue nematodes have a complex life cycle that involves an intermediate host, mostly an arthropod, except *Trichinella spiralis*, which is transmitted directly.

Trematodes (flukes). Schistosoma (spp. *haematobium, Mansoni, japonicum*, etc.) also known as blood fluke is a major flatworm infestation in Africa, South America and Middle East. Man is the definitive host and gets infected by penetration of intact skin by cercariae. Snails are the main primary intermediate host. Clinical manifestations may be

acute (dermatitis, Katayama disease) or chronic (fibro-obstructive sequelae due to egg embolism in liver, lungs and genitourinary tract).

Flukes of liver, e.g. *Clonorchis sinensis, Opisthorchis, Fasciola hepatica*, lung, e.g. *Paragonimus westermani*, and intestine, e.g. *Fasciolopsis buski, Heterophyes* are also known. These flukes have two intermediate hosts. Snail is the common primary intermediate host to all of them while fish, crabs and aquatic plants serve as secondary intermediate hosts to liver, lung and intestinal flukes, respectively. Transmission to the definitive host, i.e. man occurs through ingestion of metacercariae lodged on aquatic plants and animals, including fish.

Cestodes (tapeworms). These include giant tapeworms (*Taenia saginata, T. solium* and *Diphyllobothrium latum*), dwarf tapeworms (*Hymenolepsis nana*) and zoonotic cestodes (*Echinococcus granulosus* and *E. multilocularis*). Man acquires *Echinococcus* through ingestion of eggs, while *T. saginata* and *T. solium* infect humans through ingestion of cysticerca in contaminated food. *D. latum* infection is carried to man by ingestion of cysts in fresh water fish.

Ascaris lumbricoides (Roundworm)

Ascariasis is the most common worm infestation of the humans, infecting nearly one-fourth of the world's population. Preschool children are vulnerable to infection due to their hand to mouth behavior. Infection may also be acquired through ingestion of contaminated fruits and vegetables. Most infected individuals are asymptomatic due to low worm load. Clinical manifestations occur due to pulmonary hypersensitivity and intestinal complications.

Clinical features Symptoms may be produced by migration of larvae through lungs (pulmonary ascariasis) or the presence of adult worms in the intestine. Pulmonary ascariasis presents as Löeffler syndrome, characterized by fever, cough, dyspnea, wheeze, urticaria, eosinophilia and lung infiltrates. Pulmonary ascariasis should be differentiated from other causes of Löeffler syndrome, namely, visceral larva migrans caused by *Toxocara canis* or hookworm, schistosomiasis, pulmonary aspergillosis and tropical pulmonary eosinophilia.

Intestinal manifestations of ascariasis include abdominal distension, vomiting, vague abdominal discomfort and irritability. The child may pass adult worms in the vomitus or feces. In heavy worm infestation, small bowel obstruction can occur due to a mass of entangled worms. Occasionally, worms migrate to aberrant sites such as biliary and pancreatic ducts, where they can cause cholecystitis, cholgangitis, pancretitis and rarely intrahepatic abscess. As parasites compete with host for nutrients, heavy worm infestation may be associated with poor growth and nutritional deficiencies in young children.

Management The diagnosis is established by identification of characteristic eggs in stool samples by microscopy. Occasionally, adult worm in feces or vomitus can be recognized by its large size and smooth cream-colored surface. Ultrasound can identify worms in pancreaticobiliary ducts. Occasionally, worms can be incidentally diagnosed on contrast studies of the gastrointestinal tract, appearing as string shadows due to barium in the worms' alimentary canal, or as linear filling defects outlined by contrast media. Therapy of ascariasis is described in Table 10.16.

Enterobius vermicularis (Pinworm or Threadworm)

Enterobius vermicularis is a small (1 cm long), white, thread-like worm that lives in the cecum, appendix, ileum and ascending colon. Eggs are not usually liberated in the gut. Gravid females migrate at night into the perianal region and release eggs there. The egg become infective within 6 hr. Perianal scratching causes transfer of eggs 10 finger nails. Infection occurs when eggs are ingested. The larvae hatch and mature within the intestine. Perianal itching, especially in night is the most common complaint.

Management Stool microscopy is not useful as eggs are generally not passed in the stools. Eggs can be demonstrated by examining the perianal swab obtained early in the morning before the child has defecated. Alternatively, a strip of transparent cellulose acetate tape is applied with sticky side down on the perianal region. The tape is lifted and pressed on a glass slide with the sticky side down. All the members of the family should be treated simultaneously to prevent cross-infection and reinfection. The nails of the child should be cut short and scrubbed. Single dose mebendazole or albendazole or pyrantel pamoate are highly effective. The course may be repeated after 2 weeks (Table 10.16).

Ancylostoma duodenale and *Necator americanus* (Hookworm)

Hookworm infestation is an important cause of iron deficiency anemia. Most infected persons are asymptomatic.

Clinical features Chronic blood loss due to hookworm infestation causes iron deficiency anemia and, occasionally, hypoproteinemia. Only heavily infected children become symptomatic.

Infective larvae may produce a pruritic maculopapular eruption known as ground itch; at the site of skin penetration. Larvae migrating through lungs may also cause transient lung infiltration, but this is less common than with Ascaris. Nonspecific complaints like abdominal pain, anorexia, and diarrhea have also been attributed to the hookworm infection.

Diagnosis The diagnosis is established by identifying the characteristic oval hookworm eggs in the feces. Eggs of the two species are indistinguishable. Blood examination reveals microcytic, hypochromic anemia, occasionally eosinophilia.

Table 10.16: Therapy of helminthiasis

Infestation	*Drug*	*Oral dose*	*Comments*
Roundworm	Albendazole[1]	400 mg once	Drug of choice
	Mebendazole	100 mg q 12 hr for 3 days *or* 500 mg once	Drug of choice
	Ivermectin[2]	150 to 200 µg/kg once	Drug of choice
	Nitazoxanide	Age 1–3 yr: 100 mg q 12 hr for 3 days Age 4–11 yr: 200 mg q 12 hr for 3 days Age >11 yr: 500 mg q 12 hr for 3 days	Option
Hookworm	Albendazole[1]	400 mg once	Drug of choice
	Mebendazole	100 mg 12 hr for 3 days *or* 500 mg once	Drug of choice
	Pyrantel pamoate[3]	11 mg/kg (max 1 g) daily for 3 days	Drug of choice
Pinworm[4]	Albendazole[1]	400 mg once; repeat in 2 weeks	Drug of choice
	Mebendazole	100 mg once; repeat in 2 weeks	Drug of choice
	Pyrantel pamoate[3]	11 mg/kg base (max 1 g)once; repeat in 2 weeks	Drug of choice
Trichuriasis, whipworm	Albendazole[1]	400 mg once daily for 3 days	Drug of choice
	Mebendazole	100 mg q 12 hr for 3 days	Alternative
	Ivermectin[2]	200 µg/kg once daily for 3 days	Alternative
Filariasis	Diethylcarbamazine	2 mg/kg q 8 hr for 12 days	Drug of choice
	Doxycycline	100–200 mg once daily for 6–8 weeks	Adjunctive; kills symbiotic bacteria within worms
	Albendazole[1]	400 mg once	Adjunctive; reduces microfilaria
	Antihistamines or steroids		Adjunctive; reduce allergic reactions to disintegrating microfilariae
Strongyloidiasis[5]	Ivermectin[2]	200 µg/kg once daily for 2 days	Drug of choice
	Albendazole[1]	400 mg once daily for 7 days	Alternative
Adult tapeworm	Praziquantel[6]	5–10 mg/kg once	Drug of choice
	Niclosamide[7]	50 mg/kg once	Alternative
Dwarf tapeworm	Praziquantel[6]	25 mg/kg once	Drug of choice
	Niclosamide[7]	5–15 kg: 1 g on day 1; then 500 mg/day for 6 days >15 kg: 1.5 g on day 1; then 1 g/days for 6 day	Alternative
Cysticercosis	Albendazole[1]	7.5 mg/kg (max 400 mg) q 12 hr for 8–30 day;	Drug of choice
	Praziquantel[6]	33.3 mg/kg q 8 hr on day 1; then 16.7 mg/kg	Drug of choice
	Anticonvulsants; corticosteroids; surgery	q 8 hr for 29 days	Adjunctive role in neurocysticercosis
Hydatid cyst	Albendazole[1]	7.5 mg/kg (max 400 mg) q 12 hr for 1–6 mo	Drug of choice
Visceral larva migrans	Albendazole[1]	400 mg q 12 hr for 5 days (up to 20 days)	Drug of choice
	Mebendazole	100–200 mg q 12 hr for 5 days (up to 20 days)	Drug of choice
	Corticosteroids		Adjunctive role in severe disease, eye involvement
Cutaneous larva migrans	Albendazole[1]	400 mg daily for 3 days	Drug of choice
	Ivermectin[2]	200 µg/kg once daily for 1–2 days	Drug of choice
Tropical pulmonary eosinophilia	Diethylcarbamazine	2 mg/kg q 8 hr for 12–21 days	Drug of choice

[1]Taken with food; fatty meal increases bioavailability
[2] Taken on an empty stomach with water; safety not established for children <15 kg
[3]Suspension can be mixed with milk or fruit juice
[4]Entire household should be treated
[5] Severely affected and immunocompromised individuals may require longer treatment course and/or combination of the two therapies
[6]Taken with liquids during a meal
[7]Must be thoroughly chewed or crushed and swallowed with a small amount of water

Treatment Eradication of worms is achieved with albendazole, mebendazole or pyrantel pamoate (Table 10.16) Anemia is treated with oral iron therapy. Severe anemia may require a packed cell transfusion.

Filariasis

Lymphatic filariasis is caused by *Wuchereria bancrofti, Brugia malayi or Brugia timori*. These thread-like parasites reside in the lymphatic system of the host. Most heavily

infested areas in India are the States of Andhra Pradesh, Tamil Nadu, Kerala, Orissa, Bihar and Eastern Uttar Pradesh. In India, most of the cases (98%) are accounted for by bancroftian filariasis. Brugian filariasis is mostly found in Kerala.

Epidemiology *W. bancrofti* is mainly transmitted in India through *Culex quinquefasciatus* and has no animal reservoirs. *Brugia malayi* is transmitted through *Mansonia annulifera* and *M. uniformis* mosquitoes; reservoirs have been observed in cats, dogs and monkeys.

The infected mosquito bites a person and deposits the larvae in the skin. These may remain in the skin or cross this barrier to enter the lymphatics. In humans, larvae develop into adult male or female worms over a period of 4–6 months. Adult worms reside in afferent lymphatics. Adult female worms produce microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when a mosquito ingests microfilariae during a blood meal. Mosquito serves as the intermediate host in whom the microfilariae develop into infective larval stage.

Clinical features Following the inoculation of infective larvae into man, a time lag of 8–16 months may occur before the clinical symptoms appear. Alternatively, microfilaremia may remain asymptomatic.

Acute clinical manifestations are characterized by recurrent attacks of fever, associated with inflammation of the lymph nodes (lymphadenitis) and lymph vessels (lymphangitis). Episodes can recur as frequently as 10 times per yr and usually subside spontaneously over 7 to 10 days. Lymph nodes are enlarged. Both upper and lower limbs are involved in bancroftian and brugian infections. Genital lymphatic involvement occurs exclusively in bancroftian infections.

Chronic stage. Lymphadenitis may progress to lymphatic obstruction resulting in changes associated with elephantiasis. The chronic signs usually do not develop before the age of 25 yr. In bancroftian filariasis, major chronic signs consist of hydrocele, chyluria, lymphedema and elephantiasis. In brugian filariasis, leg below the knee and arm below the elbow are characteristically involved.

Management Microfilariae can be detected in blood, urine (in chyluria), hydrocele fluid, or tissues. Examination of a thick blood film is still the best diagnostic tool. Adult worm may be detected in biopsy of lymph nodes. Lymphoscintigraphy may demonstrate lymphatic abnormalities even in asymptomatic patients. Diethylcarbamazine is the drug of choice for lymphatic filariasis and is active against both adult worms and microfilariae. Repeated courses may be required for complete parasitic cure (Table 10.16). Ivermectin is effective against microfilariae in a single oral dose of 400 µg/kg of body weight. A combination of ivermectin and albendazole is also effective in clearing microfilariae.

Tropical Pulmonary Eosinophilia

It occurs in persons having filarial infection. The most common age group is 20–30 yr. The syndrome is thought to represent an allergic and inflammatory response elicited by rapid clearance of microfilariae from bloodstream by immune mechanisms. There is paroxysmal nocturnal cough. dyspnea, fever, wheeze, loss of weight and easy fatigability. There may be lymphadenopathy and hepatosplenomegaly. Chest radiographs may be normal but generally show increased bronchovascular markings, discrete opacities or diffuse miliary mottling. The diagnosis is suggested by residence in filarial endemic area, compatible clinical presentation, eosinophilia (>2000/mm^3), elevated IgE levels (>1000 IU/ml) and high titers of antimicrofilarial antibodies in the absence of microfilaria in bloodstream. Microfilariae may be demonstrable in the lungs and lymph nodes. Patients respond to diethylcarbamazine with improvement in symptoms within 3 to 7 days.

Visceral Larva Migrans

Visceral larva migrans is caused by nematodes that are normally parasitic for other species, namely, *Toxocara canis* (dog roundworm) or *Toxocara cati* (cat roundworm). Following ingestion of *Toxocara* eggs, the larvae hatch and invade the intestinal mucosa to be carried by bloodstream to different organs. There is intense host inflammatory response.

Clinical manifestations include fever, cough, wheezing hepatomegaly, pulmonary, infiltration endophthalmitis and neurological disturbances. Patients may have low grade fever with recurrent respiratory tract infections. Marked eosinophilia is present. The diagnosis is confirmed by ELISA for toxocaral antibodies.

Albendazole and mebendazole are effective drugs (Table 10.16). Alternative drugs include diethylcarbamazine and thiabendazole (25 mg/kg twice daily for 1–3 weeks).

Taenia solium and *saginata*

These worms are also known as the pork tapeworm (*T. solium*) and beef tapeworm (*T. saginata*), reflecting the principal intermediate hosts for each of them. Man is the only definitive host for both the parasites. Pork tapeworm consists of a scolex with suckers and hooks by means of which it attaches to the intestinal wall. Hooks are absent in *T. saginata*. Usually, only one adult worm is found in the intestine which may live for up to 25 yr.

Clinical features Most infections with adult worms are asymptomatic. Some children may develop nonspecific complaints like nausea, pain in abdomen, and diarrhoea. Carriers have an increased risk of developing cysticercosis by repeated autoinfection.

Cysticercosis Infection with the intermediate stage (larvae) of *T. solium* results in cysticercosis. Neuro-

cysticercosis is the most common parasitic infection of the CNS and may account for as high as 20–50% cases of seizures. Following ingestion, eggs develop into larvae in the small intestine. Larvae migrate across the intestinal wall and are carried to the target organs by bloodstream. The common target organs for cysticerci are brain, muscle and subcutaneous tissue. The larvae mature into cysticerci in about two months time. The size of cysticerci varies from 2 mm to 2 cm. Clinical manifestations depend on the location, number and size of cysts in the brain and host inflammatory response. Viable cysts generally do not elicit a strong response. On the other hand, degenerating cysts provoke a vigorous host response. Most cysts remain viable for 5–10 yr. Neurocysticercosis may manifest as partial or generalized seizure, raised intracranial tension, focal neurological deficits, or disturbances unconsciousness or behavior.

Management The diagnosis of taeniasis is established by the demonstration of eggs or proglottids in the stools. patients may pass motile segments of worms through anus. Diagnosis of neurocysticercosis is made by CT and MRI of brain. Detection of antibodies by enzyme-linked immunotransfer blot (EITB) has more than 90% sensitivity and specificity. CSF eosinophilia is a helpful finding.

Treatment of taeniasis is similar for both infestations. Niclosamide or praziquantel are effective drugs.

There is no consensus on the management of neurocysticercosis. Various options include observation, anticonvulsant medication, antiparasitic drugs, surgery or a combination of these. Children having seizures and calcified, inactive lesions on CT do not require specific therapy, apart from anticonvulsants. There are two effective anti-cysticercal drugs: albendazole and praziquantel (Table 10.16). During treatment, dying parasities can provoke severe life-threatening inflammatory response, which can be prevented by giving steroids for 2–3 days before and during treatment. The response to albendazole is better than praziquantel. Anti-cysticercal therapy is contraindicated for spinal or ocular disease as drug induced inflammation may produce irreversible organ damage. These lesions, as well as those within the ventricular system, are best managed surgically.

Echinococcosis

Human echinococcosis is caused by larval stages of *E. granulosus* or *E. multilocularis*, and is characterized by production of unilocular or multilocular cystic disease of lung and liver. Clinical manifestations are also known as hydatid disease or hydatidosis.

Clinical feature Symptoms occur due to mass effect of the cysts and are related to the organ in which they occur. Liver cysts present with abdominal pain and a palpable mass. Lung cyst may present with chest pain, hemoptysis and breathlessness. There may be passage of cysts in the urine (hydatiduria) and hematuria following hydatid disease of the kidneys. Rupture or leakage from a hydatid cyst may cause fever, itching, rash, anaphylaxis and dissemination of infectious scolices.

Management Diagnosis is made by ultrasonography and CT scan. USG can reveal the internal membranes of cyst, floating ectogenic cyst material (hydatid sand) and daughter cysts within the parent cyst. These findings are of value in differentiating hydatid cyst from simple cysts of liver. Diagnostic aspiration is generally contraindicated because of risk of infection and anaphylaxis. Antibody detection by ELISA is more sensitive but less specific.

When feasible, surgical removal of cyst is the definitive treatment. Recently surgical excision has been replaced by USG or CT-guided percutaneous aspiration instillation of hypertonic saline or another scolicidal agent and aspiration after 15 min. Medical therapy includes albendazole in a dose of 15 mg/kg/day bid for two weeks repeated for 3–12 courses with 15 days drug-free interval in between two courses (Table 10.16). The efficacy rate is 40–60%. The response to medical therapy is monitored by serial ultrasonography. Surgical removal can be contemplated for a large solitary cyst following albendazole therapy.

Suggested Reading

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11 Diseases of Gastrointestinal System and Liver

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GASTROINTESTINAL SYSTEM

Most diseases of the gastrointestinal (GI) tract present with a few symptoms, such as vomiting, dysphagia, abdominal pain, distension, diarrhea, constipation, gastrointestinal bleeding and failure to thrive. Additionally, other diseases may present with symptoms attributed to the gastrointestinal tract. Appropriate evaluation requires an assessment of symptoms and signs, listing differential diagnosis and planning investigations in order of least to most invasive.

Investigations

The chief tools for evaluating gastrointestinal disorders are broadly classified as follows:

Stool examination. pH, reducing substances, microscopy for pus cells, blood, fat, eosinophils or parasites; culture; ELISA for specific pathogens, toxin assay for *Clostridium difficile*.

Radiological imaging. These provide information on both structural and functional abnormalities, and include plain abdominal radiograph; barium studies (swallow, meal, follow-through, enteroclysis and enema); ultrasonography and guided tissue sampling; computed tomography (CT) plain, angiography, enterogrphay or enteroclysis); magnetic resonance imaging (MRI); plain, angiography, enterography or cholangiopancreatography.

Transit studies. Include video fluoroscopy for swallowing, small bowel and colonic transit.

Nuclear medicine tests using radioisotopes. Meckel scan, ^{99m}Tc tagged red blood cell scan for GI bleeding, gastric emptying scan, and urea breath test for *Helicobacter pylori*.

Endoscopy. Upper GI study, colonoscopy, enteroscopy, double balloon enteroscopy, capsule endoscopy, endoscopic retrograde cholangiopancreatography (ERCP).

Manometry. Esophageal, antroduodenal, colonic and biliary; useful in diagnosing motility disorders of esophagus, small and large intestine and sphincter of Oddi. 24 hr pH metry and impedance monitoring provide information on gastroesophageal reflux.

Tests for evaluation of malabsorption. D-xylose assay; estimation of fecal fat, fecal α-1 antitrypsin (protein-losing enteropathy); chymotrypsin or elastase (pancreatic insufficiency); pancreatic stimulation test; lactose or lactulose hydrogen breath test; Schilling test (vitamin B12 malabsorption).

Histopathology. Biopsy of esophagus, stomach, or small or large intestine; special stains and immunohistochemistry enable detection of pathogens or tumor cells.

Serology. Antibodies to *H. pylori*; anti-tissue transglutaminase (celiac disease); antinuclear cytoplasmic antibodies (inflammatory bowel disease); antienterocyte antibody (autoimmune enteropathy) and serology for HIV.

Vomiting

Vomiting refers to acute expulsion of gastric contents through the mouth. Vomiting should be differentiated from regurgitation, especially in infants. Regurgitation is the involuntary and effortless expulsion of small amounts of gastric contents that is not accompanied by nausea. Recurrent or persistent vomiting requires thorough evaluation and treatment. Persistent vomiting may be complicated by dehydration, hypokalemic hypochloremic metabolic alkalosis, malnutrition and constipation. Vigorous vomiting can uncommonly result in esophageal tear (Mallory-Weiss syndrome) or rupture (Boerhaave syndrome).

Vomiting is a common, but often nonspecific, symptom that may be acute, chronic or recurrent (Table 11.1). Short-lasting vomiting with acute onset is the most common form and is often caused by viral infections. Chronic vomiting may be (i) cyclic, characterized by ≥5 stereotype episodes occurring at high intensity (≥4 emesis/hr) and infrequently (≤2 episodes/week), with normalcy in between; or (ii) chronic, characterized by frequent episodes

Table 11.1: Causes of vomiting

Gastrointestinal	*Nongastrointestinal*
Acute	
Gastroenteritis	Infections, e.g. urinary tract infection, meningitis, encephalitis, pertussis
Hepatitis	Raised intracranial tension
Appendicitis	Diabetic ketoacidosis
Small intestinal obstruction, (malrotation, volvulus, intussusception)	Defects in fatty acid oxidation or respiratory chain
Cholecystitis	Drug or toxin induced
Pancreatitis	
Chronic	
Gastroesophageal reflux	Raised intracranial tension
Gastritis	Chronic sinusitis
Gastric outlet obstruction (hypertrophic pyloric stenosis, peptic ulcer)	Uremia
Small bowel obstruction (duodenal stenosis, annular pancreas, superior mesenteric artery syndrome)	Overfeeding
Food allergy	
Achalasia cardia	
Gastroparesis	
Eosinophilic esophagitis	
Recurrent	
Cyclic vomiting	Urea cycle defects
Abdominal migraine	Diabetic ketoacidosis
Malrotation with volvulus	Addison disease

(>2/week) at low intensity (1–2 emesis/hr). While chronic vomiting is usually caused by a gastrointestinal etiology, cyclic vomiting is predominantly due to neurologic, metabolic and endocrine causes.

Evaluation

A detailed history and examination often gives clue to the diagnosis. The etiology of vomiting varies according to age; while infectious causes occur across all ages, most congenital anomalies, e.g. atresia or stenosis and metabolic disorders, present in the neonatal period or infancy. The first step is to find out whether the vomitus is bilious or nonbilious. This determines the site of disease. Lesions beyond the ampulla of Vater cause bilious vomiting and those proximal to it lead to nonbilious vomiting. Associated features may indicate etiology, e.g. vomitus containing stale food of previous day (suggests gastric outlet obstruction), visible peristalsis (obstruction), vomiting in early morning (intracranial neoplasm or cyclic vomiting syndrome), vertigo (middle ear disorder) and hypotonia (mitochondrial disorders). The 'red flag' symptoms and signs in a child with vomiting are the presence of blood or bile in the vomitus, severe abdominal pain with abdominal distension or tenderness, projectile vomiting, persistent tachycardia or hypotension, neck stiffness and/or photophobia. These patients need immediate investigation in a hospital.

Workup for chronic vomiting should include evaluation for cause with blood chemistry (blood sugar, electrolytes, serum amylase and liver enzymes); ultrasound abdomen, upper gastrointestinal endoscopy and, as indicated by available clues, barium studies (meal and small bowel follow-through), gastric emptying scan, CT or MRI brain, metabolic testing or urine analysis. It is important to remember that children with cyclic vomiting should be evaluated during symptomatic attack before starting intravenous fluids since test results are typically noncontributory during asymptomatic periods.

Evaluation of a child with acute vomiting should include assessment of hydration, electrolytes, creatinine and plain X-ray abdomen (in suspected surgical causes). Promethazine and ondansetron are useful in postoperative vomiting and to abort episodes of cyclical vomiting. Ondansetron, given alone or with dexamethasone, is preferred for chemotherapy related vomiting. Domperidone and metoclopramide are useful in patients with gastroparesis. Antihistaminics like diphenhydramine help in motion sickness. Management of the underlying condition is essential.

Some common disorders presenting with vomiting are described below:

Idiopathic Hypertrophic Pyloric Stenosis

Hypertrophic pyloric stenosis is the most common surgical disorder of the gastrointestinal tract in infants. The pylorus is thickened and elongated with narrowing of its lumen due to hypertrophy of the circular muscle fibers of pylorus.

Clinical presentation. The classical presentation is with nonbilious vomiting that gradually increases in frequency and severity to become projectile in nature. The disorder is 4–6 times more common in boys than girls. Most patients present with vomiting starting beyond 3 weeks of age; however, about 20% are symptomatic since birth and presentation is delayed until 5 months of age in others. Constipation is common. Recurrent and persistent vomiting causes dehydration, malnutrition and hypochloremic alkalosis. As the stomach muscles contract forcibly to overcome the obstruction, a vigorous peristaltic wave can be seen to move from left hypochondrium to umbilicus, particularly on examination after feeding. A firm olive-shaped mass is palpable in the midepigastrium in 75–80% infants, especially after feeds.

Evaluation. Ultrasound abdomen is the diagnostic investigation and shows muscle thickness of >4 mm and pylorus length of >16 mm. The ultrasound is 100% sensitive and nearly 90% specific in diagnosis of hypertrophic pyloric stenosis. However, in case of doubt, an upper GI barium study can show a consistent elongation of the pyloric channel (Fig. 11.1) or an upper GI endoscopy is performed.

11

Differential diagnosis. Gastroesophageal reflux disease, cow milk protein allergy, antral or pyloric web are considered in patients without a palpable pyloric mass and normal ultrasound.

Management. The treatment includes rapid correction of dehydration and electrolyte abnormalities. The treatment of choice is surgical; a pyloromyotomy (Ramstedt's operation) is performed.

Cyclic Vomiting

This is defined as occurrence of stereotypic episodes of intense nausea and vomiting as defined previously, with complete normalcy between episodes and the absence of a metabolic, neurologic or gastrointestinal disorder. An episode may last for an hour to 10 days and occurs at least 1 week apart. Episodes are often triggered by physical or emotional stress. The patient should have had at least 5 episodes in all or 3 episodes during a 6-month period. Typically the attacks begin in early morning with symptoms of autonomic surge, e.g. lethargy, pallor, mild fever, headache, tachycardia, hypertension, diarrhea and abdominal pain. Most subjects have onset in preschool or school age. Family history of migraine and/or motion sickness is noted in 30–40% cases.

Evaluation. A thorough history and physical examination at presentation helps identify children that require further diagnostic testing. Presence of bilious vomiting, abdominal tenderness and/or severe abdominal pain; attacks precipitated by intercurrent illness, fasting and/or high protein meal; abnormalities on neurological examination (altered sensorium, papilledema or motor asymmetry), or development of continuous or chronic vomiting help identify subjects with high likelihood of an organic disease of the gastrointestinal, or neurologic system or a metabolic defect. Symptoms may, overlap with abdominal migraine.

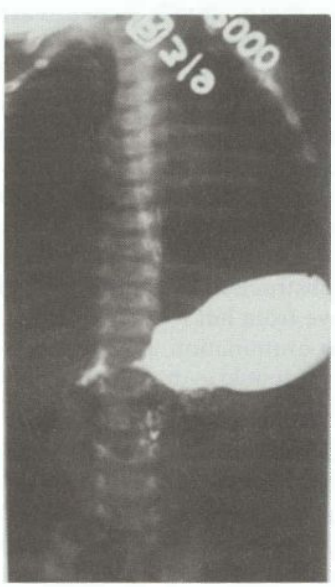

Fig. 11.1: Upper gastrointestinal barium study show narrowing and elongation of pyloric channel in idiopathic hypertrophic pyloric stenosis

Management. Known precipitants of the episodes should be avoided. Management of an attack includes providing a quiet environment, administration of intravenous fluids, use of serotonin 5 HT3 antagonists such as ondansetron (0.3–0.4 mg/kg/dose IV q 4–6 hr up to 20 mg) and sedation with lorazepam (0.05–0.1 mg/kg/dose IV every 6 hr). Agents recommended for prophylaxis against future attacks are cyproheptadine (0.25–0.5 mg/kg/day in two or three divided doses) in children below 5 yr and, in older children, amitriptyline (initiate at 0.25–0.5 mg/kg/day at bedtime; may increase upto maximum of 1.0–1.5 mg/kg/day) or propranolol (0.25–1 mg/kg/day; up to 10 mg q 8–12 hr).

Gastroesophageal Reflux Disease (GER)

GER is passage of gastric contents into the esophagus with or without regurgitation and vomiting. GER is a normal physiologic process that occurs several times a day in healthy infants, children and adults. When this reflux of gastric contents causes troublesome symptoms and/or complications, it is known as GER disease (GERD). About 50% of healthy 3–4-month-old infants regurgitate at least once per day and most of them outgrow this by 1 yr of age. Followup studies suggest that infants with persistent spilling beyond 3 months of age are at an increased risk of developing GERD in childhood. Children with obesity, repaired esophageal atresia, cystic fibrosis, hiatal hernia, preterm babies and a family history of GERD are at risk of developing severe chronic GERD. Neurologically impaired children like those with cerebral palsy have increased risk of severe GERD due to multiple factors like low pressure of the lower esophageal sphincter and predominant supine position.

Clinical features The common symptoms associated with GERD in children are: (i) recurrent regurgitation with or without vomiting; (ii) weight loss or poor weight gain; (iii) irritability (in infants); (iv) heartburn or chest pain (older children); (v) hematemesis, dysphagia and odynophagia (if complicated by esophagitis or stricture esophagus); (vi) wheezing, stridor, cough and hoarseness; and (vii) Sandifer syndrome, an uncommon manifestation, characterized by spasmodic torsional dystonia with arching of the back and opisthotonic posturing.

Evaluation A detailed history and physical examination are generally sufficient to establish the diagnosis of GER. Useful investigations are as follows.

24 hr ambulatory esophageal pH monitoring is a validated method for quantitative measurement of esophageal acid exposure. It is also used to evaluate the efficacy of antisecretory therapy and to correlate symptoms (e.g. cough, chest pain) with acid reflux episodes.

Combined 24 hr multiple intraluminal impedance and pH monitoring detects acid, weakly acid and nonacid reflux episodes. It is thus superior to pH monitoring alone which detects only acid reflux episodes. Its main utility is to evaluate the temporal relationship between symptoms and GER episodes.

Upper GI endoscopy may show erosions or mucosal breaks in the distal esophageal mucosa, the most reliable evidence of reflux esophagitis. Mucosal erythema and pallor are highly subjective and nonspecific findings. Complications like stricture esophagus (Fig. 11.2) and Barrett's esophagus can be picked up at endoscopy. Histological features like elongated rete pegs, basal cell layer hyperplasia and dilated intercellular spaces, alone or in combination, are suggestive of reflux esophagitis.

Endoscopic biopsy is important to evaluate other causes of esophagitis and to diagnose Barrett's esophagus. While not useful for the diagnosis of GERD, *barium contrast radiography* helps rule out anatomic abnormalities of the upper gastrointestinal tract that may cause symptoms similar to those of GERD. This investigation should be done in all infants with vomiting.

Tests of esophageal motility are not required for diagnosis of GERD.

Nuclear scintigraphy has a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms due to GERD.

Empiric trial of acid suppression. Using proton pump inhibitors for up to 4 weeks is justified in older children or adolescents with typical symptoms suggesting GERD (heart burn or chest pain). There is no evidence to support its use as a diagnostic test in infants and young children where symptoms of GERD are less specific.

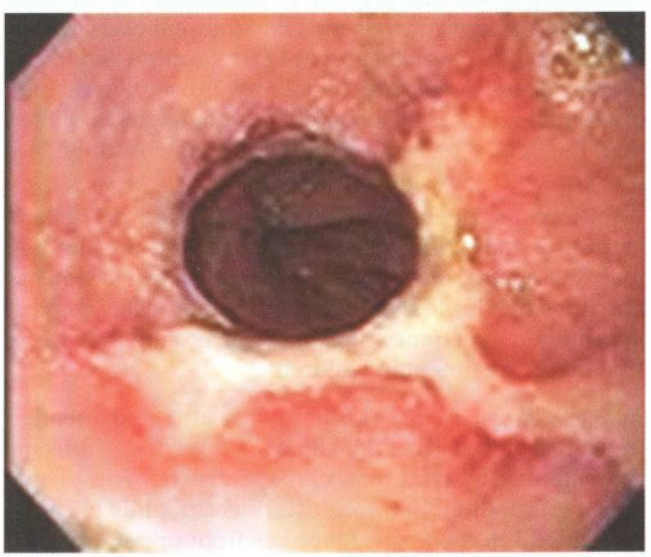

Fig. 11.2: Upper gastrointestinal endoscopy showing ulceration with stricture formation in reflux esophagitis

Management Treatment of GERD depends on patient's age and nature and severity of symptoms and includes lifestyle changes, pharmacologic therapy and surgery.

Lifestyle changes Parental education, guidance and support are essential and usually sufficient to manage healthy, thriving infants with symptoms due to physiologic GER. Infants should be placed in left lateral position with the head end elevated by 30° in the postprandial period to reduce the frequency of reflux. Cow milk protein allergy is sometimes a cause of unexplained crying and vomiting in infants. Therefore, formula-fed infants with recurrent vomiting may benefit from a 2–4 weeks trial of an extensively hydrolyzed protein formula. Adding thickening agents such as rice cereal (one tablespoon, i.e. ~10 g in 60 ml milk) to formula does not decrease the time with pH <4 (reflux index) measured by esophageal pH studies, but it does decrease the frequency of overt regurgitation. Infants with inadequate weight gain because of losses by regurgitation may benefit from increasing the energy density of formula. Careful followup with charting of caloric intake and weight gain is essential.

For children and adolescents with GERD, measures that are useful include: dietary modification (to avoid caffeine, chocolate and spicy foods), weight loss if obese, sleeping in the left lateral position with elevation of the head-end of the bed, avoidance of alcohol and cessation of smoking.

Pharmacologic therapies. Medications used for GERD include agents to buffer or suppress gastric acid secretion. *Histamine-2 receptor antagonists* like ranitidine decrease acid secretion by inhibiting receptors on gastric parietal cells. They are superior to placebo but less effective than proton pump inhibitors (PPI) for relief of symptoms and healing of esophageal mucosa. Development of tachyphylaxis is a major problem with these agents. They are chiefly used in infants with GERD in whom PPI are still not approved for use.

Proton Pump Inhibitors (PPIs) inhibit acid secretion by blocking Na^+–K^+-ATPase, the final common pathway of parietal cell acid secretion. PPIs are the agent of choice for GERD. PPI maintain intragastric pH ≥4 for long periods and inhibit meal-induced acid secretion. PPIs currently approved for use in children are omeprazole (0.7–3.3 mg/kg/day, max 80 mg), lansoprazole (0.6–1.6 mg/kg/day; weight <30 kg: 15 mg, >30 kg: 30 mg; max 60 mg) and esomeprazole (<20 kg: 5–10 mg, >20 kg: 10–20 mg OD). Children with typical symptoms of chronic heartburn should be treated with lifestyle changes and 2–4 weeks trial of PPI. In patients with endoscopically diagnosed reflux esophagitis or established nonerosive reflux disease, PPIs for 3 months constitute initial therapy. Headache, diarrhea, constipation and nausea may be seen in 10–14% of children on PPIs. In addition, PPIs may increase rates of community-acquired pneumonia and gastroenteritis.

Antacid therapy is not recommended for most patients with GERD. Currently, there is insufficient evidence to

justify the routine use of *prokinetic or other agents* such as cisapride, metoclopramide, domperidone, bethanechol, erythromycin or baclofen for GERD.

Surgical therapy. Fundoplication decreases reflux by increasing the baseline lower esophageal sphincter (LES) pressure, decreasing the number of episodes of transient lower esophageal sphincter relaxation and the nadir pressure during swallow-induced relaxation, increasing the length of intra-abdominal esophagus, accentuating the angle of His and reducing a hiatal hernia if present. Antireflux surgery may be of benefit in selected children with chronic-relapsing GERD. Children with underlying disorders predisposing to the most severe GERD are also at the highest risk for operative morbidity and post-operative failure.

Suggested Reading

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Dysphagia

Dysphagia refers to a sensation of food being hindered in its passage from the mouth to the stomach, i.e. difficulty in swallowing. *Odynophagia* is painful swallowing and *globus* is the sensation of a lump in the throat. Dysphagia can be divided into two distinct groups:

Oropharyngeal or transfer dysphagia. Presence of drooling, choking, coughing and nasal regurgitation suggests oropharyngeal dysphagia. Disorders involving chewing, oral transfer or pharyngeal phase of swallowing cause this. The main causes are cerebral palsy, bulbar poliomyelitis, muscular dystrophy, brainstem tumors and neuropathy.

Esophageal dysphagia. This occurs due to conditions involving esophageal phase of swallowing, i.e. coordinated peristalsis of esophageal body with simultaneous relaxation of LES. Etiology of esophageal dysphagia can be broadly divided into two groups: motor causes (e.g. achalasia cardia and diffuse esophageal spasm) and structural causes (e.g. strictures, foreign body, Schatzki's ring, esophageal web, eosinophilic esophagitis and extrinsic compression by aberrant vessel or mediastinal mass).

Differential Diagnosis and Evaluation

The important causes of dysphagia and their evaluation are shown in Table 11.2 as well as discussed below.

Congenital esophageal stenosis. This may be of three types: web or diaphragm, fibromuscular stenosis and stenosis due to cartilaginous tracheobronchial remnants. Symptoms of vomiting or chest infection due to aspiration typically develop around 6 months of age when weaning is started. The cartilaginous type occurs in distal esophagus and should be differentiated from achalasia and peptic stricture. Children with this type of congenital stenosis have high risk of perforation on endoscopic dilatation and should be treated surgically.

Foreign bodies in esophagus. Infants and toddlers are at maximum risk due to the habit of oral exploration. Sharp foreign bodies and batteries can cause damage by perforation secondary to pressure or chemical necrosis and can present with dysphagia, mediastinitis and/or upper gastrointestinal bleeding. The vast majority of foreign bodies pass unimpeded through the GI tract. The most frequent sites of impaction are at the cricopharynx, mid esophagus at tracheal bifurcation and just above the LES.

The child presents acutely with choking and dysphagia. Sometimes the ingestion is unwitnessed and the foreign body is completely asymptomatic initially, presenting days to weeks later with complications like abscess, fistula or bleed. Guidelines for management recommend that no foreign body should be left in esophagus for more than 24 hr. Endoscopic removal under sedation or anesthesia is the standard of therapy.

Achalasia cardia. This is a motor disorder of the esophagus characterized by loss of esophageal peristalsis, increased LES pressure and absent or incomplete relaxation of LES with swallow.

Children present with dysphagia, vomiting, weight loss, respiratory symptoms and slow eating whereas toddlers present with coughing and feeding aversion with failure to thrive. The onset is gradual and the average age at diagnosis in children is around 8–9 yr. The barium swallow shows esophageal dilatation with beak-like narrowing at the LES (Fig. 11.3). Manometry is the most sensitive and specific tool and shows absent peristalsis in esophagus; incomplete/absent LES relaxation and raised intraesophageal pressure. Endoscopy is useful to exclude other etiologies, of dysphagia. The esophagus is dilated and the scope passes through the gastroesophageal junction with some gentle pressure.

Endoscopic pneumatic balloon dilatation or Heller's cardiomyotomy with antireflux procedure are the two main therapeutic modalities. Botulinum toxin injection has been tried but due to short duration of action (a few months) and limited experience, it cannot be recommended as a first line of treatment in children.

Eosinophilic esophagitis. This entity has attracted attention in the recent past. This is a clinicopathological syndrome characterized by symptoms of food impaction, dysphagia and regurgitation, presence of ≥15 eosinophils per high power field in esophageal biopsies from upper, mid and lower esophagus and exclusion of other disorders with similar presentation, such as GERD. Diagnosis is based

Table 11.2: Evaluation and management of esophageal lesions that cause dysphagia

Etiology	*Investigation*	*Finding*	*Treatment*
Corrosive (acid or alkali) stricture	Barium swallow and meal; upper GI endoscopy	Narrowing in one or multiple, short or long, segments of esophagus; may show contracted stomach or pyloric stenosis	Endoscopic dilatation (Balloon or Savary Gilliard dilators)
Stricture after repair of tracheo-esophageal fistula	Barium swallow	Narrowing of a short segment of esophagus	Endoscopic dilatation
Congenital stricture	Barium swallow; CT chest	Stricture in middle or lower esophagus; carti-laginous tissue in stricture	Endoscopic dilatation or surgery
Postsclerotherapy stricture	Barium swallow; upper GI endoscopy	Narrowing in lower end of esophagus	Endoscopic dilatation
Peptic stricture	Barium swallow; endoscopy; 24 hr pH study	Narrowing in lower esophagus; may show hiatus hernia or erosions	Endoscopic dilatation; proton pump inhibitor after dilatations
Foreign body	Plain X-ray; upper GI endoscopy	Type of foreign body and site of impaction	Endoscopic retrieval
Achalasia cardia	Barium swallow; esophageal manometry	Beak-like narrowing in lower esophagus	Pneumatic dilatation; Heller's cardiomyotomy
Infectious esophagitis (in immunocompromised children)	Upper GI endoscopy; endoscopic biopsy	White curd-like deposits (*Candida*); ulcers (cyto-megalovirus, herpes)	Fluconazole (*Candida*); ganciclovir (cytomegalovirus) or acyclovir (herpes)

GI gastrointestinal

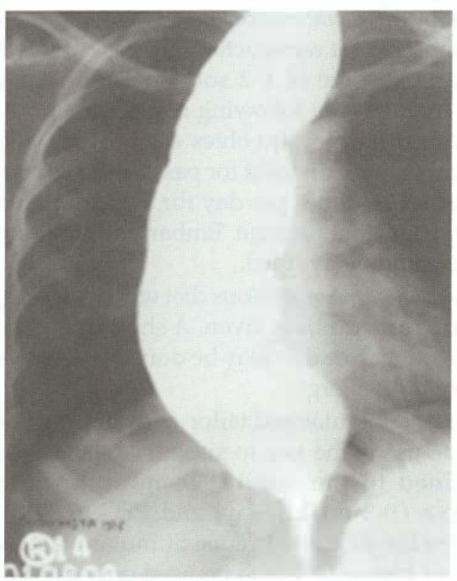

Fig. 11.3: Barium swallow showing achalasia cardia

on typical endoscopic features of plaques, furrows or concentric rings (called 'trachealization' of esophagus) and histology. Treatment options include the use of elemental formula, elimination diets, or topical corticosteroids. Resolution of the condition with food elimination diets provides evidence that it is a food-antigen driven process.

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Constipation

Constipation is defined as a delay or difficulty in defecation, present for 2 or more weeks and sufficient to cause significant distress to the patient. It is increasingly being recognized as a very common problem in children and is associated with both physical and psychological morbidity and a poor quality of life. The normal stool frequency decreases from 4 or more per day during infancy to once per day at 4 yr of age. A stool frequency of <2/week is considered abnormal for all ages. Consti-pation can be divided into two groups: functional or organic. The organic causes of constipation are listed in Table 11.3. In a study of 135 Indian children with constipation, 85% had functional constipation and 15% had an organic etiology (most commonly, Hirschsprung disease, cerebral palsy and meningomyelocele).

Approach

A detailed history and physical examination is the most useful tool for making a diagnosis of constipation. The

details about pattern of stooling, time of first passage of meconium, presence of blood in stools, diet, stressful life events, drug intake and previous surgeries should be known. A predominantly liquid and low fiber diet (milk based) is common and contributes to constipation. A complete physical and neurological examination is essential. Examination for features of spina bifida (pigmentation or tuft of hair on lower back), power in lower limbs, perianal sensation, voluntary contraction and tone of anal sphincter and amount and consistency of stool in rectum on per rectal examination are extremely useful for diagnosis. Presence of 'red flags' like failure to thrive, blood in stools, recurrent fever with loose stools (enterocolitis), recurrent vomiting, lump in abdomen, recurrent chest infections and features of hypothyroidism should alert the physician to suspect organic etiology.

Functional Constipation

The increase in intake of low residue diet and sedentary lifestyle is responsible for the increase in functional constipation in children. Functional constipation is defined by the presence of at least 2 or more of the following criteria: (i) two or fewer defecations in the toilet per week; (ii) at least 1 episode of fecal incontinence per week; (iii) history of retentive posturing or excessive volitional stool retention; (iv) history of painful or hard bowel movements; (v) presence of a large fecal mass in the rectum; and (vi) history of passage of large diameter stools that may obstruct the toilet.

Children with functional constipation pass large or hard stools and display stool withholding behavior, characterized by stiffening of whole body and screaming in infants, to walking on tiptoes or tightening of buttocks in older children. This is often misunderstood by parents as if the child is trying to defecate. Often an acute illness, change in diet, coercive toilet training or nonavailability of clean toilet leads to nonpassage of stools. The stools become hard and cause pain on passage which leads to association of defecation with pain and withholding. This further increases stool size and hardness with more pain on defecation and a vicious cycle of constipation is initiated. Children with functional constipation often have abdominal pain (10–70%), anorexia (10–25%), enuresis or urinary tract infections (30%) and psychological problems (20%).

Table 11.3: Causes of constipation

Intestinal nerve/muscle disorders: Hirschsprung disease, intestinal neuronal dysplasia, pseudo-obstruction, spinal cord abnormalities (tethered cord, myelomeningocele)
Anorectal: Anteriorly placed anus, anal stenosis, rectal stricture, pelvic mass (sacral teratoma)
Systemic disease: Hypothyroidism, celiac disease, diabetes insipidus, diabetes mellitus, hypercalcemia, cystic fibrosis, myotonic dystrophy
Developmental: Mental retardation, autism
Drugs: Opiates, anticholinergic agents, phenobarbitone, vincristine, lead

Management No investigations are required for diagnosis in the majority of children with functional constipation. However, an X-ray abdomen may be done to document impaction in select situations, e.g. an obese child who is not willing for a per rectal examination. Two main steps in the management are disimpaction and maintenance therapy.

Disimpaction is required in patients who have a rectal impaction, i.e. presence of a large hard mass of feces on per rectal examination. Rectal impaction is responsible for progressive dilatation of the rectum over time and increased threshold volume for rectal sensation and defecation. This 'clean out' is essential if maintenance therapy is to be effective. The oral route is preferred over rectal as it is less invasive. Total bowel wash is done to clean the entire colon using polyethylene glycol (PEG) in a dose of 1.5 g/kg/day for 3–4 days at home. Alternatively, PEG electrolyte solution can be given in the dose of 15–40 ml/kg/hr till the rectal output is clear and devoid of solid fecal material. In young children, this should be done using a nasogastric tube and in hospital under supervision. The child should be fasting for PEG administration. Intravenous fluids may be required in small children during this period to maintain adequate hydration. An alternative to oral administration of PEG is the use of phosphate enema or sodium dioctylsulfosuccinate enema, 30–60 ml/10 kg body weight to a maximum of 120 ml, once or twice daily for 1–2 days. Repeated rectal enemas should be avoided in children.

The aim of the *maintenance phase* is to promote regular stooling and prevent reimpaction. Success of this therapy is defined as passage of 1–2 soft stools per day and no soiling. It includes the following components:

i. Behavioral training involves establishing a positive routine of sitting on toilet for passing stools after meals regularly (2–3 times per day for 5–10 min) and documenting all stool passage. Embarrassment or punishment should be avoided.
ii. *Dietary changes.* A nutritious diet with fruit/vegetables and adequate fluids is given. A short trial of milk and milk product free diet may be done in cases suspected to have milk allergy.
iii. *Medication.* Regular and tailor-made (as per response) laxative use is the key to success and this should be explained to the family. Osmotic laxatives like lactulose (1–3 ml/kg/day) and PEG (0.8–1.0 g/kg/day) are the first line agents. Stimulant laxatives like senna or bisacodyl are to be used only intermittently as a rescue therapy to avoid impaction. Prokinetics like cisapride are not recommended. In infants, mineral oil and stimulant laxatives should not be used. Glycerin suppository is preferred over enema for impaction in infants. Premature withdrawal of medications is a very common cause of relapse.

Prognosis Most of the children need maintenance therapy for 6–24 months. About 50–60% patients achieve success

at 1 yr and 70–80% in the longterm. Nearly 50% patients will have a relapse after successful therapy. In nearly one-third patients, constipation persists even after puberty.

Other Etiologies of Constipation

A subgroup of children with constipation who fail to respond to medical management despite compliance or have red flags will need evaluation for organic disorders. The main modalities of investigation are as follows.

Rectal biopsy A full thickness rectal biopsy or suction biopsy with mucosa and submucosa is required to rule out Hirschsprung disease, neuronal intestinal dysplasia and hypoganglionosis.

Anorectal manometry In normal persons the internal anal sphincter shows relaxation on distension of rectum with a balloon (or stools). This is known as rectoanal inhibitory reflex and its presence excludes the diagnosis of Hirschsprung disease.

Metabolic screen It is useful to look for hypothyroidism, cystic fibrosis, hypercalcemia, celiac disease and lead poisoning.

MRI of lumbosacral spine It is useful for diagnosis of spina bifida occulta or tethered cord.

Colonic transit study Assessment of total and segmental colonic transit time is done either by radio-opaque markers or by scintigraphy. Based on transit studies, various patterns of colonic motility have been defined: normal colonic transit, slow transit constipation (prolonged transit throughout the colon) and outlet obstruction (delayed transit through anorectum).

Hirschsprung Disease

Hirschsprung disease is the commonest congenital gut motility disorder with an incidence of 1 in 5000 and is characterized by lack of ganglionic cells in the submucosal and myenteric plexuses of the distal intestine. The distal rectum is aganglionic and the aganglionosis extends proximally in a variable length of colon. The absence of enteric neurons leads to tonic contraction of the aganglionic segment and functional obstruction. This multigenic disorder can be familial or sporadic. Down syndrome is one of the most common associated malformations. Hirschsprung disease is classified by the length of involved intestine, with ~75% cases involving only the colon distal to splenic flexure (classic form or short segment disease), ~20% involving colon proximal to splenic flexure and ~5% cases involving entire colon and small bowel as well.

Affected infants present shortly after birth with constipation and signs of distal obstruction. About 60–90% children with Hirschsprung disease fail to pass meconium in first 48 hr of life. Occasionally, the disease is missed and the child presents later with chronic constipation, failure to thrive and episodes of enterocolitis (loose stools with blood and mucus). Presence of empty rectum on per rectal examination with a gush of liquid stools on withdrawal of finger suggests the diagnosis of Hirschsprung disease.

In neonatal period, plain X-ray abdomen reveals bowel distension with multiple air-fluid levels and paucity of air in pelvis. A carefully performed barium enema without prior colonic preparation and slow injection of contrast clearly delineates the narrow aganglionic bowel, transition zone and proximal dilated colon in Hirschsprung disease (Fig. 11.4). In contrast, in functional constipation the rectum is grossly dilated, with a rectum to sigmoid ratio of >1 and absence of transition zone. However, a normal study does not exclude Hirschsprung disease. Absence of rectoanal inhibitory reflex on anorectal manometery suggests Hirschsprung disease. Rectal biopsy is the gold standard in diagnosing Hirschsprung disease, with full thickness biopsy being ideal. Documentation of the absence of ganglionic cells in the myenteric and submucosal plexi is essential for the diagnosis. Hypertrophied nerves with increase in acetyl cholinesterase activity in the parasympathetic nerve fibers are seen in the aganglionic segment. The main differences between functional constipation and Hirschsprung disease are shown in Table 11.4.

Management depends on timing of diagnosis and is essentially surgical; the role of medical management is restricted to stabilizing the general condition and treating episodes of enterocolitis. Definitive surgical treatment involves resection of the aganglionic bowel, pull through and anastomosis of normally innervated ganglionic bowel close to the anal margin. Effort is made to preserve the anal canal and sphincter mechanism, thus preserving

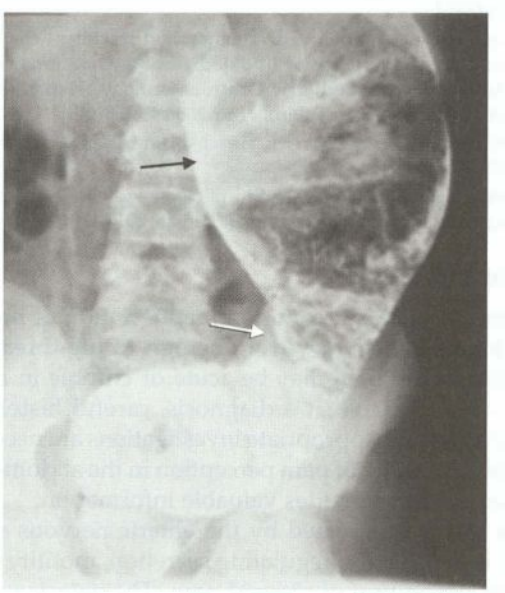

Fig. 11.4: Barium enema showing Hirschsprung disease. Black arrow shows the dilated proximal segment and white arrow shows the transition zone

Table 11.4: Differences between functional constipation and Hirschsprung disease

Feature	*Functional constipation*	*Hirschsprung disease*
Passage of meconium	Normal	Delayed
Onset of symptoms	Beyond 1 yr of age	Within infancy
Encopresis	Yes	No
Stool withholding behavior	Yes	No
Episodes of enterocolitis	No	Yes
Growth failure	No	Yes
Abdomen	Not distended; may have palpable fecoliths	Distended
Per rectal examination	Soft to hard stools present	Empty rectum with gush of stools on removing the finger
Barium enema	Rectum larger than sigmoid; ratio >1	Rectosigmoid ratio <1; transition zone seen
Anorectal manometry	Rectoanal inhibitory reflex present	Rectoanal inhibitory reflex absent
Rectal biopsy	Ganglions present	Ganglions absent

continence. In patients with delayed presentation, a colostomy in the ganglionic bowel is performed initially to relieve the obstruction and allow the dilated hypertrophied proximal bowel to return to normal. Subsequently, definitive surgery is performed. Now less invasive, laparoscopic and single staged surgeries are performed, in comparison to previous 2–3 staged procedure. In the longterm, majority show improvement but nearly two-thirds of patients have some form of constipation or continence problem.

In subjects with other organic cause of constipation, treatment is targeted towards the etiology, e.g. gluten free diet for celiac disease, surgery for tethered cord and hormone supplementation for hypothyroidism.

Suggested Reading

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Abdominal Pain

Abdominal pain is a common manifestation of multiple pathologies which vary from benign to life-threatening conditions. The pain may be acute or chronic in nature. To be able to arrive at a diagnosis, careful history and examination and appropriate investigations are necessary. An understanding of pain perception in the abdomen and location of pain provides valuable information.

The gut is innervated by the enteric nervous system which is involved in regulating secretion, motility and in sensory perception of visceral pain. The enteric nervous system is also influenced by the central nervous system. Stretching of the visceral peritoneum overlying or inflammation results in pain sensation. The pain from the stomach and proximal intestine is sensed in the epigastrium; from the midgut to the periumbilical area; and from the transverse colon to the suprapubic area. The inflammation in the parietal peritoneum causes pain in the overlying abdominal wall. Thus, the pain of appendicitis is referred to the periumbilical area when the inflammation is restricted to the visceral peritoneum, but is perceived in the right iliac fossa when the inflammatory fluid comes in contact with the parietal peritoneum. Pain arising from retroperitoneal structures is referred to the back as it is sensed by the somatic nerves in the posterior abdominal wall. Referred pain is common in abdominal pathologies; a subdiaphragmatic collection on the right side may manifest as right shoulder pain and ureteric pain is referred to the corresponding side as testicular pain. Radiation of pancreatic pain to the back and ureteric pain from loin to groin are also known.

Information obtained from the history and examination that aid in the diagnosis include the age of the patient, duration, type and frequency of pain, any nocturnal episodes, association with eating or defecation, vomiting, blood in stools, diarrhea, constipation or obstipation, fever, joint pain, dysuria, hematuria, weight loss, jaundice, abdominal distension, fever and history of drug intake. Other systemic findings are also important as abdominal pain may be a manifestation of metabolic conditions like diabetic ketoacidosis and acute intermittent porphyria. Lower lobe pneumonia has been reported to account for 2.5–5% of abdominal pain.

Physicians must distinguish abdominal pain due to emergent diagnoses like appendicitis or intussusception from benign conditions like gastroenteritis or constipation. Examination should be meticulous including examination of genitalia as torsion of testes or incarcerated hernia can be easily overlooked. The accuracy of abdominal examination may be improved by distracting a child with toys or engaging in conversation. In infants and young children the manifestation of pain may initially be as incessant cry. Differential diagnosis should be considered in terms of age as many diagnoses are seen more commonly in children of certain age groups as shown in Table 11.5.

Table 11.5: Common causes of abdominal pain

Infants and young children (<2 yr of age): Colic, acute gastroenteritis, intussusception, malrotation of gut with volvulus, incarcerated hernia, trauma, necrotising enterocolitis

Preschool children (2–5 yr of age): Acute gastroenteritis, urinary tract infections, constipation, intussusception, acute appendicitis, malrotation of gut with volvulus, intestinal perforation with peritonitis, choledochal cyst, lower lobe pneumonia, incarcerated hernia, torsion testis, acute pancreatitis, diabetic ketoacidosis, Henoch-Schönlein purpura, Meckel diverticulum, trauma

Older children and adolescents: Acute gastroenteritis, gastritis, acute appendicitis, Crohn disease, constipation, urinary tract infections, dysmenorrhea, pelvic inflammatory disease, ectopic pregnancy, Mittelschmerz, renal calculi, acute pancreatitis, cholecystitis, pneumonia, trauma, early phase of acute viral hepatitis, testicular or ovarian torsion, intestinal obstruction, perforation or peritonitis

The management of these acute conditions includes initial stabilization of the patient followed by specific management which may or may not be surgical. Some of these acute conditions are described briefly:

Acute Appendicitis

Acute appendicitis is the commonest pediatric surgical emergency and is more common in older children. The condition is considered as occurring due to obstruction of the appendiceal lumen by either fecolith or lymphoid tissue, e.g. following viral infection. The obstruction, distention and infection in the appendix causes progressive inflammation and, subsequently, perforation. The patient presents with fever and anorexia followed by pain in the periumbilical area. Vomiting follows the periumbilical pain, unlike in gastroenteritis. As the inflammatory fluid spreads, the pain is then felt in the right iliac fossa (McBurney point) towards which the child characteristically points with a finger. A retrocecal inflamed appendix may be difficult to diagnose and may manifest as spasm at the hip. The diagnosis is most often based on clinical suspicion after history and examination. Palpation reveals localized tenderness and is best elicited if there is rebound tenderness.

Hemogram shows polymorphonuclear leukocytosis. Urine microscopy should be done to rule out urinary tract infection. Abdominal ultrasound detects a dilated (>6 mm) tubular, aperistaltic structure which is not compressible and is surrounded by fluid. Ultrasound has a sensitivity of 85–90% and specificity of 95–100% for diagnosing appendicitis. Computed tomography may be done occasionally if the diagnosis is in doubt. In up to a third of patients, the appendix ruptures before surgery. Intravenous fluids and antibiotics for gram-negative and anaerobic coverage should be given in all cases. Early surgery is necessary to prevent complications like perforation, appendiceal abscess and sepsis.

Intussusception

This is a common cause of intestinal obstruction in children between 3 months and 6 yr. Intussusception refers to the telescoping of a proximal segment of intestine (intussusceptum) into a distal segment (intussuscipiens). This may be ileocolic, colocolic or ileoileal. Most cases occur in infants during the weaning period following introduction a new food, vaccination or upper respiratory tract infection. An area of enlarged submucosal Peyer's patch probably acts as a lead point. Beyond two years of age, the possibility of a submucosal lead point like lipoma and polyp that needs surgical resection should be considered as failure to resect them will lead to recurrence. Inflammatory conditions like Henoch-Schönlein purpura also result in intussusception. As a result, there is venous congestion, bowel edema leading to arterial obstruction, bowel ischemia, necrosis, perforation and shock. The classic triad of abdominal pain, red currant jelly stools (blood and mucus) and palpable mass is seen only in a small percentage of children. X-ray abdomen shows paucity of air in right lower quadrant. Ultrasound is the investigation of choice that confirms the diagnosis ('dough nut' sign) and provides information about presence of a mass as lead point. Vascularity of bowel is best assessed on color Doppler. Barium enema shows a characteristic 'claw' sign if the intussusception involves colon. Early reduction either with saline (under ultrasound guidance), barium contrast (both diagnostic and therapeutic) or with air insufflation is advisable. Reduction with air is safer with lower recurrence rates. Failure of radiological reduction or suspected intestinal gangrene may necessitate surgery and resection.

Gallstones (Cholelithiasis)

Gallstones are of three main types: cholesterol stones with >50% cholesterol, pigment (black or brown) stones and mixed types. Pigment stones are common in children with hemolytic anemia. High-risk groups for gallstones include children with hemolytic anemia, obesity, ileal resection or disease, intake of drugs like ceftriaxone, progressive familial intrahepatic cholestasis type III and total parenteral nutrition. Overall, hemolytic anemia and other predisposing conditions account for 20–30% and 30–40% of gallstones, respectively, while 30–40% cases remain idiopathic.

Clinical presentation. Typical presentation is with acute or recurrent episodes of right upper quadrant or epigastric pain which may radiate to the right shoulder. Icterus and pain radiating to the back is suggestive of a stone in common bile duct or ampulla causing pancreatitis. Fever does not usually occur; however, if present, it suggests presence of cholecystitis or cholangitis.

Diagnosis. Serum bilirubin and alkaline phosphatase are elevated if the stone is in the common bile duct. Raised amylase suggests pancreatitis. Ultrasonography is the investigation of choice for diagnosis of gallstones. MRCP or ERCP have a better accuracy than ultrasonography in diagnosing common bile duct stones. These children

should be investigated with hemoglobin, reticulocyte count, peripheral blood picture and other investigations to look for hemolytic disease.

Management. Symptomatic cholelithiasis is treated by open or laparoscopic cholecystectomy. Common bile duct calculi can be removed by ERCP or at surgery by common bile duct exploration. Children with asymptomatic gallstones without underlying predisposing factors can be safely followed up. Patients with sickle cell disease should be subjected to prophylactic cholecystectomy even if gallstones are asymptomatic. Children with other hemolytic anemias should be screened by ultrasonography if they are being considered for splenectomy and cholecystectomy should be done along with splenectomy in those having gallstones.

Choledochal Cyst

Choledochal cyst refers to abnormal cystic dilatation of biliary tree either as a single or multiple dilatations. This may or may not have associated intrahepatic cystic dilatations. It can present in the neonatal period as cholestasis, mimicking biliary atresia (5% of all neonatal cholestasis), or in the older child with recurrent episodes of pain, obstructive jaundice or mass in right upper quadrant. Acute or recurrent pancreatitis may be the presentation of choledochal cyst, either due to stone impaction at lower end of common bile duct, or due to anomalous pancreatobiliary junction known to be associated with choledochal cyst. Biliary peritonitis secondary to bile duct perforation can complicate a choledochal cyst. Untreated cases may go on to develop secondary biliary cirrhosis.

Ultrasonography is the investigation of choice to diagnose choledochal cyst. MRCP is done to define the anatomy of the pancreaticobiliary ductal system before surgical excision. Definitive treatment is with cyst resection and hepaticojejunostomy in the majority as there is a risk of malignancy (cholangiocarcinoma) in the epithelium of the cyst if left *in situ*. Antibiotics and supportive therapy are required before surgery for a child presenting with obstructive jaundice and cholangitis.

Malrotation

Rotational abnormalities developing during the maturation of the gut cause recurrent obstruction, occurring as either the Ladd's band or volvulus of the gut over the narrow mesenteric pedicle. About 80–90% cases of volvulus occur within the first year of life. Abdominal pain with bilious vomiting suggests small bowel obstruction; abdominal distension may not be a prominent finding. Findings of malrotation are confirmed on barium meal follow through (BMFT), which shows duodenojejunal junction on the right of the spine (rather than to the left of midline at the level of pylorus), an abnormally positioned caecum and small bowel loops on the right side of abdomen (Fig. 11.5). If volvulus is also present, the contrast

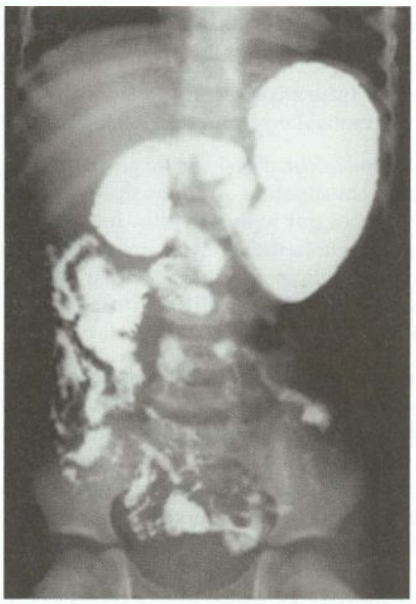

Fig. 11.5: Barium meal follow through showing malrotation of intestine

abruptly tapers into a corkscrew appearance at the level of the second portion of duodenum.

After resuscitation, emergency laparotomy is required for correction of the defect, usually by the Ladd's procedure, which includes derotation of the volvulus, division of the Ladd's band, widening of the base of the mesentery, placement of bowel in a state of nonrotation and appendicectomy.

Peptic Ulcer

Both gastric and duodenal ulcers occur infrequently in children. Ulcers may be primary, i.e. related to *Helicobacter pylori* or secondary, e.g. due to drugs (NSAIDs, steroids), stress (shock, sepsis and ischemia), corrosives, Ménétrier disease, Crohn disease and Zollinger-Ellison syndrome.

Clinical presentation depends on the age. Neonates typically present with bleeding and perforation from a gastric ulcer, usually occurring in the setting of another underlying problem, such as sepsis or respiratory distress. Older infants and toddlers frequently vomit, eat poorly and have upper GI bleeding. Older children may have the classical epigastric pain which is relieved by eating. However, this is noted only in a minority; most patients have pain that is ill-localized and similar to that seen in functional dyspepsia. Overt or occult bleeding is seen in approximately half of school-age children with ulcer disease. Gastrointestinal bleeding, vomiting with obstruction and severe pain due to perforation suggest complicated ulcers. Ulcers associated with *Helicobacter pylori* infection affect older children, family history of ulcer disease is usually noted and upper GI endoscopy shows antral nodularity as compared to ulcers without such infection Mechanical ventilation and coagulopathy increase risk of bleeding in stress ulcers.

Diagnosis is established by upper GI endoscopy by direct visualization of location (gastric or duodenal), number and size of ulcer (Fig. 11.6). Endoscopic management can be done at the same time in ulcers with active bleeding or ooze or those with a visible vessel. One can also obtain gastric biopsies for *Helicobacter pylori* testing.

Proton pump inhibitors are the mainstay of therapy. Actively bleeding ulcers require endoscopic therapy, with sclerosant or adrenaline injection, application of heater probe or bipolar electrocoagulation, or placement of hemoclip over bleeding vessel. Evaluation for *Helicobacter pylori* is essential in all cases with peptic ulcer and merits specific therapy with two of three antibiotics (amoxicillin, metronidazole, clarithromycin) and proton pump inhibitor. Predisposing factors, including NSAIDs, should be avoided. Surgery is indicated in children presenting with gastric outlet obstruction or uncontrolled bleeding despite drug and endoscopic treatment.

Acute Pancreatitis

Acute pancreatitis is less common in children than adults and occurs chiefly due to trauma, drugs (valproate, L-asparaginase), viral infections (mumps), hemolytic uremic syndrome, congenital biliary anomalies, Henoch-Schönlein purpura and occasionally, gallstones, hypercalcemia or hypertriglyceridemia. Diagnosis is based on presence of upper abdominal pain (with or without radiation to the back), elevated serum amylase or lipase and radiological imaging (ultrasonography, CT scan) showing bulky, edematous pancreas. Acute severe pancreatitis may result in acute respiratory distress syndrome, acute renal failure, shock, GI bleed, disseminated intravascular coagulation, hypoglycemia, hypocalcemia or infected pancreatic necrosis. Late complications include pancreatic abscess and pseudocyst formation. Early supportive care in intensive care is critical in severe acute pancreatitis. Radiological, endoscopic or surgical interventions may be required for patients with pseudocyst, pancreatic abscess or infected necrosis.

Chronic Abdominal Pain

Chronic abdominal pain refers to the pain that is either episodic or continuous and lasts for a period of at least 2 months. The prevalence of chronic abdominal pain in children varies from 0.5 to 19% and depending on the age group evaluated. The principles of diagnosis with regard to clinical evaluation are similar to that in acute abdominal pain but the etiologies differ. In addition to organic causes, an important cause is nonorganic abdominal pain which is responsible for nearly 75% of all cases. As per the Rome III criteria, such pain is termed 'abdominal pain related to functional gastrointestinal disorders.'

Chronic Pancreatitis

This condition is characterized by recurrent episodes of abdominal pain and exocrine and/or endocrine pancreatic insufficiency. On imaging, diagnosis is based on demonstration of pancreatic calcification and/or dilated pancreatic duct. Chronic pancreatitis in children may be idiopathic or hereditary, autoimmune, tropical, metabolic (hypercalcemia) or secondary to recurrent acute pancreatitis.

Children present initially with repeated episodes of pancreatic pain. Chronic diarrhea with fat malabsorption (exocrine insufficiency) and symptoms of diabetes mellitus develop later along with failure to thrive. Local complications include pseudocyst, pancreatic ascites, pancreatic duct stricture, biliary strictures and portal hypertension due to splenic vein thrombosis. These patients are also at an increased risk of pancreatic carcinoma, particularly those with hereditary pancreatitis.

X-ray abdomen may show pancreatic calcification. Ultrasound and CT scan demonstrates ductal dilatation (Fig. 11.7), strictures, calcification and altered size or echotexture of pancreas. ERCP or MRCP help define the pancreatic ductal anatomy (e.g. prominent stricture,

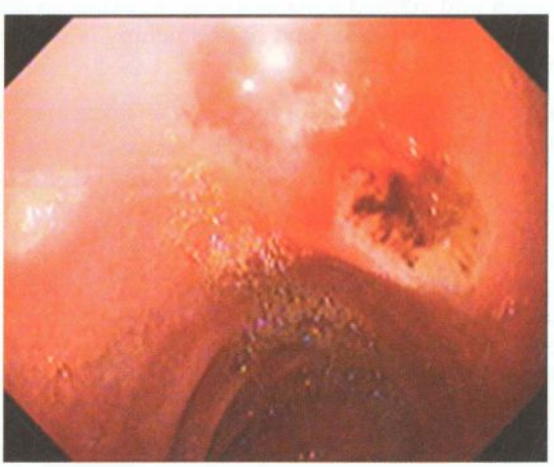

Fig. 11.6: Upper gastrointestinal endoscopy showing duodenal ulcer in the first part of duodenum

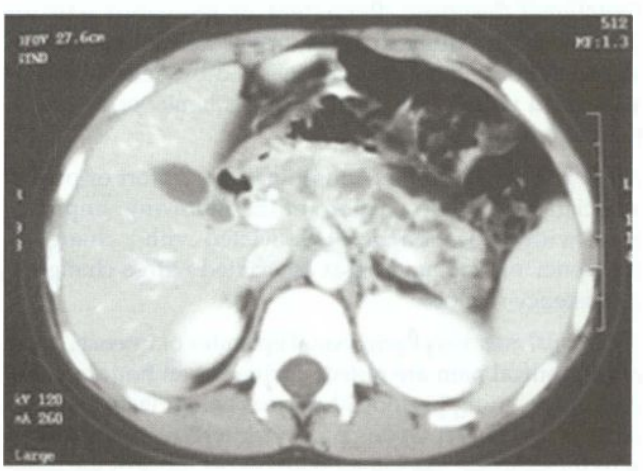

Fig. 11.7: CT scan showing dilated main pancreatic duct in chronic pancreatitis

intraductal calculi) and planning of endoscopic or surgical therapy. Exocrine pancreatic insufficiency is confirmed by demonstrating excess fat and reduced pancreatic elastase or chymotrypsin in stool. Fasting and postprandial blood sugar help evaluate for endocrine insufficiency. Evaluation for etiology should include looking for hypercalcemia or hyperlipidemia and testing for mutations in cationic trypsinogen gene to confirm hereditary pancreatitis.

Treatment includes supportive therapy during acute attacks, administration of antioxidants and oral pancreatic enzyme supplements for exocrine pancreatic insufficiency and endoscopic, radiological or surgical treatment for pseudocyst, ductal stricture and other complications. Surgical procedures like partial pancreatectomy or lateral pancreatojejunostomy are required in patients not responding to medical therapy. Celiac ganglion block is another alternative for pain control. Management of diabetes mellitus, if present, is essential.

Abdominal Pain Related to Functional Gastrointestinal Disorders

Abdominal pain related to functional GI disorders is diagnosed in the presence of pain that is present at least once a week in the preceding 2 months and the absence of an organic cause such as an inflammatory, anatomic, metabolic and neoplastic process. The pain is typically periumbilical and is clearly localized by the child.

After extensive studies, the most accepted understanding of childhood functional abdominal pain is of 'visceral hyperalgesia', referring to an altered excessive perception of normal gut motility that is interpreted by the child as pain. This perception is influenced by the psychosocial stressors in the school and family. The focus on the pain is further heightened by the growing concern in the family and the frequent visits to the doctors. Children of parents with increased anxiety and functional GI problems have an increased risk of developing abdominal pain. The following types are recognized.

Functional dyspepsia. Persistent or recurrent pain or discomfort is centered in the upper abdomen, located above the umbilicus and not relieved by defecation nor associated with a change in stool frequency or form (i.e. no irritable bowel syndrome).

Irritable bowel syndrome. Abdominal discomfort or pain is associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool and onset associated with a change in consistency of stool.

Abdominal migraine. Paroxysmal episodes of intense, acute periumbilical pain are noted, lasting for an hour or more with intervening periods of normal health lasting weeks to months. The episodes of pain interfere with normal activities and are associated with two or more of the following: anorexia, nausea, vomiting, headache, photophobia and pallor.

Childhood functional abdominal pain syndrome. This refers to episodic or continuous abdominal pain that meets insufficient criteria for other types. The criteria for childhood functional abdominal pain are satisfied if the child has one or more of the following symptoms at least 25% of the time: some loss of daily functioning and additional somatic symptoms such as headache, limb pain, or difficulty in sleeping.

Among the various types mentioned above, functional abdominal pain is the most common. The diagnosis of childhood functional abdominal pain hinges on confidently ruling out organic etiology using a careful history and examination; extensive investigations are unnecessary. The history should include not only details of pain but also family details, child's emotional environment in home and school, personality, coping skills, school performance and stress factors. The presence of alarming symptoms (Table 11.6) increases the probability of organic disorder and justifies further diagnostic testing. In the absence of red flags, the diagnostic yield of investigations is poor. Hemogram, ESR, stool routine and occult blood, and urine microscopy should be carried out in all cases to rule out organic disease. Abdominal ultrasonography is not helpful; the presence of lymph nodes of <10 mm is not a significant finding. Further investigation is required only in those with alarm symptoms and based on the likely diagnosis.

The aim of management of children with functional abdominal pain is to make a positive diagnosis, normalize the lifestyle to not allow pain to curtail daily activities or school performance, and to rectify psychological factors. The crux of management is counseling the parents and the child, both jointly and separately. Parents need to be reassured about the benign nature of the ailment and emphasis is laid upon avoiding too much attention to the child. The concept of visceral hyperalgesia should be explained to parents. Provision of a nutritious diet with adequate fiber and avoiding intake of carbonated beverages and refined food helps in reducing bloating. The role of amitriptyline and hypnotherapy is restricted to a few refractory cases.

Table 11.6: 'Red flag' signs or features that indicate serious illnesss in a child with abdominal pain

Pain localized away from umbilicus in right upper or lower quadrant
Nocturnal pain
Failure to thrive; weight loss
Significant vomiting; bilious vomiting
Gastrointestinal blood loss
Chronic diarrhea
Persistent fever
Jaundice
Arthritis; rash
Family history of inflammatory bowel disease
Localized tenderness or mass in abdomen; organomegaly
Perianal fistulae

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ACUTE DIARRHEA

Diarrhea is defined as a change in consistency and frequency of stools, i.e. liquid or watery stools, that occur >3 times a day. If there is associated blood in stools, it is termed *dysentery*. In the vast majority of cases, these acute episodes subside within 7 days. Acute diarrhea may persist for >2 weeks in 5–15% cases, which is labeled as *persistent diarrhea*.

The global annual burden of diarrhea is huge, affecting 3–5 billion cases and causing approximately 2 million deaths a year. Diarrhea accounts for over 20% of all deaths in underfive children. The two most important consequences of diarrhea in children are malnutrition and dehydration. Malnutrition and diarrhea form a vicious cycle, since malnutrition increases the risk and severity of diarrhea. Impaired absorption, loss of nutrients, increased catabolism and improper feeding in diarrhea aggravate the severity of malnutrition. A child may lose as much water and electrolytes from the body during an episode of diarrhea as an adult, which translates into a higher proportion of total body water loss in the child. Significant dehydration with abnormal electrolyte and acid-base status occurs in 2–5% of all cases of diarrhea, which may be fatal.

Etiology

Intestinal infections are the most common cause of acute diarrhea. However, certain drugs, food allergy, systemic infections (e.g. urinary tract infection and otitis media) and surgical conditions (e.g. appendicitis or Hirschsprung disease) can also present as acute onset diarrhea. Causative agents of acute diarrhea (Table 11.7) can be identified in nearly 70–80% episodes of acute diarrhea. Rotavirus remains the leading cause of severe, dehydrating gastroenteritis worldwide. In India, rotavirus and enterotoxigenic *E. coli* account for nearly half of the total diarrheal episodes among children. In rotavirus diarrhea, vomiting is an early feature and diarrhea is more severe. Cholera accounts for 5–10% cases; it is endemic in some parts and may occur in outbreaks. In cholera, stools are like rice water, vomiting is common and rapid onset of severe dehydration occurs within hours. Apart from enterotoxin producing *E. coli* (ETEC), which accounts for nearly 20% of childhood diarrhea, enteroinvasive *E. coli* (EIEC) and enterohemorrhagic *E. coli* (EHEC) can cause dysentery. EHEC may also a cause of hemolytic uremic syndrome. *Shigella* and *Salmonella* species are isolated in 3–7% of childhood diarrheas. *Shigella* accounts for majority of cases of dysentery whereas *Entamoeba histolytica* accounts for only 5% of dysentery. *Giardia lamblia* rarely causes acute diarrhea. Infection with *Candida albicans* can cause acute diarrhea in patients with malnutrition, immunocompromised state or following prolonged antibiotic treatment. *Clostridium difficile* should be suspected in patients who have received broad spectrum antibiotics.

Table 11.7: Causes of acute diarrhea

Bacterial
Escherichia coli: Enterotoxigenic, enteropathogenic, enteroinvasive*, enterohemorrhagic* and enteroaggregative types
*Shigella**: *S. sonnei, S. flexneri, S. boydii* and *S. dysenteriae*
Vibrio cholerae serogroups O1 and O139
*Salmonella**: Chiefly *S. typhi and S. paratyphi* A, B or C
Campylobacter species*
Others: *Aeromonas* spp., *Bacillus cereus, Clostridium difficile, Clostridium perfringens, Staphylococcus aureus, Vibrio parahemolyticus, Yersinia enterocolitica, Plesiomonas shigelloides**
Viral
Rotavirus
Human caliciviruses: *Norovirus* spp.; *Sapovirus* spp.
Enteric adenoviruses serotypes 40 and 41
Others: Astroviruses, coronaviruses, cytomegalovirus, picornavirus
Parasitic
Giardia lamblia
Cryptosporidium parvum
*Entamoeba histolytica**
Cyclospora cayetanensis
Isospora belli
Others: *Balantidium coli, Blastocystis hominis, Encephalitozoon intestinalis, Trichuris trichiura**

*Cause diarrhea with or without dysentery

Risk Factors

Factors determining susceptibility to diarrhea include poor sanitation and personal hygiene, nonavailability of safe drinking water, unsafe food preparation practices and low rates of breastfeeding and immunization. Young children (<2 yr) and those with malnutrition are more susceptible to acute diarrhea and have more severe and prolonged episodes. Risk factors for prolonged and recurrent episodes of diarrhea include presence of hypo- or achlorhydria (due to *Helicobacter pylori* infection or therapy with proton pump inhibitors), selective IgA deficiency, infection with human immunodeficiency virus (HIV) and other chronic conditions. Alteration of normal intestinal microflora by antibiotics can predispose to *C. difficile* infection.

Pathogenesis and Clinical Findings

Approximately 60% of a child's body weight is water, present in two fluid compartments: the extracellular fluid

(ECF) and intracellular fluid (ICF). The ECF includes circulating blood, intestinal fluid and secretions. Diarrheal losses come from ECF, which is relatively rich in sodium and has low potassium. Loss of water from the body causes a reduction or shrinkage of ECF volume. In half of these cases, the concentration of sodium in the plasma remains nearly normal (about 140 mEq/l); in another 40–45% cases, excessive sodium is lost in the stools leading to a relative decline in serum sodium (hyponatremia) and a fall in ECF osmolality. This causes movement of water from the ECF to ICF compartment, causing further shrinkage of the already reduced extracellular compartment volume in hyponatremic dehydration. In about 5% cases of diarrhea, especially if the child has been given fluids with extra salt, serum sodium levels may be elevated to >150 mEq/l and ECF osmolalilty is increased.

Normally, skin turgor or elasticity is maintained by tissue water and fat. Shrinkage of extracellular water in both hypo- and isonatremic dehydration impairs skin elasticity. On pinching, it takes a few seconds for the skin fold to return to normal. In patients with hypernatremic dehydration, water moves from inside the cells to the ECF compartment due to the increased osmolality of ECF, and therefore, partially masks the loss of skin turgor. The skin appears soggy, doughy or leathery. In this situation, a severe case of hypernatremic dehydration is likely to be erroneously underestimated as mild dehydration, unless severe sequelae of dehydration such as circulatory or renal impairment are noted.

As the ECF compartment is depleted, the blood volume is reduced. This results in a weak, thready pulse, low blood pressure and cold extremities. Because of low hydrostatic pressure in the renal glomeruli, the filtration of urine is reduced. This is ominous because poorly functioning kidneys cannot regulate metabolic derangements. Urine flow is a good indicator of the severity of illness. Severe cases are associated with renal failure.

Diarrheal stools contain large amounts of potassium. Therefore, serum level of potassium invariably falls if diarrhea persists for more than a few days. This is more pronounced in children with severe malnutrition with already depleted potassium stores. Affected children present with abdominal distension, paralytic ileus and muscle hypotonia. Electrocardiogram may show ST depression and flat T waves. Since intestinal secretions are alkaline, considerable bicarbonate is lost in diarrheal stools and acidosis usually accompanies dehydration. Patients remain asymptomatic till the base excess falls to 12 mmol/l. Below this level, breathing becomes deep and rapid (Kussmaul breathing).

Clinical features can be summed up as follows. The child is thirsty and slightly irritable in early and mild cases of diarrhea. As the diarrhea continues and dehydration worsens, the child becomes more irritable and develops a pinched look. The fontanelle, if open, is depressed, the eyes appear sunken and the tongue and the inner side of cheeks appear dry. Abdomen may become distended in hypokalemia. The child passes urine at longer intervals. As acidosis worsens, the breathing becomes deep and rapid. In extreme cases, the child appears moribund, with weak and thready pulses, low blood pressure and reduced urine output. Children with severe dehydration may succumb rapidly if not treated promptly.

Assessment of Child with Acute Diarrhea

Goals of assessment. These are to: (i) determine the type of diarrhea, i.e. acute watery diarrhea, dysentery or persistent diarrhea; (ii) look for dehydration and other complications; (iii) assess for malnutrition; (iv) rule out nondiarrheal illness especially systemic infection; and (v) assess feeding, both preillness and during illness.

History. This should include information on: (i) onset of diarrhea; duration and number of stools per day; (ii) blood in stools; (iii) number of episodes of vomiting; (iv) presence of fever, cough, or other significant symptoms (e.g. convulsions, recent measles); (v) type and amount of fluids (including breast milk) and food taken during the illness and preillness feeding practices; (vi) drugs or other local remedies taken (including opioids or antimotility drugs like loperamide that may cause abdominal distention); and (vii) immunization history.

Examination. The most important assessment is for dehydration. The degree of dehydration is assessed as per Table 11.8. One should look at the child's general condition, whether he/she is alert, restless or irritable or lethargic or unconscious. Other important assessments are for the appearance of eyes (normal or sunken) and the ability to drink water or ORS solution, whether taken normally or refused, taken eagerly, or an inability to drink due to lethargy or coma. Dehydration is also assessed by feeling for skin turgor; following pinching, the abdominal skin may flatten immediately, go back slowly or return very slowly (more than 2 seconds). Based on the degree of dehydration after history and examination, the estimated fluid loss is calculated as follows:

Degree of dehydration	*Assessment of fluid loss*
No dehydration	<50 ml/kg
Some dehydration	50–100 ml/kg
Severe dehydration	>100 ml/kg

In addition, one should examine for features of malnutrition (anthropometry for weight and height; examination for wasting, edema and signs of vitamin deficiency), systemic infection (presence of cough, high grade fever, fast breathing and/or chest indrawing suggests pneumonia; high grade fever with splenomegaly suggests malaria) and fungal infections (oral thrush or perianal satellite lesions).

Laboratory investigations The large majority of acute diarrheal episodes can be managed effectively even in

Table 11.8: Assessment of dehydration in patients with diarrhea

Look at			
Condition[1]	Well alert	Restless, irritable	Lethargic or unconscious; floppy
Eyes[2]	Normal	Sunken	Very sunken and dry
Tears	Present	Absent	Absent
Mouth and tongue[3]	Moist	Dry	Very dry
Thirst	Drinks normally; not thirsty	Thirsty, drinks eagerly	'Drinks poorly' or is not able to drink
Feel			
Skin pinch[4]	Goes back quickly	Goes back slowly	Goes back very slowly
Decide	The patient has no signs of dehydration	If the patient has two or more signs, there is some dehydration	If the patient has two or more signs, there is severe dehydration
Treat	Use treatment **Plan A**	Weigh the patient, if possible, and use treatment **Plan B**	Weigh the patient and use treatment **Plan C** urgently

[1]A lethargic child is not simply asleep; the child cannot be fully awakened; has a dull mental state and the child may appear to be drifting into unconsciousness

[2]In some infants and children the eyes normally appear somewhat sunken. It is helpful to ask the mother if the child's eyes are normal or more sunken than usual

[3]Dryness of the mouth and tongue can also be palpated with a clean finger. The mouth may be dry in a child who habitually breathes through the mouth. The mouth may be wet in a dehydrated child owing to recent vomiting or drinking

[4]The skin pinch is less useful in infants or children with marasmus (severe wasting), kwashiorkor (severe malnutrition with edema) and in obese children

absence of laboratory investigations. *Stool microscopy* is not helpful in management except in selected situations, such as cholera (darting motion suggests *Vibrio cholerae*) and giardiasis (trophozoites). *Stool culture* is of little value in routine management of acute diarrhea. It is useful to decide on antibiotic therapy in patients with *Shigella* dysentery who do not respond to the initial empiric antibiotics. Tests for stool pH and reducing substances are not indicated in acute diarrhea. Hemogram, blood gas estimation, serum electrolytes, renal function tests are not indicated routinely and are performed only if the child has associated findings like pallor, labored breathing, altered sensorium, seizures, paralytic ileus or oliguria which suggests acid-base imbalance, dyselectrolytemia or renal failure.

Principles of Management

Management of acute diarrhea has four major components: (i) rehydration and maintaining hydration; (ii) ensuring adequate feeding; (iii) oral supplementation of zinc; and (iv) early recognition of danger signs and treatment of complications.

The cornerstone of acute diarrhea management is rehydration by using oral rehydration solutions. After the history and examination, the child's dehydration status is classified as no dehydration, some dehydration or severe dehydration and appropriate treatment started.

Physiological basis for oral rehydration therapy. In most cases of acute diarrhea, sodium and chloride are actively secreted from the gut mucosa due to pathogen induced dysfunction of several actively functioning absorption pumps. However, glucose dependent sodium pump remains intact and functional transporting one molecule of glucose and dragging along a molecule of sodium and one of water across intestinal mucosa resulting in repletion of sodium and water losses. The glucose dependent sodium and water absorption is the principle behind replacing glucose and sodium in 1:1 molar ratio in the WHO oral rehydration solution (ORS). An important consideration in making ORT is that the osmolarity of the replacement fluid should not exceed that of blood (290 mmol/l). Keeping the intestinal lumen at lower osmolarity as compared to blood allows for greater absorption of fluids into the bloodstream across concentration gradient, which also results in electrolyte absorption (by solvent drag). Since the concentration of glucose increases osmolarity, it is suggested that glucose concentration should not exceed 111 mmol/l. Meta-analysis have shown that use of low osmolarity ORS causes reduction of stool output, decrease in vomiting and decrease in the use of unscheduled intravenous fluids without increasing the risk of hyponatremia. For this reason, the recommendation for use of standard WHO ORS (having osmolarity of 311 mmol/l) was changed to low osmolarity WHO ORS (having osmolarity of 245 mmol/l). Since 2004, based on the WHO/UNICEF and IAP recommendations, the Government of India has adopted the low osmolarity ORS as the single universal ORS to be used for all ages and all types of diarrhea. The composition of the low osmolarity ORS is given in Table 11.9.

In the absence of WHO ORS, one may administer culturally acceptable appropriate homemade fluids as shown in Table 11.10. Oral solutions should be given by a spoon or katori and in sips or small volumes rather than a large volume at one time as this increases the retention of oral fluids.

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Table 11.9: Composition of WHO recommended ORS

Constituent	*g/l*	*Osmole or ion*	*mmol/l*
Sodium chloride	2.6	Sodium	75
Glucose, anhydrous	13.5	Chloride	65
Potassium chloride	1.5	Glucose, anhydrous	75
Trisodium citrate, dihydrate	2.9	Potassium	20
		Citrate	10
Total osmolarity			245

Table 11.10: Home available fluids for acute diarrhea

Acceptable home available fluids	
Fluids that contain salt (preferable)	Oral rehydration solution, salted drinks (e.g. salted rice water or salted yoghurt drink), vegetable or chicken soup with salt
Fluids that do not contain salt (acceptable)	Plain water, water in which a cereal has been cooked (e.g. unsalted rice water), unsalted soup, yoghurt drinks without salt, green coconut water, weak unsweetened tea, unsweetened fresh fruit juice
Unsuitable home available fluids	Commercial carbonated beverages, commercial fruit juices, sweetened tea

Treatment Plan A: Treatment of "No Dehydration"

Such children may be treated at home after explanation of feeding and the danger signs to the mother/caregiver. The mother may be given WHO ORS for use at home as per Table 11.11. Danger signs requiring medical attention are those of continuing diarrhea beyond 3 days, increased volume/frequency of stools, repeated vomiting, increasing thirst, refusal to feed, fever or blood in stools.

Treatment Plan B: Treatment of "Some Dehydration"

All cases with obvious signs of dehydration need to be treated in a health center or hospital. However, oral fluid therapy must be commenced promptly and continued during transport. Fluid requirement is calculated under the following three headings: (i) provision of normal daily fluid requirements; (ii) rehydration to correct the existing water or electrolyte deficits; and (iii) maintenance to replace ongoing losses to prevent recurrence of dehydration.

i. *The daily fluid requirements* in children are calculated as follows:

Up to 10 kg = 100 ml/kg
10–20 kg = 50 ml/kg
>20 kg = 20 ml/kg

As an example, the daily fluid requirement in a child weighing 15 kg will be 1250 ml (first 10 kg, 10 × 100 = 1000 ml; another 5 kg, 5 × 50 = 250 ml, total 1000 + 250 = 1250 ml).

ii. *Deficit replacement or rehydration therapy* is calculated as 75 ml/kg of ORS, to be given over 4 hr. If ORS cannot be taken orally then nasogastric tube can be used. If child's weight cannot be taken then only age may be used to calculate fluid requirement as shown in Table 11.12.
If after 4 hr, the child still has some dehydration then another treatment with ORS (as in rehydration therapy) is to be given. This therapy is effective in 95% cases. Oral rehydration therapy may be ineffective in children with a high stool purge rate of >5 ml/kg body weight/hr, persistent vomiting >3 per hr, paralytic ileus and incorrect preparation of ORS (very dilute solution).

iii. *Maintenance fluid therapy to replace losses.* This phase should begin when signs of dehydration disappear, usually within 4 hr. ORS should be administered in volumes equal to diarrheal losses, usually to a maximum of 10 ml/kg per stool. Breastfeeding and semisolid food are continued after replacement of deficit. Plain water can be offered in between.

Table 11.11: Oral rehydration therapy to prevent dehydration (Plan A)

Age	*Amount of ORS or other culturally appropriate ORT fluids to give after each loose stool*	*Amount of ORS to provide for use at home*
< 24 mo	50–100 ml	500 ml/day
2–10 yr	100–200 ml	1000 ml/day
>10 yr	Ad lib	2000 ml/day

Explain use of ORS, i.e. the amount to be given, how to mix
Give a teaspoonful every 1–2 min for a child under 2 yr
Give frequent sips from a cup for an older child
If the child vomits, wait for 10 min. Then give the solution more slowly (for example, a spoonful every 2–3 min)
If diarrhea continues after the ORS packets are used up, tell the mother to give other fluids as described above or return for more ORS

Treatment Plan C: Children with "Severe Dehydration"

Intravenous fluids should be started immediately using Ringer lactate with 5% dextrose. Normal saline or plain Ringer solution may be used as an alternative, but 5% dextrose alone is not effective. A total of 100 ml/kg of fluid is given, over 6 hr in children <12 months and over 3 hr in children >12 months as shown below.

ORS solution should be started simultaneously if the child can take orally. If IV fluids cannot be given (for reasons of access, logistic availability or during transport), nasogastric feeding is given at 20 ml/kg/hr for 6 hr (total 120 ml/kg). The child should be reassessed every 1–2 hr; if there is repeated vomiting or abdominal distension, the oral or nasogastric fluids are given more slowly. If there is no improvement in hydration after 3 hr, IV fluids should be started as early as possible.

The child should be reassessed every 15–30 min for pulses and hydration status after the first bolus of 100 ml/

Table 11.12: Guidelines for treating patients with some dehydration (Plan B)

Age	*<4 mo*	*4–11 mo*	*12–23 mo*	*2–4 yr*	*5–14 yr*	*≥15 yr*
Weight	< 5 kg	5–8 kg	8–11 kg	11–16 kg	16–20 kg	>30 kg
ORS, ml	200–400	400–600	600–800	800–1200	1200–2200	>2200
Number of glasses	1–2	2–3	3–4	4–6	6–11	12–20

The approximate amount of ORS required (in ml) can also be calculated by multiplying the patient's weight (in kg) times 75. When body weight is not known, the approximate amount of ORS solution to give in the first 4 hr is given according to age
For infants under-6 months who are not breastfed, also give 100–200 ml clean water during this period
Encourage breastfeeding

kg of IV fluid. Management following intravenous hydration end is to be done as follows:

Age	30 ml/kg	70 ml/kg
<12 mo	1 hr*	5 hr
>12 mo	30 min*	2 ½ hr

*The above can be repeated if child continues to have feeble/non-palpable radial pulse

i. *Persistence of severe dehydration.* Intravenous infusion is repeated.
ii. *Hydration is improved but some dehydration is present.* IV fluids are discontinued; ORS is administered over 4 hr according to Plan B
iii. *There is no dehydration.* IV fluids are discontinued; treatment Plan A is followed.

The child should be observed for at least 6 hr before discharge, to confirm that the mother is able to maintain the child's hydration by giving ORS solution.

Unique problems in infants below 2 months of age

Breastfeeding must continue during the rehydration process, whenever the infant is able to suck. Complications like septicemia, paralytic ileus and severe electrolyte disturbance are more likely in young infants with diarrhea than at later ages. Diarrhea in these infants should be ideally treated as inpatient by experienced physicians at treatment centers with appropriate facilities. This allows for careful assessment of need of systemic antibiotics and monitoring.

Nutritional Management of Diarrhea

Children with severe malnutrition (marasmus or kwashiorkor) are at an increased risk of developing both acute diarrhea and its complications, such as severe systemic infection, dehydration, heart failure, vitamin and mineral deficiencies. Feeding should not be restricted in such patients as this aggravates complications and increases morbidity and mortality. Early feeding during diarrhea not only decreases the stool volume by facilitating sodium and water absorption along with the nutrients, but also facilitates early gut epithelial recovery and prevents malnutrition. Once the child's status starts improving, a higher than recommended intake is given to facilitate complete catchup growth.

Following are the recommendations on dietary management of acute diarrhea:

i. In exclusively breastfed infants, breastfeeding should continue as it helps in better weight gain and decreases the risk of persistent diarrhea.
ii. Optimally energy dense foods with the least bulk, recommended for routine feeding in the household, should be offered in small quantities but frequently (every 2–3 hr).
iii. Staple foods do not provide optimal calories per unit weight and these should be enriched with fat or oil and sugar, e.g. *khichri* with oil, rice with milk or curd and sugar, mashed banana with milk or curd, mashed potatoes with oil and lentil.
iv. Foods with high fiber content, e.g. coarse fruits and vegetables should be avoided.
v. In nonbreastfed infants, cow or buffalo milk can be given undiluted after correction of dehydration together with semisolid foods. Milk should not be diluted with water during any phase of acute diarrhea. Alternatively, milk cereal mixtures, e.g. dalia, sago or milk-rice mixture, are preferable.
vi. Routine lactose-free feeding, e.g. soy formula is not required during acute diarrhea even when reducing substances are detected in the stools.
vii. During recovery, an intake of at least 125% of recommended dietary allowances should be attempted with nutrient dense foods; this should continue until the child reaches preillness weight and ideally until the child achieves a normal nutritional status.

Zinc Supplementation

Zinc deficiency has been found to be widespread among children in developing countries. Intestinal zinc losses during diarrhea aggravate pre-existing zinc deficiency. Zinc supplementation is now part of the standard care along with ORS in children with acute diarrhea. It is helpful in decreasing severity and duration of diarrhea and also risk of persistent diarrhea. Zinc is recommended to be supplemented as sulphate, acetate or gluconate formulation, at a dose of 20 mg of elemental zinc per day for children >6 months for a period of 14 days.

Symptomatic Treatment

An occasional vomit in a child with acute diarrhea does not need antiemetics. If vomiting is severe or recurrent and interferes with ORS intake, then a single dose of ondansetron (0.1–0.2 mg/kg/dose) should be given.

Children with refractory vomiting despite administration of ondansetron may require intravenous fluids.

Abdominal distension does not require specific treatment bowel sounds are present and the distension is mild. Paralytic ileus should be suspected if bowel sounds are absent and abdomen is distended. Paralytic ileus can occur due to hypokalemia, intake of antimotility agents, necrotizing enterocolitis or septicemia. In these cases, oral intake should be withheld. Hypokalemia along with paralytic ileus necessitates intravenous fluids and nasogastric aspiration. Potassium chloride (30–40 mEq/l) should be administered intravenously with parenteral fluids provided the child is passing urine.

Convulsions associated with diarrhea may be due to (i) hypo- or hypernatremia; (ii) hypoglycemia; (iii) hypokalemia following bicarbonate therapy for acidosis; (iv) encephalitis; (v) meningitis; (vi) febrile seizures; or (vii) cerebral venous or sagittal sinus thrombosis. The management depends on the etiology.

Drug Therapy

Most episodes of diarrhea are self-limiting and do not require any drug therapy except in a few situations. *Antibiotics* are not recommended for routine treatment of acute diarrhea in children. In acute diarrhea antimicrobial are indicated in bacillary dysentery, cholera, amebiasis and giardiasis. *Escherichia coli* are normal gut flora and their growth on stool culture is not an indication for antibiotics. Acute diarrhea may be the manifestation of systemic infection and malnourished, prematurely born and young infants are at a high risk. Thus such babies should be screened and given adequate days of age appropriate systemic antibiotics for sepsis. Presence of (i) poor sucking; (ii) abdominal distension; (iii) fever or hypothermia; (iv) fast breathing; and (v) significant lethargy or inactivity in well-nourished, well hydrated infants points towards sepsis.

There is little scientific evidence that *binding agents* based on pectin, kaolin or bismuth salts are useful. Their use is not recommended in acute diarrhea. *Antimotility agents* such as synthetic analogues of opiates (diphenoxylate hydrochloride or lomotil and loperamide or imodium) reduce peristalsis or gut motility and should not be used in children with acute diarrhea. Reduction of gut motility allows more time for the harmful bacteria to multiply. These drugs may cause distension of abdomen, paralytic ileus, bacterial overgrowth and sepsis and can be dangerous, even fatal, in infants.

Antisecretory agents have been used in acute diarrhea. Racecadotril is an antisecretory drug that exerts its antidiarrheal effects by inhibiting intestinal enkephalinase. Recent studies reported some evidence in favour of racecadotril over placebo or no intervention in reducing the stool output and duration of diarrhea in children with acute diarrhea. However, more data on efficacy is needed before it can be recommended for routine use in all children with acute diarrhea.

Probiotics, defined as microorganisms that exert beneficial effects on human health when they colonize the bowel, have been proposed as adjunctive therapy in the treatment of acute diarrhea. Several microorganisms like *Lactobacillus rhamnosus* (formerly *Lactobacillus casei* strain GG or *Lactobacillus* GG), *L. plantarum*, several strains of bifidobacteria, *Enterococcus faecium* SF68 and the yeast *Saccharomyces boulardii* have been shown to have some efficacy in reducing the duration of acute diarrhea if started in very early phase of illness. The efficacy of probiotic preparations is strain and concentration (dose) specific. However, the routine use of probiotics in patients with acute diarrhea is not recommended.

Prevention of Diarrhea and Malnutrition

Prevention of diarrhea and its nutritional consequences should receive major emphasis in health education. The three main measures to achieve this are:

i. *Proper nutrition*. Since breast milk offers distinct advantages in promoting growth and development of the infant and protection from diarrheal illness, its continuation should be encouraged. Exclusive breastfeeding may not be adequate to sustain growth beyond the first 6 months of life. Therefore, supplementary feeding with energy-rich food mixtures containing adequate amounts of nutrients should be introduced by 6 months of age without stopping breastfeeding.

ii. *Adequate sanitation*. Improvement of environment sanitation, clean water supply, adequate sewage disposal system and protection of food from exposure to bacterial contamination are effective longterm strategies for control of all infectious illnesses including diarrhea. Three 'Cs; clean hands, clean container and clean environment are the key messages. Mother should be properly educated about this. Complementary foods should be protected from contamination during preparation, storage, or at the time of administration.

iii. *Vaccination*. Evidence suggests that with improvement in sanitation and hygiene in developing countries, the burden of bacterial and parasitic infection has decreased and viral agents have assumed an increasingly important etiologic role. Effective vaccines are now available against the commonest agent, i.e. rotavirus and their use might be an effective strategy for preventing acute diarrhea.

Suggested Reading

Bhatnagar S, Lodha R, Choudhury P, Sachdev HPS, ShahN, Narayan S et al. IAP Guidelines 2006 on Management of Acute Diarrhea. Indian Paediatrics 2007; 44:380

The Treatment of Diarrhea: A Manual for Physicians and Other Senior Health Workers. WHO (2005). WHO/CDD/SER/80.2

Dysentery

Dysentery refers to the presence of grossly visible blood in the stools and is a consequence of infection of the colon

by either bacteria or ameba. Bacillary dysentery is much more common in children than amebic dysentery. The bacteria causing bloody diarrhea are *Shigella* species (*S. dysenteriae, S. flexneri, S. boydii* and *S. sonnei.*), enteroinvasive and enterohemorrhagic *E. coli, Salmonella* and *Campylobacter jejuni. S. flexneri* is the commonest organism reported in developing countries and *S. dysenteriae* is associated with epidemics of dysentery.

A child with bacillary dysentery presents with fever and diarrhea. Diarrhea may be watery to start with, but then shows mucus and blood mixed with stools. There is tenesmus, which refers to ineffectual defecation along with straining and suprapubic discomfort. The illness may be complicated by dehydration, dyselectrolytemia, hemolytic uremic syndrome, convulsions, toxic megacolon, intestinal perforation, rectal prolapse and, very rarely, Shigella encephalopathy.

Administration of ORS, continuation of oral diet, zinc supplementation and antibiotics are the components of treatment. Stool culture and sensitivity should be sent for before starting empirical antibiotics. Antimicrobial agents are the mainstay of therapy of all cases of shigellosis. Based on safety, low cost and efficacy, ciprofloxacin (15 mg/kg/day in two divided doses for 3 days) has been recommended by World Health Organization (WHO) as the first line antibiotic for shigellosis. However, antimicrobial resistance to fluoroquinolones had increased significantly from 2002 to 2011 and only ceftriaxone has been shown to be uniformly effective. Keeping this in mind, intravenous ceftriaxone (50–100 mg/kg/ day for 3–5 days) should be the first line of treatment in a sick child. In a stable child, either ciprofloxacin or oral cefixime may be given, but the patient should be monitored for clinical improvement within 48 hr (decrease in fever, stool frequency and blood in stools). If no improvement is seen at 48 hr, antibiotics should be changed appropriately. Oral azithromycin (10 mg/kg/day for 3 days) can be used for shigellosis but the experience is limited.

Amebic dysentery is less common among children. The onset is insidious. Tinidazole or metronidazole is the drug of choice. Any young child presenting with blood in stools and persistent abdominal pain should be suspected to have intussusception and evaluated accordingly.

PERSISTENT DIARRHEA

Persistent diarrhea is an episode of diarrhea, of presumed infectious etiology, which starts acutely but lasts for more than 14 days. It should not be confused with chronic diarrhea which has a prolonged duration but an insidious onset and includes conditions causing malabsorption.

Etiopathogenesis

Although persistent diarrhea starts as acute infectious diarrhea, the prolongation of diarrhea is not entirely due to infection. Various factors that are implicated in pathogenesis include.

i. The predominant problem is the worsening nutritional status that, in turn, impairs the reparative process in the gut. This worsens nutrient absorption and initiates a vicious cycle that can only be broken by proper nutrition. Persistent diarrhea is more common in malnourished children. Apart from malabsorption, malnutrition also results from inadequate calorie intake due to anorexia, faulty feeding and improper counseling regarding feeding by doctors. One of the major obstacles to nutritional recovery is secondary lactose intolerance, and in some cases, impaired digestion of other complex carbohydrates due to decrease in brush border disaccharidases.
ii. Pathogenic *E. coli*, especially the enteroaggregative and enteroadherent types, result in malabsorption by causing persistent infection.
iii. Associated infections of the urinary tract or another focus of infection (more commonly in malnourished children) contribute to failure to thrive and mortality.
iv. Prolongation of an acute diarrhea may rarely be a manifestation of cow milk protein allergy. The increased gut permeability in diarrhea predisposes to sensitization to oral food antigens.
v. The use of antibiotics in acute diarrhea suppresses normal gut flora. This may result in bacterial overgrowth with pathogenic bacteria and/or overgrowth of fungi, resulting in persistent diarrhea and malabsorption
vi. *Cryptosporidium* infection is frequently implicated in persistent diarrhea, even in immunocompetent children

Clinical Features

Majority of patients with persistent diarrhea pass several loose stools daily but remain well hydrated. Dehydration develops only in some patients due to high stool output or when oral intake is reduced due to associated systemic infections. The major consequences of persistent diarrhea are growth faltering, worsening malnutrition and death due to diarrheal or nondiarrheal illness. The presence of secondary lactose intolerance should be considered when the stools are explosive (i.e. mixed with gas and passed with noise) and in presence of perianal excoriation. The stool pH is low and stool test for reducing substances is positive. Unabsorbed dietary lactose once delivered to colon is converted to hydrogen and lactic acid by colonic bacteria. Lactic acid results in decreased stool pH, explosive stools are due to hydrogen and unabsorbed lactose gives positive reducing substances, if tested. There is no need for laboratory testing for stool pH and reducing substances when the history is classical and excoriation is marked.

Management

The principles of management are: (i) correction of dehydration, electrolytes and hypoglycemia; (ii) evaluation for infections using appropriate investigations (hemogram, blood culture and urine culture) and their management;

and (iii) nutritional therapy. Two-thirds of patients with persistent diarrhea can be treated on outpatient basis. Patients in need of hospital admission are those with (i) age less than 4 months and not breastfed; (ii) presence of dehydration; (iii) severe malnutrition (weight for height <3 SD, mid-upper arm circumference <11.5 cm for children at 6–60 months of age, or bilateral pedal edema); or (iv) presence or suspicion of systemic infection.

Nutrition

Feeding should be started at the earliest. Initially 6–7 feeds are given everyday and a total daily caloric intake of 100 kcal/kg/day is ensured. Caloric intake should be increased gradually over 1–2 weeks to 150 kcal/kg/day in order to achieve weight gain. Tube (nasogastric) feeding may be done initially in children with poor appetite due to presence of serious infection. To ensure absorption and decrease stool output, one may attempt to overcome varying degrees of carbohydrate maldigestion by using diets with different degrees of carbohydrate exclusion in the form of diet A (lactose reduced), diet B (lactose free) and diet C (complex carbohydrate free) diets (Table 11.13).

Initial diet A (reduced lactose diet; milk rice gruel, milk sooji gruel, rice with curds, dalia) This is based on the fact that secondary lactose intolerance exists in children with persistent diarrhea and malnutrition. Clinical trials have shown that reduced lactose diet is tolerated equally well as totally lactose-free diet, without significantly increasing stool output or risk of dehydration. If the patient is fed entirely on animal milk, the quantity should be reduced to 50–60 ml/kg providing not more than 2 g of lactose/kg/day. To reduce lactose concentration in animal milk, it should be mixed with cereals, but not diluted with water as that reduces the caloric content. Milk cereal mixtures, e.g. milk or curd mixed rice gruel, milk sooji gruel, or *dalia* are palatable, provide good quality proteins and some micronutrients and result in faster weight gain than milk-free diets.

Second diet B (lactose-free diet with reduced starch) About 65–70% of children improve on the initial diet A. The remainder have impaired digestion of starch and disaccharides other than lactose. These children, if free of systemic infection, are advised diet B which is free of milk (lactose) and provides carbohydrates as a mixture of cereals and glucose. Milk protein is replaced by chicken, egg or protein hydrolysate. The starch content is reduced and partially substituted by glucose. Substituting only part of the cereal with glucose increases the digestibility but at the same time does not cause a very high osmolarity.

Third diet C (monosaccharide-based diet) Overall, 80–85% of patients with severe persistent diarrhea will recover with sustained weight gain on the initial diet A or the second diet B. A small percentage may not tolerate a moderate intake of the cereal in diet B. These children are given diet C which contains only glucose and a protein source as egg white or chicken or commercially available protein hydrolysates. Energy density is increased by adding oil to the diet.

The strategy of carbohydrate exclusion to varying degrees in plan A, B and C diets are meant to circumvent the problem of carbohydrate malabsorption. In addition green (unripe) banana diet is gaining acceptance for treatment of persistent diarrhea. Fermentation of nondigestible soluble fibers in cooked green (unripe) banana by colonic bacteria generates short chain fatty acids which are absorbed along with sodium, thereby conserving dietary nutrients.

Indications for change from the initial diet (diet A) to the next diet (diet B or diet C) The diet should be changed to the next level if the child shows (i) marked

Table 11.13: Diets for persistent diarrhea

Diet A (reduced lactose)	*Diet B (lactose free)*	*Diet C (monosaccharide based)*
Constituents		
Milk (1/3 katori/50 ml) Puffed rice powder/cooked rice or sooji (2 tsp/6 g) Sugar (1½ tsp/7 g) Oil (1 tsp/4.5 g) Water (2/3 katori/100 ml)	Egg white (3 tsp/half egg white) Puffed rice powder/cooked rice (3 tsp/9 g) Glucose (1½ tsp/7 g) Oil (1½ tsp/7 g) Water (3/4 katori/120 ml)	Chicken puree (5 tsp/15 g) or egg white (3 tsp/half egg white) Glucose (1½ tsp/7 g) Oil (1½ tsp/7 g) Water (1 katori/150 ml)
Preparation		
Mix milk, sugar and rice, add boiled water and mix well, add oil.	After whipping the egg white, add rice, glucose and oil and mix well. Add boiled water and mix rapidly to avoid clumping	Boil chicken and make puree after removing bones. Mix it with glucose and oil. Add boiled water to make a smooth flowing feed
Nutrient content		
85 kcal and 2.0 g protein per 100 g	90 kcal and 2.4 g protein per 100 g	67 kcal and 3.0 g protein per 100 g

increase in stool frequency (usually more than 10 watery stools/day) at any time after at least 48 hr of initiating the diet; (ii) features of dehydration any time after initiating treatment; or (iii) failure to gain weight gain by day 7 in the absence of initial or hospital acquired systemic infection. Unless signs of treatment failure occur earlier, each diet should be given for a minimum period of 7 days.

Resumption of regular diet after discharge. Children discharged on totally milk free diet should be given small quantities of milk as part of a mixed diet after 10 days. If they tolerate this and have no signs of lactose intolerance (abdominal pain, abdominal distension and excessive flatulence) then milk can be gradually increased over the next few days. Age appropriate normal diet can then be resumed over the next few week.

Supplement vitamins and minerals Supplemental multivitamins and minerals, at about twice the RDA, should be given daily to all children for at least 2–4 weeks. Iron supplements should be introduced only after the diarrhea has ceased. Vitamin A (as a single dose) and zinc are supplemented as both of them enhance the recovery from persistent diarrhea. A single oral dose of vitamin A should be given routinely, at 2,00,000 IU for children >12 months or 100,000 IU for children 6–12 months. Children weighing less than 8 kg, irrespective of their age, should be given 1,00,000 IU of vitamin A. One should administer 10–20 mg per day of elemental zinc for at least 2 weeks to children between 6 months and 3 yr of age.

Additional supplements for severely malnourished infants and children Magnesium and potassium supplementation is provided to these children. Magnesium is given by intramuscular route at 0.2 ml/kg/dose of 50% magnesium sulphate twice a day for 2–3 days. Potassium is supplemented at 5–6 mEq/kg/day orally or as part of intravenous infusion during the initial stabilization period.

Role of antibiotics The indiscriminate use of antibiotics in the treatment of acute diarrhea is among the reasons for persistent diarrhea. Hence, the use of empirical antibiotics at admission is to be individualized and reserved for children with either of the following features: (i) severe malnutrition (majority of these children have associated systemic infections and clinical signs of infection may not be obvious); and (ii) evidence of systemic infection. A combination of cephalosporin and aminoglycoside can be started empirically and thereafter changed according to reports of culture/sensitivity. Urinary tract infection is common (seen in 10–15%) and should be treated appropriately.

Monitoring Response to Treatment

Successful treatment is characterized by adequate food intake, reduced frequency of diarrheal stools (<2 liquid stools/day for 2 consecutive days) and weight gain. Most children will lose weight in the initial 1–2 days and then show steady weight gain as associated infections are treated and diarrhea subsides. All children should be followed regularly even after discharge to ensure continued weight gain and compliance with feeding advice.

Prognosis

Most patients with persistent diarrhea recover with an approach of stepped up dietary management as discussed above. A small subgroup (<5%) may be refractory and require parenteral nutrition and extensive workup. These patients generally have high purge rate, continue to lose weight, do not tolerate oral feeds and require referral to specialized pediatric gastroenterology centers.

CHRONIC DIARRHEA

Chronic diarrhea is a common problem in children. It is defined as an insidious onset diarrhea of >2 weeks duration in children and >4 weeks in adults. The term chronic diarrhea is not synonymous with persistent diarrhea. The approach, etiology and management of chronic diarrhea along with a brief outline of some common causes is discussed.

Approach

Approach to chronic diarrhea must be considered with the following points in mind:

Age of onset. A list of common causes of chronic diarrhea according to age of onset is shown in Table 11.14.

Small or large bowel type of diarrhea. Features in history and examination that help in differentiating small bowel from large bowel diarrhea is shown in Table 11.15. Typically, large volume diarrhea without blood and mucus suggests *small bowel* type of diarrhea and small volume stools with blood and mucus suggest *large bowel* type of diarrhea.

Gastrointestinal versus systemic causes: Diarrhea is most commonly of intestinal origin and sometimes pancreatic, or rarely, hepatobiliary in etiology. Cholestasis due to biliary obstruction or intrahepatic cause can cause diarrhea due to fat malabsorption. Pruritus and malabsorption of fat soluble vitamins (A, D, E and K) and calcium are commonly associated. Maldigestion due to deficiency of pancreatic enzymes leads to pancreatic diarrhea in cystic fibrosis, Shwachman-Diamond syndrome (cyclic neutropenia and bone abnormalities) or chronic pancreatitis. Other causes include Zollinger-Elison syndrome, and secretory tumors like VIPoma, carcinoid or mastocytosis. Diarrhea may also be a systemic manifestation of other conditions like sepsis or collagen vascular disorders.

Specific questions in history should include:

i. Duration of symptoms; nature, frequency and consistency of stools; and presence of blood, mucus or visible oil in stools
ii. Age of onset; relationship of dietary changes, e.g. introduction of milk or milk products and wheat or

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Table 11.14: Causes of chronic diarrhea according to age of onset (in order of importance)

Age <6 mo	*Age >6 mo to 5 yr*	*Age >5 yr*
Cow milk protein allergy	Cow milk protein allergy	Celiac disease
Lymphangiectasia	Celiac disease	Giardiasis
Urinary tract infection*	Giardiasis	Gastrointestinal tuberculosis
Short bowel syndrome**	Toddler diarrhea	Inflammatory bowel disease
Immunodeficiency states	Lymphangiectasia	Immunodeficiency
Cystic fibrosis	Short bowel syndrome**	Bacterial overgrowth
Anatomical defects	Tuberculosis	Lymphangiectasia
Intractable diarrheas of infancy***	Inflammatory bowel disease	Tropical sprue
Microvillous inclusion disease	Immunodeficiency	Immunoproliferative small intestinal disease
Tufting enteropathy	Bacterial overgrowth	Pancreatic insufficiency
Autoimmune enteropathy	Pancreatic insufficiency	
Glucose galactose malabsorption		
Congenital sodium/chloride diarrhea		

* Should be considered in young infants with chronic diarrhea, particularly if fever is noted
** Consider if there is antecedent history of small bowel surgery
*** These rare conditions should only be considered if the diarrhea is very early in its onset (neonate to 3 months) and common conditions have been ruled out

Table 11.15: Differentiating small bowel from large bowel diarrhea

Features	*Small bowel diarrhea*	*Large bowel diarrhea*
Stool volume	Large	Small
Blood in stool	No	Usually present
Rectal symptoms, e.g. urgency, tenesmus	No	Yes
Steatorrhea (greasy stools)	Yes	No
Carbohydrate malabsorption	Yes, explosive	No
Protein malabsorption	Yes	No
Pain (if any)	Periumbilical, no reduction after passage of stool	Hypogastric, reduced after passage of stool
Color of stool	Pale	Normal
Smell of stool	Unusually offensive	Normal
Nutrient deficiency	Frequent	Can occur due to blood loss

wheat products, with onset of diarrhea; and any specific dietary preferences, like avoidance of juices

iii. Family history of atopy (food allergy, asthma or allergic rhinitis), celiac disease, Crohn disease or cystic fibrosis
iv. History of abdominal surgery, drug intake, systemic disease, features of intestinal obstruction, pedal edema, anasarca, recurrent infections at multiple sites, previous blood transfusion and coexisting medical problems which predispose the child to diarrhea (e.g. congenital immunodeficiency, diabetes mellitus, hyperthyroidism, cystic fibrosis)

Important components of physical examination include

i. Anthropometry
ii. Signs of dehydration
iii. Signs of vitamin or mineral deficiencies (e.g. conjunctival xerosis, Bitot spots, angular stomatitis, glossitis, cheilitis, rickets, phrynoderma)
iv. Edema, whether symmetric or asymmetric; pitting or non pitting (lymphedema)
v. Fever and signs of systemic sepsis
vi. Extragastrointestinal manifestations in eye, skin, joints, oral cavity (suggest inflammatory bowel disease, IBD)
vii. Inspection of perianal area for fissures, anal tags and fistulae (seen in IBD)
viii. Oral thrush and scars of recurrent skin infections (suggest immunodeficiency)
ix. Abdominal distention, localized or generalized tenderness, masses, hepatosplenomegaly and ascited.

Approach based on age of onset In infants <6 months, cow milk protein allergy and intestinal lymphangiectasia should be considered first. The important clues to each etiology is given in Table 11.16.

In young children, celiac disease is the most common cause of chronic diarrhea in North India. *Cow milk protein allergy* usually resolves by 3–5 yr; hence, this diagnosis should not be considered in children with onset of diarrhea beyond 5 yr. *Toddler diarrhea* is a diagnosis of exclusion after common causes have been ruled out. The onset of diarrhea is between 6 months and 3 yr of age. The child passes 3–6 loose stools, mostly during waking hour. Diarrhea worsens with low residue, low fat or high carbohydrate diet. The child is well thriving, there is no anemia or vitamin deficiencies and the diarrhea resolves spontaneously by about 4 yr of age. Treatment is with dietary modification; a high (>40%) fat,

low carbohydrate diet (especially with decreased intake of juices) and increase in dietary fiber is recommended. *IBD* is less common in this age group as compared to older children. *Giardiasis* can be diagnosed if multiple fresh stool samples (at least 3 in number) are tested for trophozoites. The laboratory may be asked to use *concentration methods*. Presence of cysts of giardia in immunocompetent patients does not merit a therapy of giardiasis.

Limited etiologies cause chronic diarrhea in older children (Table 11.16). A brief description of common causes of chronic diarrhea is given below.

Celiac Disease

This is an enteropathy caused by permanent sensitivity to gluten in genetically susceptible subjects. It is the most common cause of chronic diarrhea in children over 2 yr of age in North India. High-risk groups include subjects with Type 1 diabetes mellitus, Down syndrome, selective IgA deficiency, autoimmune thyroid disease, Turner syndrome, Williams syndrome, autoimmune liver disease and first-degree relatives of celiac disease patients. These subjects are at an increased risk of developing celiac disease and thus should be screened.

Presentation The classical presentation is with small bowel diarrhea, growth failure and anemia. A temporal association of diarrhea and introduction of wheat products at weaning may be present. Onset of diarrhea before introduction of wheat products in diet negates a diagnosis of celiac disease. It may also present without chronic diarrhea as refractory iron deficiency or dimorphic anemia not responding to oral supplements, short stature, delayed puberty, rickets and osteopenia. Examination reveals failure to thrive, loss of subcutaneous fat, clubbing, anemia, rickets and signs of other vitamin deficiencies.

A high index of suspicion for celiac disease is the key to diagnosis.

Table 11.16: Diagnostic clues to important causes of chronic diarrhea

Cow milk protein allergy	Onset of diarrhea after introduction of cow or buffalo milk or formula Rectal bleeding (due to colitis) Anemia; failure to thrive Family history of allergy or atopy Response to milk withdrawal
Lymphangiectasia	Nonpitting pedal edema suggesting lymphedema Recurrent anasarca Hypoalbuminemia and hypoproteinemia Lymphopenia Hypocalcemia
Cystic fibrosis	History of meconium ileus Predominant or associated lower respiratory tract infections Severe failure to thrive Clubbing History of sibling deaths High sweat chloride (>60 mEq/l)
Immuno-deficiencies	Predominant fever Recurrent infections involving other sites History of sibling deaths Organomegaly Opportunistic infections on stool examination

Diagnosis The main investigations required for making a diagnosis include:

i. *Serology.* IgA antibody against tissue transglutaminase (tTG) is an ELISA based test, recommended for initial testing of celiac disease. It has a high sensitivity (92–100%) and specificity (91–100%) in both children and adults. IgA antiendomysial antibody is an equally accurate test (sensitivity 88–100%; specificity 91–100%) but is more difficult to perform. The diagnosis of celiac disease should not be based only on celiac serology as serology may be false positive, false negative and interlaboratory variations are also present.

ii. *Upper GI endoscopy.* It may be normal or show absence of folds or scalloped folds (Fig. 11.8A). Multiple (4–6 in number) endoscopic biopsies from the bulb and second/third part of duodenum should be taken in all cases.

iii. *Histology.* The characteristic histological changes in celiac disease are increased intraepithelial lymphocytes (>30/100 enterocytes), increased crypt length, partial to total villous atrophy, decreased villous to crypt ratio and infiltration of plasma cells and lymphocytes in lamina propria (Fig. 11.8B).

Diagnosis of celiac disease (based on the modified criteria of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition, ESPGHAN) requires the following:

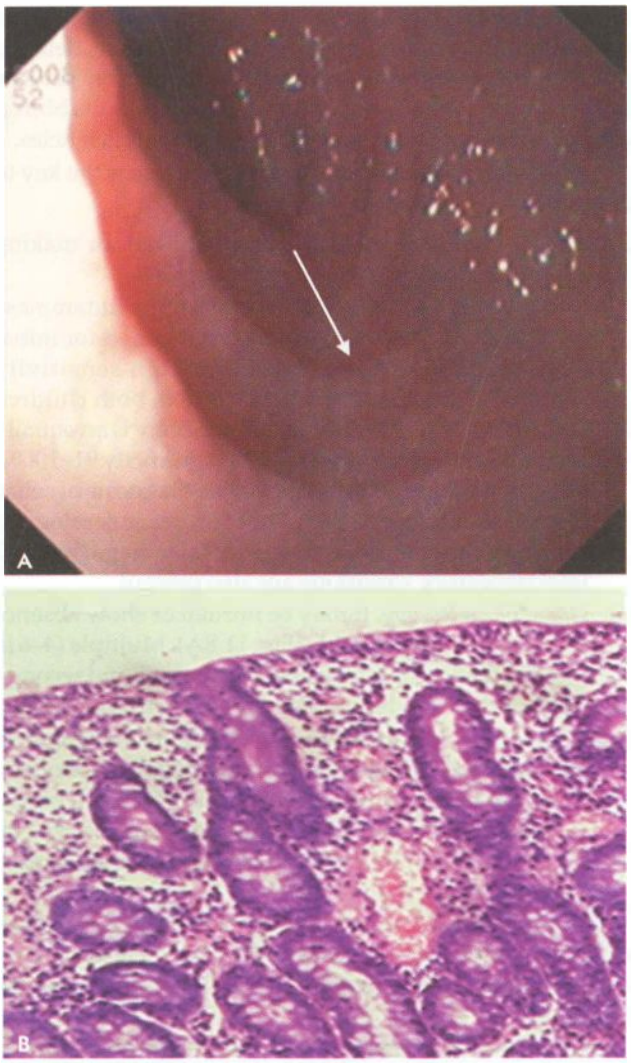
i. Clinical features compatible with diagnosis.
ii. Positive intestinal biopsy as described above with or without serology.
iii. Unequivocal response to gluten free diet (GFD) within 12 weeks of initiation of GFD.

A positive serology makes the diagnosis more definite especially in developing countries where other causes of villous atrophy are common due to intercurrent infections or undernutrition.

Treatment The treatment involves life-long GFD and correction of iron, folate and other vitamin/mineral deficiencies by supplementation. The patient should be assessed at 3 months for response to GFD. After initiation of GFD, all symptoms should subside and weight and height gain should be present. Repeated explanation to patient and parents by doctors is very helpful in sustaining compliance after the child has become asymptomatic.

Cow Milk Protein Allergy

Cow milk protein allergy (CMPA) affects 2 to 5% of all children in the West, with the highest prevalence during the first year of life. In India, CMPA accounts for ~13% of



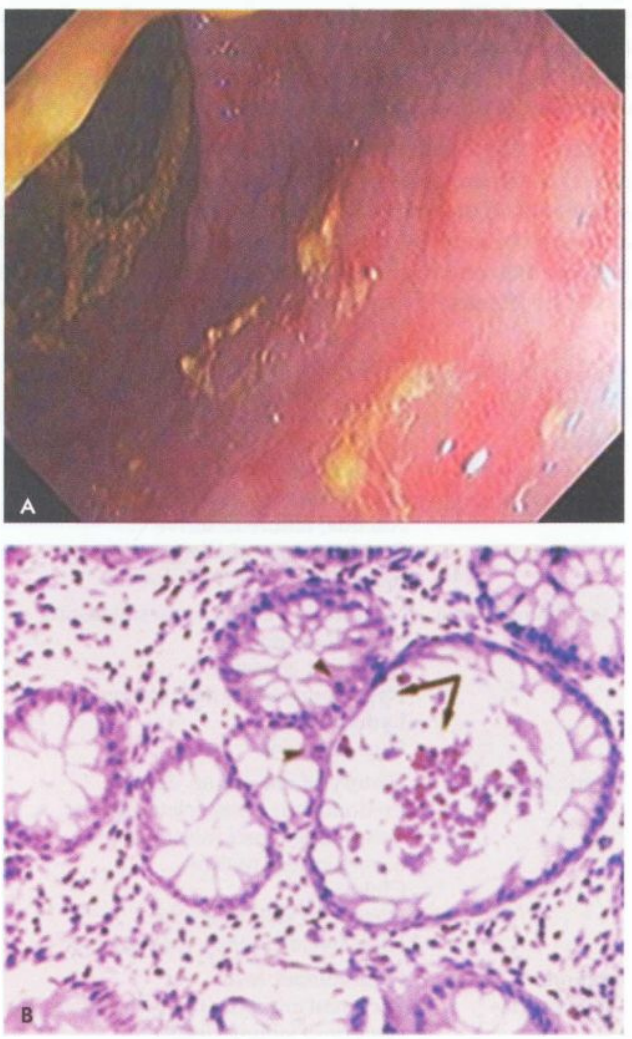
Figs 11.8A and B: Celiac disease. (A) Upper gastrointestinal endoscopy showing scalloping of duodenal folds (arrow); (B) duodenal histology showing total villous atrophy

all malabsorption cases in children <2 yr of age. A family history of atopy is common in children with CMPA. Nearly 50% children outgrow the allergy by 1 yr and ~95% by 5 yr of age. It is the most common food allergy in small children who are topfed but can also occur occasionally in breastfed babies due to passage of cow milk antigen in breast milk.

There are two kinds of reactions to cow milk: (i) *Immediate*, i.e. IgE mediated: It occurs within minutes of milk intake and is characterized by vomiting, pallor, shock-like state, urticaria and swelling of lips. (ii) *Delayed*, i.e. T cell mediated: It has an indolent course and presents mainly with GI symptoms.

Symptoms The most common presentation is with diarrhea with blood and mucus. Depending upon the site and extent of involvement, the child may have small bowel, large bowel or mixed type diarrhea. In an Indian study 40% children presented with bloody diarrhea, 33% watery and 7% with a mixed type of diarrhea. Uncommonly reflux symptoms and hematemesis may be present indicating upper GI involvement. Respiratory symptoms (allergic rhinitis and asthma) and atopic manifestations (eczema, angioedema) may be seen in 20–30% and 50–60% cases respectively. Iron deficiency anemia, hypoproteinemia and eosinophilia are commonly present.

Diagnosis In India non-IgE mediated CMPA is more common. Sigmoidoscopy (aphthous ulcers and nodular lymphoid hyperplasia as seen in Fig. 11.9A and rectal biopsy (plenty of eosinophils as seen in Fig. 11.9B give clue to the diagnosis in >95% cases irrespective of the clinical presentation and should be the first line of investigation in suspected cases. The gold standard for diagnosis of any food allergy is the elimination and challenge test. Typically the symptoms subside after milk withdrawal and recur within 48 hr of re-exposure to milk.

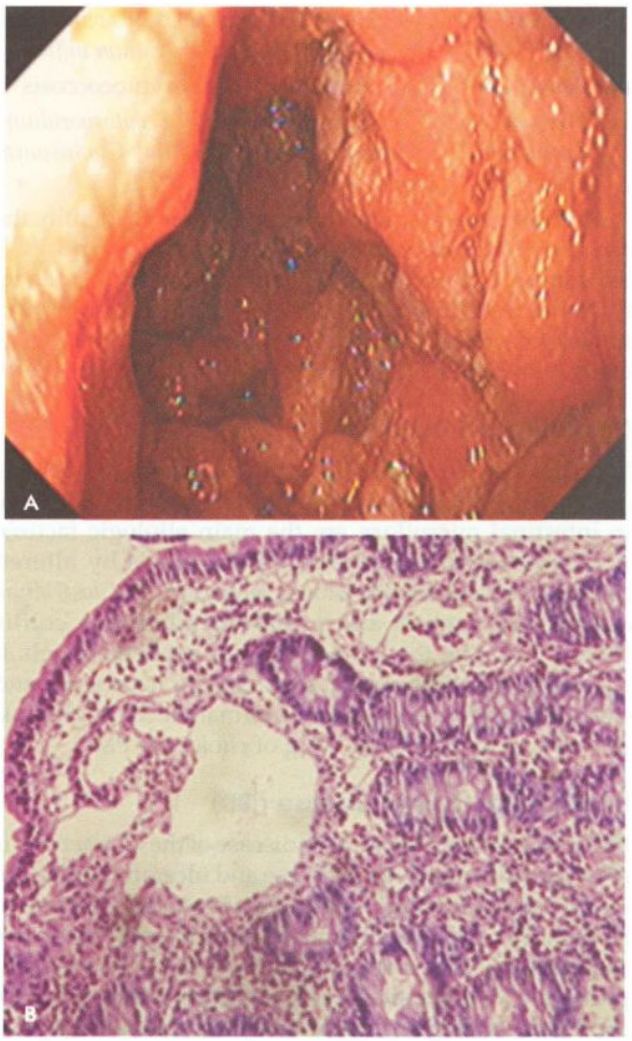


Figs 11.9A and B: Cow milk protein allergy. (A) Sigmoidoscopy showing aphthous ulcers; (B) rectal biopsy showing eosinophilic infiltration with crypt abscess

Treatment All animal milk/milk products have to be removed from the diet. Soy or extensively hydrolyzed formula, both of which are equally effective in terms of growth and nutrient intake can be used as alternatives. Although soy is more palatable and cheap but it is not recommended in infants <6 months of age. Also 10–15% of CMPA have concomitant soy allergy, thus necessitating use of extensively hydrolyzed formulae. A minority of children may not tolerate the extensively hydrolyzed formulae and need elemental amino acid formulas. Parental education regarding diet and calcium supplementation is essential.

Intestinal Lymphangiectasia

It is characterized by ectasia of the bowel lymphatic system, which on rupture causes leakage of lymph in the bowel. The disease is often associated with abnormal lymphatics in extremities. Signs and symptoms include peripheral edema which could be bilateral and pitting due to hypoalbuminemia or asymmetrical and nonpitting due to lymphedematous limb. Diarrhea, abdominal distension and abdominal pain are commonly present. Abdominal and/or thoracic chylous effusions may be associated. Presence of hypoalbuminemia, low immunoglobulins, hypocalcemia and lymphopenia is characteristic of lymphangiectasia. Barium meal follow-through shows thickening of jejunal folds with nodular lucencies in mucosa. On UGI endoscopy after fat loading with 2 gm/kg of butter at bedtime scattered white plaques or chyle like substance covering the mucosa may be seen (Fig. 11.10A). Duodenal biopsy reveals dilated lacteals in villi and lamina propria (Fig. 11.10B). The treatment consists of a low fat, high protein diet with MCT oil, calcium and fat soluble vitamin supplementation. Intravenous albumin is required for symptomatic management and total parenteral nutrition (TPN) is reserved for management of chylous effusions. Resection may be considered if the lesion is localized to a small segment of intestine.



Figs 11.10A and B: Intestinal lymphangiectasia. (A) Upper gastrointestinal endoscopy showing white deposits; (B) duodenal histology shows dilated lacteals

Immunodeficiency

Both congenital and acquired immunodeficiency can cause chronic diarrhea. It should be suspected if there is history of recurrent infections at multiple sites (chest/GI/skin) and wasting. The common immunodeficiency conditions presenting with diarrhea include IgA deficiency, severe combined immunodeficiency (SCID), common variable immunodeficiency (CVID) and chronic granulomatous disease (CGD). There is increased risk of celiac disease (10–20-fold increase) and Crohn disease in patients with *IgA deficiency*. Diarrhea is either due to enteric infections like giardia, cryptosporidium, CMV, etc. or due to bacterial overgrowth. Diagnosis is made by measuring serum immunoglobulins, T cell counts and functions, phagocytic function (nitro blue tetrazolium reduction test) depending upon the suspected etiology. Treatment involves administration of antimicrobials for bacterial overgrowth and opportunistic infections and therapy for underlying cause (IV immunoglobulins, γ interferon or bone marrow transplantation).

Acquired immunodeficiency syndrome (AIDS) Chronic diarrhea is a common feature in children with AIDS. The impaired mucosal immunity results in recurrent opportunistic infections and the altered maturation and function of enterocytes results in increased permeability and decreased functional absorptive surface with or without bacterial overgrowth. AIDS enteropathy is characterized by chronic diarrhea and marked weight loss in absence of enteric pathogens. The children are often sick with other clinical manifestations but sometimes diarrhea may be the only symptom. Presence of oral thrush, lymphadenopathy hepatosplenomegaly and parotiditis (10–20% cases) gives clue to the diagnosis. The common infections include:

i. *Viral*. Cytomegalovirus, herpes simplex, adenovirus, norovirus

ii. *Bacterial. Salmonella, Shigella, Mycobacterium avium* complex (MAC), *Campylobacter jejuni, Clostridium difficile*
iii. *Fungi.* Candidiasis, histoplasmosis, cryptococcosis
iv. *Protozoa. Microsporidium, Isospora belli, Cryptosporidium, Entamoeba histolytica, Giardia lamblia, Cyclospora, Blastocystis hominis*

Multiple stool examinations are required to identify the causative etiology by using special stains and PCR techniques. Colonic/terminal ileum biopsy and duodenal fluid examination are the other ways of diagnosing opportunistic infections. Treatment is with specific antimicrobials along with HAART (highly active anti-retroviral therapy).

Drug Induced Diarrhea

Diarrhea can be a side effect of many pharmacologic agents. Altered GI motility, mucosal injury and/or change in intestinal microflora are the main etiologic factors. Antibiotics can cause loose watery stools by altered bacterial flora or bloody stools secondary to *Clostridium difficile* overgrowth and pseudomembranous colitis (PMC). Stopping the offending agent is often enough. If suspicion of PMC is present then stool for toxin assay and sigmoidoscopy is required for confirmation. Metronidazole or oral vancomycin is the drug of choice for PMC.

Inflammatory Bowel Disease (IBD)

IBD is a chronic inflammatory disease of the GI tract and is of two main types, Crohn disease and ulcerative colitis. In ~10% cases the findings are non specific and subjects cannot be classified into one of the above two groups. These cases are labelled as indeterminate colitis. Nearly 25% of all IBD presents in the pediatric age group. Worldwide the incidence of IBD is increasing in children with increase in recent reports of both ulcerative colitis and Crohn disease from India. The average age of presentation in children is ~10–11 yr. Genetics is a very important risk factor for IBD and up to 30% patients may have a family member with IBD.

Clinical features Children with ulcerative colitis present with diarrhea and rectal bleeding which raises alarm and leads to early workup and diagnosis. In Crohn disease abdominal pain, diarrhea and growth failure are the predominant complaints. The classical triad of Crohn disease, i.e. pain, diarrhea and weight loss is seen in only 25% cases. Fever, fatigue and anorexia are present in 25–50% cases. The absence of blood in stools and non-specific complaints are responsible for delay in diagnosis of Crohn disease in children.

Extraintestinal manifestations are seen in 25–30% children with IBD. They can precede, follow or occur concurrently with the intestinal disease and may be related/unrelated to activity of the intestinal disease. Arthralgia/arthritis is most common extraintestinal manifestation seen in 15–17% cases. Uveitis, erythema nodosum and sclerosing cholangitis are the other extra-intestinal manifestations.

Disease distribution Ulcerative colitis is classified as distal colitis (proctitis/proctosigmoiditis), left side colitis (up to splenic flexure) and pancolitis with majority of children having pancolitis. Majority of patients with Crohn disease (50–70%) have ileocolonic disease, with isolated colonic involvement in 10–20% and small bowel in 10–15% patients. Upper GI involvement is present in 30–40% cases and perianal disease in 20–25% cases. Crohn disease is also classified as predominantly inflammatory, fistulizing or stricturing disease based on the clinical features.

As the management and prognosis of Crohn disease and ulcerative colitis is different, so a correct diagnosis is essential. Table 11.17 lists the main differentiating features between ulcerative colitis and Crohn disease.

Diagnosis The initial evaluation of a child with suspected IBD includes a detailed clinical, family and treatment history. A complete examination with growth charting, perianal and rectal examination for fistulae, tags and fissures is essential. Simple lab tests like hemogram, ESR, C reactive protein, total protein, serum albumin and stool for occult blood helps in screening for IBD and confirming presence of bowel inflammation.

According to the recommendations of the IBD working group, upper GI endoscopy with biopsy, colonoscopy

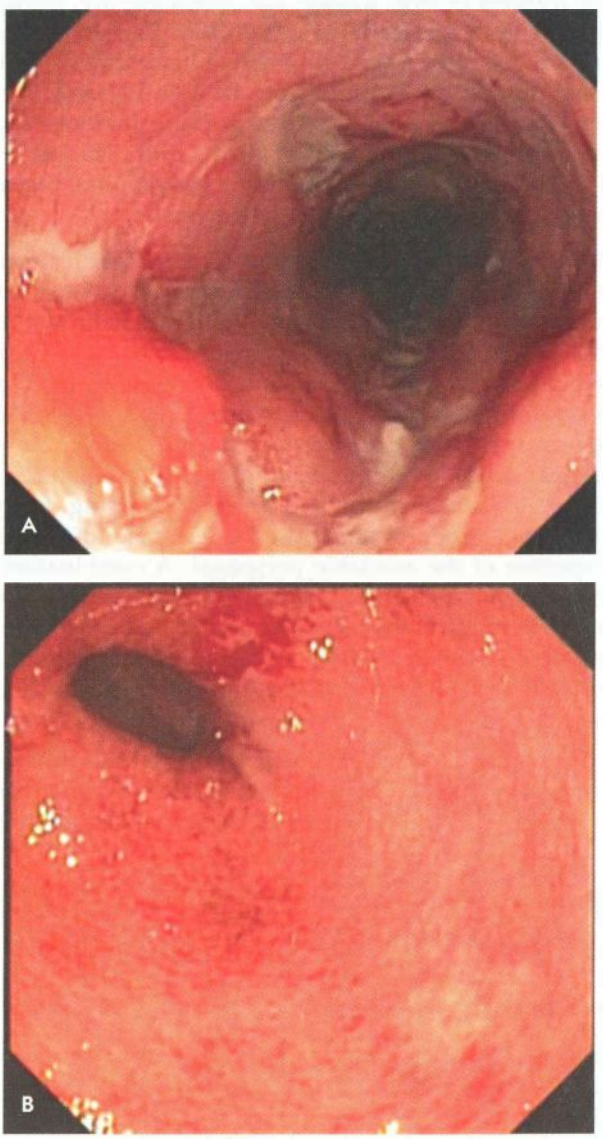
Table 11.17: Differentiation between Crohn disease and ulcerative colitis

	Crohn disease	*Ulcerative colitis*
Distribution	Entire gastrointestinal tract Discontinuous lesions	Colon only Continuous involvement
Bloody diarrhea	Less common	Common
Abdominal pain	Common	Less common
Growth failure	Common	Less common
Perianal disease	Abscess; fistulae	Absent
Serology	Anti sacchromyces cerevisae antibody (ASCA) positive	Perinuclear anti neutrophilic cytoplasmic antibody (p-ANCA) positive
Endoscopy	Deep irregular serpigenous or aphthous ulcers with normal intervening mucosa (skip lesions)	Granularity, loss of vascular pattern, friability and diffuse ulceration
Histopathology	Transmural inflammation with non-caseating granuloma	Mucosal disease with cryptitis, crypt distortion, crypt abscess and goblet cell depletion

with ileal intubation and biopsy is essential for all cases (Figs 11.11 A and B). Small bowel evaluation with BMFT, CT enteroclysis or MR enterography should be done for correct classification into ulcerative colitis or Crohn disease and to determine the disease extent.

Treatment The goal of treatment is to control inflammation, improve growth and ensure a good quality of life with the least toxic therapeutic regimen. As IBD is a chronic disease with remissions and exacerbations, proper counseling of both patient and family at diagnosis is essential. The main drugs used for IBD are 5 aminosalicylates (5-ASA), steroids and immunomodulators (6-mercaptopurine, azathioprine, methotrexate and monoclonal antibodies against tumor necrosis factor, i.e. infliximab). Ensuring proper nutrition with caloric supplementation (~120% of RDA) is a necessity for children with IBD. Calcium and vitamin D supplementation should be given as these children are at an increased risk of osteoporosis.

Surgery is indicated in ulcerative colitis patients with severe acute colitis refractory to medical disease. Uncontrolled hemorrhage, perforation, toxic megacolon, abscesses and obstruction are the other indications for surgery in patients with IBD.



Figs 11.11A and B: Inflammatory bowel disease. (A) Deep, linear, serpigenous ulcers on colonoscopy in Crohn disease; (B) confluent superficial ulcerations with friability on colonoscopy in ulcerative colitis

Abdominal Tuberculosis

The gastrointestinal tract, peritoneum, lymph nodes and/or solid viscera can be involved in abdominal tuberculosis. The peritoneal involvement is of two types: wet (or ascitic) and dry (or plastic) type. On the other hand, the intestinal involvement may be ulcerative, hypertrophic or ulcerohypertrophic type.

The clinical presentation is varied and depends upon the site of disease and type of pathology. Clinical features may include chronic diarrhea, features of subacute intestinal obstruction (abdominal pain, distension, vomiting, obstipation), ascites, lump in abdomen (ileocecal mass, loculated ascites, lymph nodes) and/or systemic manifestations (fever, malaise, anorexia and weight loss).

A high index of suspicion followed by documenting presence of acid fast bacilli (fine needle aspiration cytology from lymph nodes, ascitic fluid, endoscopic biopsies) on Ziehl-Neelsen staining, PCR or culture leads to a definitive diagnosis. Presence of tubercular granuloma with caseation in the biopsies (endoscopic, peritoneal or liver) also helps make the diagnosis. CT abdomen shows enlarged lymph nodes with central necrosis (Fig. 11.12). An exudative ascites (low serum to ascitic fluid albumin gradient) with lymphocyte predominance and high adenosine deaminase is typical of tubercular ascites. In absence of above features, a probable diagnosis of abdominal tuberculosis is made when suggestive clinical features and response to antitubercular therapy is present. It is important to differentiate intestinal TB from Crohn

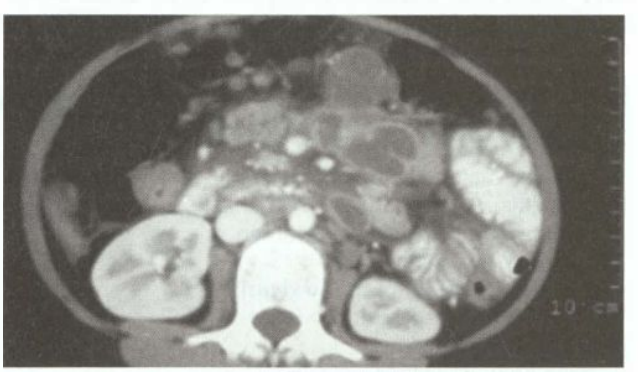


Fig. 11.12: CT scan showing multiple enlarged lymph nodes with central necrosis in para-aortic and mesenteric region in abdominal tuberculosis

disease as they mimic each other in clinical presentation but have different treatments.

Antitubercular drugs are the mainstay of treatment. Surgery is indicated if there is bowel perforation, obstruction or massive hemorrhage. One should suspect multidrug resistant tuberculosis in patients with a definite diagnosis of abdominal tuberculosis but a poor response to standard antitubercular therapy.

Suggested Reading

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GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding is a commonly encountered problem in children. *Upper gastrointestinal bleeding* is defined as bleeding from a site proximal to the ligament of Treitz (at the level of duodenojejunal flexure). *Lower gastrointestinal bleeding* is defined as bleeding from a site distal to ligament of Treitz.

Hematemesis is passage of blood in vomiting and suggests an upper GI site of bleeding. The vomitus may be bright red or coffee-ground in color depending upon the severity of hemorrhage and the duration it stayed in contact with gastric secretions. *Melena* is passage of black tarry stools and suggests an upper GI or small bowel source of bleed. *Hematochezia* is passage of bright red blood in stools. *Hemobilia* refers to bleeding from the biliary tree while pseudohematobilia is bleeding from the pancreas. *Obscure GI bleed* is defined as bleeding from gastrointestinal tract that persists or recurs without any obvious etiology after a diagnostic esophagogastroduodenoscopy and colonoscopy. It accounts for ~5% of all GI bleeds.

Upper GI Bleeding

The causes of hemorrhage from upper GI tract vary in different age groups as shown in Table 11.18. Varices, esophagitis and gastritis are the commonest causes of upper GI bleeding in Indian children.

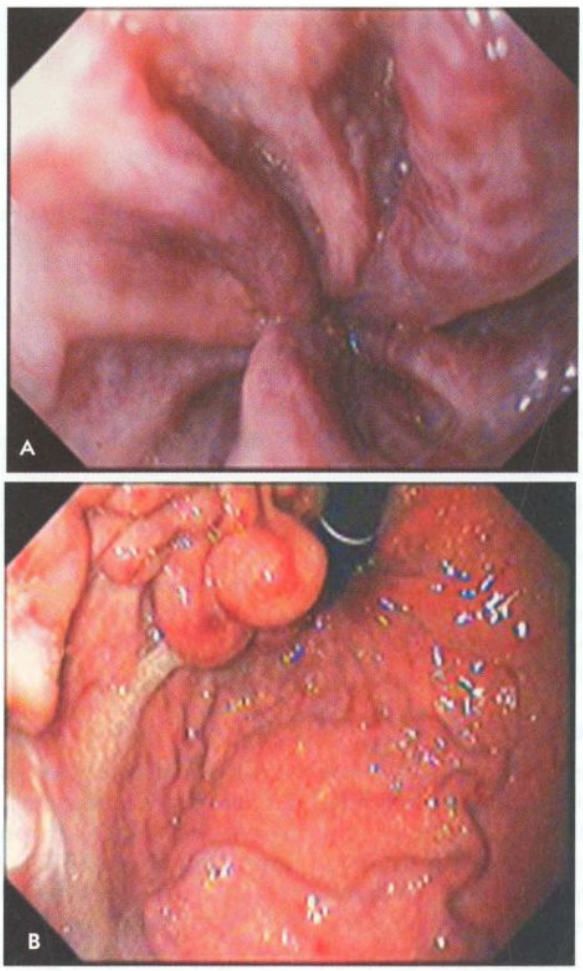
Painless passage of large amount of blood in vomitus points towards variceal bleeding. One should always look for features of liver disease like splenomegaly, jaundice and ascites. In portal hypertension, the spleen may reduce in size just after a bout of massive hematemesis and is thus missed on examination. In a child with portal hypertension, esophageal varices are the commonest cause of upper GI bleeding (Fig. 11.13A). Gastric varices (Fig. 11.13B), congestive gastropathy and gastric antral vascular ectasia can also present with hematemesis.

Management. General supportive measures, including establishing a good venous access, intake output monitoring, oxygen supplementation (if required) and charting of vital signs are mandatory. Blood transfusion should be given to achieve hemoglobin of 8 g/dl. Short-term antibiotic prophylaxis (third generation cephalosporin for 7 days) may reduce bacterial infection and variceal rebleeding, and should be administered in children with cirrhosis and variceal bleeding. *Specific treatment* depends upon the patient's condition and expertise of the available personnel. A combination of pharmacologic and endoscopic therapy is preferred. Early administration of vasoactive drugs should be followed by endoscopic therapy within 12 hr of bleed. Following an episode of acute variceal bleeding, all patients should receive secondary prophylaxis to prevent rebleeding.

Administration of somatostatin or octreotide decreases the splanchnic and azygous blood flow, thus reducing portal pressures. Both agents are equally effective; limited

Table 11.18: Causes of upper gastrointestinal bleeding

Neonate or infant	*Children >2 yr*
Swallowed maternal blood	Esophagitis due to reflux, medications, infections
Esophagitis	Mallory-Weiss tear
Gastroduodenal erosion or ulceration	Gastric erosions; duodenal or gastric ulcer
Sepsis or coagulopathy	Portal hypertension causing esophageal/gastric varices; congestive gastropathy; gastric antral vascular ectasia
Hemorrhagic disease of the newborn	Caustic ingestion, foreign body impaction
Esophageal varices (children >4 mo)	Vascular malformation, Henoch-Schönlein purpura
Vascular malformation	Tumors: leiomyoma, lymphoma
Foreign body impaction	*Rare:* gastrointestinal duplication, hemobilia, radiation gastritis, coagulopathy
Rare: Antral/duodenal web, gastric cardia prolapse, heterotopic pancreatic tissue, esophageal duplication	



Figs 11.13A and B: Upper gastrointestinal endoscopy showing (A) esophageal varices; (B) large gastric varices

studies in children have shown control of bleeding in 64–71% children. Infusion should be given for at least 24–48 hr after the bleeding has stopped to prevent recurrence and should not be discontinued abruptly.

Endoscopic sclerotherapy (EST) or variceal ligation (EVL) are the two main methods used to manage esophageal varices. Using a fiberoptic endoscope, the varices are inspected and their location, size and extent are documented. In EST, 2–3 ml of sclerosant (1% ethoxysclerol) is injected into each variceal column. EVL is done with a device called multiple band ligator. The variceal column is sucked into a cylinder attached at the tip of the endoscope and the band is deployed by pulling the trip wire around the varix. Both EST and EVL have 90–100% efficacy in controlling acute bleeding.

Gastric varices are managed with endoscopic injection of tissue adhesive glue, i.e. N-butyl-2-cyanoacrylate or isobutyl-2-cyanoacrylate. These agents harden within 20 seconds of contact with blood and result in rapid control of active bleeding.

Tamponade of varices is required only when the endoscopic and pharmacologic measures have failed. Sengstaken-Blakemore tube is a triple lumen tube with connection to an esophageal balloon, a gastric balloon and one perforated distal end which helps in aspiration of the stomach contents. The tube is relatively cheap, requires little skill compared to EST and has efficacy of above 75% in controlling acute variceal bleeding.

Transjugular intrahepatic portosystemic shunt (TIPS) involves insertion of a multipurpose catheter through the jugular vein and superior vena cava with the aid of the puncture device. The catheter is passed via hepatic vein into a branch of portal vein through the hepatic parenchyma. The passage is dilated by a balloon and an expansile metallic mesh prosthesis is placed to maintain the communication directly between the portal vein and hepatic vein. This procedure results in bypassing liver resistance and consequently decreases the portal pressure. Experience of this procedure in children is limited.

Surgical management is required when above measures have failed or when bleeding is from ectopic varices that cannot be effectively controlled by endoscopic procedures. Surgery can be done either in the form of portocaval shunt (selective or nonselective) or devascularization with esophageal staple transection.

Lower Gastrointestinal Bleeding

The causes of lower gastrointestinal bleeding in children are shown in Table 11.19. History and physical examination helps narrow down the differential diagnosis. Increased

Table 11.19: Causes of lower gastrointestinal bleeding

Neonate or infant	*Children >2 yr*
Colitis	
Infectious colitis	Infectious colitis
Cow milk protein allergy	Inflammatory bowel disease
Necrotising enterocolitis	Tuberculosis
Hirschsprung enterocolitis	Pseudomembranous colitis
	Cow milk protein allergy
Systemic vasculitis	Uncommon: Amebiasis, cytomegalovirus, neutropenic colitis
Noncolitic	
Anal fissure	Fissure
Intussusception	Polyp or polyposis syndrome
Duplication cyst	Solitary rectal ulcer syndrome
Arteriovenous malformation	Meckel's diverticulum
	Rectal varices or colopathy
Rectal prolapse	NSAID induced ulcer
Meckel's diverticulum	Hemorrhoids
Hemorrhagic disease of newborn	Henoch-Schönlein purpura
	Arteriovenous malformation
Coagulopathy	Coagulopathy

frequency of stools with blood and mucus with crampy abdominal pain points towards a colitic illness and infectious colitis is by far the commonest cause in children across all ages. A sick preterm with abdominal distension, blood in stools, feed intolerance and systemic instability is likely to have necrotizing enterocolitis. Delayed passage of meconium followed by constipation, abdominal pain and distension is seen in Hirschsprung's disease. Allergic colitis is mostly seen in infants who are top fed with cow milk and present with loose stools mixed with blood and anemia. Onset of bloody diarrhea after antibiotic use points towards pseudomembranous colitis. Presence of extraintestinal manifestations like aphthous ulcers, joint pains and iritis gives clue to the diagnosis of inflammatory bowel disease (IBD). History of painful defecation and passage of hard stools with blood streaking of stools is seen in anal fissure. In a patient with history of constipation, straining at stools and digital evacuation, the most likely cause of bleeding is solitary rectal ulcer syndrome (SRUS). Intussusception is characterized by episodes of abdominal pain, vomiting and red currant-jelly stools, i.e. mixture of blood, mucoid exudates and stool. Painless bleeding is seen commonly in polyps, Meckel's diverticulum, ulcer or vascular anomaly. Presence of typical cutaneous lesions as seen in blue rubber bleb nevus syndrome often suggests the diagnosis. Children with HIV infection or immunosuppression secondary to chemotherapy can develop CMV enterocolitis or polymicrobial inflammation of cecum (typhlitis), both of which can lead to significant rectal bleeding.

On examination, presence of fissure and fleshy anal tags suggests Crohn disease whereas characteristic orobuccal pigmentation is seen in Peutz-Jegher syndrome. Abdominal examination is useful in detecting sausage shaped mass in intussusception. A gentle per rectal examination can detect polyps in the rectum and also stool impaction. Presence of palpable purpura in lower limbs with abdominal pain suggests a diagnosis of Henoch-Schönlein purpura. Asking the child to strain will show presence of rectal prolapse.

The aim of investigations in a child with lower gastrointestinal bleeding is to localize the site of bleeding, i.e. small bowel or colon and also to determine the etiology in order to manage it appropriately. The approach is as shown in Table 11.20. Supportive treatment is similar to that of upper gastrointestinal bleeding and the specific treatment is dependent upon the cause.

Table 11.20: Evaluation for etiology of lower gastrointestinal tract bleeding

Colitic presentation
Hemogram, ESR
Stool examination for trophozoites, culture sensitivity, assay for *Clostridium difficile* toxin
Colonoscopy with biopsy for histology, culture, immunohistochemistry
Noncolitic presentation
Hemogram, ESR, prothrombin time
Colonoscopy and biopsy or polypectomy
Based on presentation
Ultrasonography abdomen (suspected intussusception)
^{99m}Tc pertechnate scan (Meckel diverticulum or intestinal duplication)
Triple phase CT angiography and selective cannulation of mesenteric vessel for embolization (ongoing aneurysmal bleed)
Wireless capsule endoscopy, double balloon endoscopy and push endoscopy (obscure site of bleeding in the small bowel)
Preoperative enteroscopy (significant ongoing bleeding from unknown site)

Suggested Reading

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Intestinal Failure

Ther term intestinal failure refers to a malabsorptive state in which the residual intestinal function is inadequate. It is the end result of any disease that causes chronic dependence on total parenteral nutrition (TPN) to maintain growth, hydration or micronutrient balance. The most common etiologies are:

i. Short bowel syndrome: Midgut volvulus, gastroschisis, trauma, necrotizing enterocolitis
ii. Mucosal enteropathy: Microvillous inclusion disease, tufting enteropathy and autoimmune enteropathy.
iii. Dysmotility syndrome: neuropathic or myopathic

Short bowel syndrome is the commonest cause and usually results from surgical resection of the small bowel.

The aim of management is to provide adequate nutrition for growth and development and to promote bowel adaptation. The identification of etiology is important as conditions like primary enterocyte disorders require early referral to an intestinal transplant centre. Catheter associated infections and TPN related liver diseases are important complications that affect long term survival. Intestinal transplantation in isolation or combined small bowel and liver transplant (in presence of TPN related liver disease) is the treatment of choice for patients with refractory disease.

Suggested Reading

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DISORDERS OF THE HEPATOBILIARY SYSTEM

The liver has immense regenerative capacity and plays a vital role in maintaining normal body metabolism. It stores excess carbohydrates as glycogen and releases glucose during fasting by glycogenolysis or gluconeogenesis. It also synthesizes proteins like albumin, fibrinogen, transferrin, low-density lipoproteins, ceruloplasmin and complement and coagulation factors. The liver is also responsible for lipid metabolism by fatty acid oxidation and detoxification of drugs. The primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in liver and excreted in bile which helps in bile flow and fat absorption. Hepatomegaly, jaundice, pruritus, growth failure, portal hypertension (splenomegaly and ascites), variceal bleeding and hepatic encephalopathy are common manifestations of liver disease in children.

Evaluation

After accurate history and physical examination, a judicious selection of laboratory tests helps in arriving to a definite diagnosis.

Biochemical Tests

Bilirubin. Total and fractionated (unconjugated and conjugated) bilirubin helps to differentiate between elevation caused by hemolysis versus hepatocellular or biliary dysfunction.

Transaminases (aspartate aminotransferase or serum glutamate-oxaloacetate transferase (AST, SGOT) and alanine amino-transferase or serum glutamate pyruvate transferase (ALT, SGPT). ALT is present mainly in liver and in lower concentration in muscle while AST is derived from other organs as well (muscles, kidney, red blood cells). Most marked increase in transaminases occurs with acute hepatocellular injury secondary to inflammation or ischemia, while in chronic liver disease transaminases are mildly or moderately elevated.

Alkaline phosphatase (ALP). Normal values are higher in growing children due to bone isoenzyme fraction. If elevation is associated with increased gamma glutamyl transpeptidase (GGT), it suggests cholestasis. GGT is more specific for hepatobiliary disease. The values are higher in newborns and reach normal adult values by 6–9 months.

Prothrombin time (PT) and international normalized ratio (INR). Deficiency of factors V and vitamin K dependent factors (II, VII, IX and X) occurs in liver disease. PT is a marker of synthetic function of liver. INR is a standardized way of reporting the prothrombin time. It is the ratio of a patient prothrombin time to a normal sample, raised to the power of the international sensitivity index (ISI) value for the analytical system used. ISI ranges between 1.0 and 2.0 and shows how a batch of tissue factor compares to an internationally standardized sample.

$$INR = (PT\ test/PT\ normal)^{ISI}$$

The reference range for prothrombin time is usually around 11–16 seconds; the normal range for the INR is 0.8–1.2. A prolongation of PT by >3 seconds is abnormal.

Serum proteins. The half-life of albumin is 20 days; albumin is a marker of liver synthetic functions and is low in chronic liver disease. Gamma globulins are increased in autoimmune hepatitis; the ratio of albumin to globulin is reversed in cirrhosis, particularly in autoimmune liver disease. Low serum albumin and prolonged PT (un-responsive to vitamin K) indicate poor synthetic liver functions, raised ALT and AST indicate inflammation and raised ALP and GGT suggest cholestasis.

Serum ammonia levels. Levels are raised in hepatic encephalopathy.

Cholesterol. Levels are increased in cholestasis.

Radiological Tests

X-ray abdomen. Hepatomegaly, calcification in space occupying lesions in liver, air under the diaphragm (pneumoperitoneum) or in a space occupying lesion (liver abscess) or in portal vein (necrotizing enterocolitis) can be seen on plain X-ray of the abdomen.

Ultrasonography. It is an extremely useful, cost effective and easily available imaging tool. It provides information regarding: (i) liver and spleen size, echotexture and space occupying lesion, (ii) splenoportal axis and hepatic venous system by Doppler ultrasonography, (iii) ascites, lymph nodes, and (iv) gallbladder, biliary tree and pancreas.

CT scan. It provides information similar to ultrasonography and has the advantage of better resolution especially for evaluation of pancreas, focal lesions like cysts and tumors and vascularity of a lesion following intravenous contrast injection. CT allows visualization at different levels by selecting cuts through the organs and reconstruction in axial planes.

Radionuclide scanning. This technique depends on selective uptake of radiopharmaceutical agent, its pattern and excretion. ^{99m}Tc iminodiacetic acid is taken up by hepatocytes and excreted in bile. It is useful in the assessment of neonatal cholestasis, acute cholecystitis and bile duct perforation.

Cholangiography. It is the direct visualization of the biliary tree after contrast injection. Endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) are commonly done. Sometimes cholangiography is done by the percutaneous transhepatic route.

Liver Biopsy

Biopsy, using a Trucut needle or Bard biopsy gun, is a useful investigation for making a histologic diagnosis especially in neonatal cholestasis, congenital hepatic fibrosis, storage disorders like glycogen storage diseases

and histiocytosis. It is useful for enzymatic estimation in metabolic diseases and for copper in Wilson disease. It is helpful in diagnosis of infectious diseases by immunohistochemistry and monitoring response to therapy in autoimmune liver disease. Liver biopsy also helps in understanding the stage of liver disease, e.g. chronic hepatitis or cirrhosis, degree of fibrosis and inflammation. Contraindications of liver biopsy are presence of deranged coagulation (prolonged INR, decreased platelets), ascites or large vascular or cystic lesions in the liver. Complications include intraperitoneal hemorrhage, hematoma formation, bile leak and pneumothorax (*see* Chapter 28).

Hepatomegaly

A palpable liver does not always indicate enlargement. It only reflects the relation of the liver to adjacent structures. In normal children, the liver is palpable one cm and in infants up to 2 cm below the costal margin. When the costal angle is wide, liver may not be palpable and may be more than 2 cm below the rib margin if the costal angle is narrow. Liver is pushed down in pneumothorax, bronchiolitis and emphysema. Visceroptosis associated with rickets and Riedel lobe cause pitfalls in the interpretation of the liver size. It is therefore important to measure the liver span to determine the presence of hepatomegaly. The liver span varies with age: infants 5–6.5 cm; 1–5 yr; 6–7 cm; 5–10 yr; 7–9 cm; and 10–15 yr; 8–10 cm. The liver is also examined for tenderness, consistency and character of the surface. Abdomen should be palpated for other masses or enlargement of the spleen. The liver may be enlarged due to: (i) inflammation, (ii) fatty infiltration, (iii) Kupffer cell hyperplasia, (iv) congestion, (v) cellular infiltration, and (vi) storage of metabolite (Table 11.21).

Splenomegaly

Common causes of splenomegaly are listed in Table 11.22. The spleen is massively enlarged, >8 cm or crossing the umbilicus in the following conditions:

Table 11.21: Causes of hepatomegaly

Chronic liver disease (cirrhosis or chronic hepatitis): Wilson disease, chronic hepatitis B and C, autoimmune liver disease, Budd-Chiari syndrome, cryptogenic
Metabolic or storage disorders: Glycogen storage disease, Gaucher disease, Niemann-Pick disease, progressive familial intrahepatic cholestasis, nonalcoholic fatty liver disease
Infective: Viral hepatitis, liver abscess (pyogenic or amebic), tuberculosis, salmonella, malaria, kala-azar, hydatid disease
Tumors: Lymphoma, leukemia, histiocytosis, neuroblastoma, benign hemangioendothelioma, mesenchymal hamartoma, hepatoblastoma, hepatocellular carcinoma
Biliary: Caroli disease, choledochal cyst, congenital hepatic fibrosis, cystic disease of liver; extrahepatic biliary obstruction
Miscellaneous: Congestive heart failure, constrictive pericarditis, sarcoidosis

Table 11.22: Common causes of splenomegaly

Portal hypertension: Cirrhosis, extrahepatic portal venous obstruction; congenital hepatic fibrosis, noncirrhotic portal fibrosis, Budd-Chiari syndrome
Storage disorders: Niemann-Pick disease, Gaucher disease, mucopolysaccharidosis
Hematological malignancies: Leukemia, lymphoma, histiocytosis
Increased splenic function: Collagen vascular disorders, autoimmune hemolytic anemia, inherited hemolytic anemias
Infections: Malaria, enteric fever, viral hepatitis, infectious mononucleosis, kala-azar; congenital infections
Extramedullary hematopoiesis: Osteopetrosis

i. Noncirrhotic portal hypertension due to extrahepatic portal venous obstruction, congenital hepatic fibrosis and noncirrhotic portal fibrosis
ii. Hematologic malignancies: chronic myeloid leukemia, myeloproliferative disorders; splenic lymphoma
iii. Osteopetrosis
iv. Hemolytic anemia: thalassemia major
v. Storage disorders: Gaucher disease
vi. Infections: kala-azar, chronic malaria; congenital syphilis.

Liver Abscess

Pyogenic liver abscess is more common than amebic liver abscess in children. The infection reaches the liver by one of the following routes: (i) portal vein, e.g. in intra-abdominal sepsis, umbilical vein infection; (ii) biliary tree obstruction and cholangitis, e.g. choledochal cyst; (iii) systemic sepsis, e.g. endocarditis, osteomyelitis; and (iv) direct inoculation, e.g. in trauma. In children on immunosuppressive medications or with defects of neutrophil function, e.g. chronic granulomatous disease) there is an increased risk of developing abscesses, especially due to *S. aureus*.

Invasive intestinal amebiasis can lead to *amebic liver abscess* although a history of amebic colitis in the preceding period is not common. Amebic liver abscess is usually solitary and in the right lobe of liver whereas pyogenic abscesses may be multiple (secondary to cholangitis) or single. Nearly three quarters of pyogenic liver abscesses are in the right lobe of liver.

Clinical features. The child presents with fever and right upper quadrant abdominal pain. Jaundice is uncommon. Examination reveals tender hepatomegaly. Empyema, pneumonia, subphrenic abscess and cholecystitis can have a similar clinical presentation and should be differentiated. Complications include spontaneous rupture into peritoneum, pericardium, pleura or bronchial tree and metastatic spread to lungs or brain.

Diagnosis. Leukocytosis and elevated ESR are usually present. Transaminases and alkaline phosphatase are mildly elevated. X-ray abdomen shows an elevated right

dome of diaphragm with or without pleural effusion. Diagnosis is confirmed by imaging; ultrasound provides good details about abscess size, number, rim and liquefaction. Contrast enhanced CT scan may be required in patients with complications (Fig. 11.14). Amebic serology (indirect hemagglutination test) is positive in >95% children with amebic liver abscess and helps to differentiate it from pyogenic abscess.

Management. Patients with pyogenic liver abscesses are treated with broad spectrum antibiotics (against gram-positive, gram-negative aerobic and anerobic bacteria) for 4–6 weeks. Metronidazole is used for 10–14 days in patients with amebic liver abscess. Ultrasound guided percutaneous needle aspiration and/or catheter drainage is required for abscesses that fail to improve after 3–4 days of antibiotic therapy, large abscesses in left lobe and impending rupture (narrow rim <1 cm). Surgery is required for abscesses complicated by frank intraperitoneal rupture or multiseptate abscesses not responding to percutaneous catheter drainage and antibiotics.

Prognosis. The abscess cavity takes 3–6 months to resolve completely. Cure rate following management with antibiotics and percutaneous drainage is excellent.

Liver Tumors

Liver tumors account for ~0.5–2% of all neoplasms in children. Hepatoblastoma, hemangioendothelioma and mesenchymal hamartoma are seen primarily in young children whereas hepatocellular carcinoma, undifferentiated embryonal sarcoma and focal nodular hyperplasia present in the older child. The most common tumors are hepatoblastoma, hepatocellular carcinoma and infantile hemangioendothelioma.

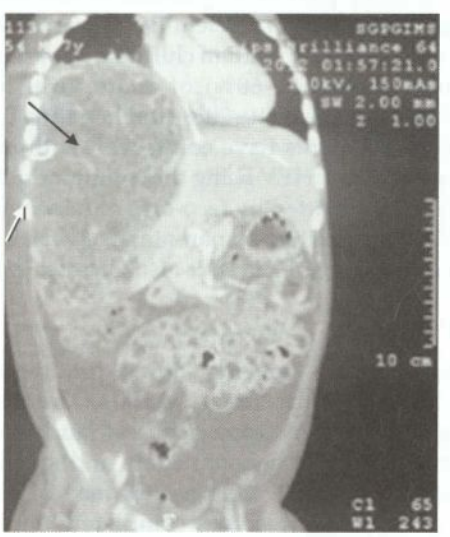

Fig. 11.14: Computed tomography scan shows a multiloculated liver abscess in the right lobe (black arrow) with elevated right dome of diaphragm and ascites. Percutaneous drainage catheter is seen *in situ* (white arrow)

Infantile hepatic hemangioendothelioma is a benign tumor and presents in first 6 months of life with an abdominal mass. Jaundice, skin hemangiomas and congestive heart failure may be associated. The lesion may be single or multiple and is made of thin vascular channels. Observation is recommended for focal lesions. Treatment options for multifocal and diffuse lesions include corticosteroids, hepatic artery ligation with or without corticosteroids, hepatic artery embolization, surgical resection or liver transplantation.

Hepatoblastoma is the most common malignant liver tumor in children. It is of two types: epithelial (fetal or embryonal malignant cells) and mixed (epithelial and mesenchymal elements) and presents with an abdominal mass and anorexia. Weight loss and pain in abdomen usually appear late; metastasis occurs to lungs and lymph nodes and alphafetoprotein is raised in the majority of cases. Ultrasound helps to differentiate between malignant and vascular lesions. CT and MRI are used to define tumor extent and resectability. The survival of patients with a hepatoblastoma has markedly improved in recent years by combining surgery with pre- and postoperative chemotherapeutic agents such as cisplatin and doxorubicin. Liver transplantation is an option for unresectable hepatoblastoma following chemotherapy in absence of visible extrahepatic disease.

Hepatocellular carcinoma is usually multicentric. The risk is increased in patients with chronic hepatitis B or C infection, tyrosinemia, glycogen storage disease or prior androgen therapy. The tumor presents as a liver mass with abdominal distension, anorexia and weight loss. Liver functions are usually normal and anemia may be present; alphafetoprotein is raised. Imaging with CT/MRI helps in targeting the tumor for needle biopsy, confirming the diagnosis and determining resectability. Bone scan and CT chest should be done to screen for metastasis. Treatment options include surgical resection along with chemotherapy; chemoembolization and liver transplantation.

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Jaundice

The term jaundice means a yellow discoloration of skin, sclera and mucous membrane due to increase in the serum bilirubin levels. Nearly 250–300 mg of bilirubin is produced daily, approximately 70% from breakdown of old erythrocytes in reticuloendothelial system. Bilirubin is cleared by the liver in three steps. It is first transported into hepatocytes by specific carriers. Then it is conjugated

to 1–2 molecules of glucoronide. Thereafter the conjugated bilirubin moves to the canalicular membrane where it is excreted into the bile canaliculi by other carrier proteins. Most of the conjugated bilirubin is excreted in the stool and small amount is reabsorbed after deconjugation by colonic bacteria. Colonic bacteria also reduce bilirubin to urobilinogen, which is reabsorbed and excreted in urine.

Serum bilirubin should be >2.5–5 mg/dl for jaundice to be visible. Hyperbilirubinemia is classified as unconjugated (conjugated bilirubin fraction <15% of total bilirubin and normal colored urine) and conjugated hyperbilirubinemia (conjugated bilirubin fraction >20% with high colored urine). Conjugated bilirubin is cleared by kidneys; thus in renal failure, bilirubin levels are increased. Any abnormality of the above steps can cause jaundice (Table 11.23).

Congenital Enzyme Deficiencies

Gilbert syndrome is the most common cause of unconjugated hyperbilirubinemia and affects 3–8% of the population. It results from a partial deficiency of the enzyme uridine diphosphate glucuronyl transferase (UDP-GT) and thus, impaired conjugation. Most patients are asymptomatic and exhibit chronic or recurrent jaundice (up to 6 mg/dl) precipitated by intercurrent illness, fasting or stress. Mild fatigue, nausea, anorexia or abdominal pain may be present in some patients. Other liver functions remain normal. No specific treatment is necessary for this disorder.

Crigler-Najjar syndrome (CN) type I is an autosomal recessive disorder characterized by absence of UDP-GT activity.

Table 11.23 Causes of jaundice in children

Unconjugated hyperbilirubinemia
Hemolysis: Blood group incompatibility (Rh, ABO), drugs, infection related, glucose-6-phosphate dehydrogenase deficiency, autoimmune hemolysis
Bilirubin overproduction: Ineffective erythropoiesis, large hematoma
Specific conditions in neonates: Physiologic jaundice, breast milk jaundice
Enzyme defects: Gilbert syndrome, Crigler-Najjar syndrome
Miscellaneous: Hypothyroidism, fasting
Conjugated hyperbilirubinemia
Neonatal cholestasis
Infections: Sepsis, acute viral hepatitis, enteric fever, malaria, leptospirosis
Chronic liver disease
Liver tumor: Primary, secondaries
Infiltration: Histiocytosis, leukemia
Enzyme defects: Dubin-Johnson syndrome, Rotor syndrome
Biliary: Choledochal cyst, choledocolithiasis, ascariasis, sclerosing cholangitis
Miscellaneous: Drug toxicity (hepatocellular, cholestatic), total parenteral nutrition, veno-occlusive disease

Patients develop severe unconjugated hyperbilirubinemia and die by 18–24 months of age if untreated. Phototherapy, plasmapheresis and exchange transfusion are required for managing these cases in initial phases. Serum bilirubin levels should be kept below 20 mg/dl during first several months of life to prevent brain damage. Definitive treatment is possible by liver transplantation, preferably auxiliary, if available.

Crigler-Najjar syndrome type II is also known as Aria syndrome. There is marked reduction of UDP-GT. In comparison to type I, jaundice is less severe and does not result in kernicterus. The condition responds to drugs like phenobarbitone that stimulate hyperplasia of the endoplasmic reticulum. The bilirubin level significantly decreases in type II CN following administration of phenobarbitone, while no change is seen in type I patients.

Dubin-Johnson syndrome is an autosomal recessive disorder resulting from impaired hepatic excretion of bilirubin and causes conjugated hyperbilirubinemia (2–6 mg/dl). The transaminases and synthetic liver functions are normal. Most patients are asymptomatic apart from jaundice. Pregnancy and oral contraceptives may worsen jaundice. Liver biopsy is often done for exclusion of other causes and shows brown-black pigmentation.

Rotor syndrome is a rare, autosomal recessive disorder manifesting as mild conjugated hyperbilirubinemia. The primary defect appears to be a deficiency in the intracellular storage capacity of the liver for binding anions. The liver histology is normal.

ACUTE VIRAL HEPATITIS

Viruses can affect the liver, either primarily, e.g. hepatitis A, B, C, E or as part of a systemic involvement, e.g. cytomegalo-virus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV). In Indian children, hepatitis A is the commonest cause (40–60%) of acute viral hepatitis, followed by hepatitis E (10–20%) and hepatitis B (7–17%). Nearly 8–20% patients have coinfection with more than one virus, HAV and HEV being the commonest. Hepatitis A and E are transmitted by feco-oral route whereas HBV and HCV are transmitted by parenteral or vertical (mother to baby) route (Table 11.24) (*see* also Chapter 10).

Clinical Features

Following exposure, patients show a prodrome characterized by low grade fever, malaise, anorexia and vomiting, followed by appearance of jaundice. Examination shows icterus, hepatomegaly and splenomegaly (small, soft in 15–20%). Mild ascites may be present in 10–15% cases, which resolves completely on followup. Over the next few weeks, the appetite improves, jaundice resolves and the child gets better. In young children asymptomatic and anicteric presentation of hepatitis A infection can occur.

Table 11.24: Epidemiological profile of different hepatitis viruses

Virus	*A*	*B*	*C*	*E*
Type of virus	RNA	DNA	RNA	RNA
Incubation period, days	15–40	50–150	30–150	15–45
Route of infection				
Feco-oral	+	–	–	+
Parenteral or others	Rare	Usually perinatal, by sexual contact	Usually perinatal, by sexual contact	–
Chronic liver disease	–	+	+	–
Vaccine	Available	Available	No	No (being developed)
Diagnostic test	IgM; anti-HAV	HBsAg; IgM anti-HBc	Anti-HCV antibody; HCV RNA	IgM anti-HEV

Differential Diagnosis

The conditions, which mimic the clinical features of viral hepatitis include enteric fever, falciparum malaria, leptospirosis and viral hemorrhagic fever. Other conditions that need to be differentiated include drug induced hepatitis, acute presentation of autoimmune liver disease or Wilson disease.

Investigations

Direct hyperbilirubinemia with markedly elevated ALT/AST and normal albumin and prothrombin time are usual. Mild leukopenia with relative lymphocytosis is seen. Ultrasound is not routinely required, but shows mildly enlarged liver with increased echogenicity and edema of gallbladder wall. Viral serologies help determine the etiology of acute viral hepatitis, as shown in Table 11.24.

Complications

These include:

i. *Acute liver failure.* The appearance of irritability, altered sleep pattern, persistent anorexia and uncorrectable coagulopathy (despite administration of vitamin K) suggests the development of acute liver failure.
ii. Aplastic anemia
iii. Pancreatitis
iv. Serum sickness, vasculitis-like reaction may be seen in hepatitis B infection
v. Hemolysis (cola-colored urine) with renal failure in subjects with glucose-6-phosphate dehydrogenase deficiency
vi. *Chronic liver disease:* In patients with viral hepatitis due to HBV, repeat testing for hepatitis B surface antigen should be done after 6 months to document clearance or persistence of infection. A majority (95%) clear hepatitis B infection after acute icteric infection.

Management

Maintaining adequate oral intake is essential intravenous fluids are given if persistent vomiting and dehydration are present. There is no advantage of enforced bed rest, but vigorous activity should be avoided. No specific dietary modification is recommended. The child should be monitored for appearance of complications like encephalopathy.

Prevention

Public health measures like sanitation, safe drinking water supply, hand washing and proper food hygiene are of utmost importance, especially in epidemics of hepatitis A or E. Proper screening of blood and blood products and safe injection practices are essential. Universal immunization against hepatitis B is the most effective way of preventing hepatitis B related disease.

Suggested Reading

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LIVER FAILURE

Liver failure refers to a clinical state resulting from hepatocyte dysfunction or necrosis and not a specific disease etiology. It may occur *de novo* in normal children without any evidence of pre-existing liver disease where it is known as acute liver failure (ALF).

Acute liver failure. An international normalized ratio ≥1.5 with hepatic encephalopathy or an international normalized ratio ≥2 without hepatic encephalopathy along with biochemical evidence of liver injury in the absence of underlying chronic liver disease is considered as acute liver failure. The presence of hepatic encephalopathy is not essential for diagnosis of ALF in children. All international normalized prothrombin values refer to that measured after 8 hr of parenteral vitamin K administration. This definition has evolved with the understanding that detection of mild grades of hepatic encephalopathy in small children is difficult and any behavioral change or irritability in this age group may not be necessarily due to hepatic encephalopathy.

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Patients with chronic liver disease may manifest with features of hepatocellular failure due to progressive worsening of liver function as part of the natural course of the disease or as a sudden dysfunction due to a superimposed hepatic insult resulting in *acute* on *chronic liver failure*. Superimposed insult can be due to hepatotropic virus (hepatitis A, E, B) infection, hepatotoxic drug intake or sepsis and varies with the geographical area.

ALF in children is a condition associated with high mortality and the etiology varies among different age groups (Table 11.25). Autoimmune liver disease and Wilson disease, important causes of chronic liver disease in children, may have an acute presentation mimicking ALF. Drugs, especially antituberculosis therapy and anticonvulsants are a major cause of ALF. In the West, paracetamol poisoning is a common cause of ALF. Herbal medicines and mushroom poisoning are also known to cause ALF. In the neonatal period, liver failure may be a result of metabolic conditions like neonatal hemochromatosis, galactosemia, hereditary fructose intolerance, tyrosinemia type 1 and Niemann-Pick disease, infections and hematological conditions like hemophagocytic lymphohistiocytosis. A careful history and rapid investigations are necessary to identify the etiology, which has prognostic and therapeutic implications. However, 30–40% cases are idiopathic.

Clinical Features

The early clinical manifestations of ALF are nonspecific and characterized by lethargy, anorexia, malaise, nausea and vomiting. Central nervous system manifestations include hepatic encephalopathy and cerebral edema with raised intracranial tension. Hepatic encephalopathy is a result of inability of the liver to process and excrete endogenous toxins. Raised levels of ammonia, GABA, false neurotransmitters and pro-inflammatory cytokines are implicated in its pathogenesis. Hepatic encephalopathy is classified into four stages (Table 11.26). Identification of hepatic encephalopathy in children can be challenging as in the early stages they present with nonspecific findings such as excessive somnolence, reversal of sleep-wake cycle or behavioral and personality changes.

Table 11.26: Stages of hepatic encephalopathy in children

Stage	*Clinical features*	*Reflexes*
I	Inconsolable crying, inattention to task, not acting like self, disturbed sleep-wake cycle	Normal or hyper-reflexic; asterixis absent
II	Same as in stage I	Normal or hyper-reflexic; asterixis easily elicited
III	Somnolence, stupor, combative	Hyper-reflexic; asterixis present
IV	Comatose, responsive to pain (IVA) or non-responsive to pain (IVB)	Decerebrate or decorticate; asterixis absent

Coagulopathy due to impaired production of coagulation factors results in bleeding. Platelet counts are affected in the setting of infection. The patient may manifest with hypoglycemia, electrolyte imbalance and metabolic acidosis. Infections are common in ALF as the immune system is dysfunctional and invasive procedures are performed commonly. This results in gram-positive, gram-negative and fungal infections. Infection may manifest as hypotension, disseminated intravascular coagulation, worsening metabolic acidosis, worsening encephalopathy, oliguria and azotemia.

Investigations for specific causes if suspected are important as specific treatment is needed in these cases (Table 11.27).

Management

The management of liver failure in children is based on: (i) diagnosis of etiology as it influences the prognosis and management; (ii) assessment of severity of liver failure and timely liver transplantation if indicated; and (iii) anticipation, prevention and treatment of complications. Patients should be treated and monitored closely in an intensive care unit (Table 11.28). Elective intubation

Table 11.25: Causes of acute liver failure in children

Infections	Common: Viral hepatitis (A, B, E) Uncommon: Adenovirus, Epstein-Barr, parvovirus, cytomegalovirus, echovirus, varicella, dengue, herpes simplex virus I and II*
Others	Septicemia*, malaria, leptospirosis
Drugs	Isoniazid with rifampicin, pyrazinamide, acetaminophen, sodium valproate, carbamazepine, ketoconazole
Toxins	Herbal medicines, *Amanita phalloides* poisoning, carbon tetrachloride
Metabolic	Wilson disease, galactosemia*, tyrosinemia*, hereditary fructose intolerance*, hemochromatosis*, Niemann-Pick disease type C*, mitochondrial cytopathies*, congenital disorder of glycosylation
Autoimmune	Autoimmune liver disease
Vascular	Acute Budd-Chiari syndrome, acute circulatory failure
Infiltrative	Leukemia, lymphoma, histiocytosis*
Idiopathic	

* More common in neonates and infants

Table 11.27: Investigations for specific causes of acute liver failure

Infectious	
	IgM anti-HAV (hepatitis A virus)
	IgM anti-HEV(hepatitis E virus)
	Hepatitis B surface antigen, IgM antihepatitis B core antigen (hepatitis B virus) CMV PCR (cytomegalovirus) IgM VZV (varicella zoster virus, IgM viral capsid antigen (Epstein-Barr virus)
Metabolic	
Wilson disease	Ceruloplasmin, Kayser-Fleischer ring, 24 hr urinary copper
Autoimmune hepatitis	Anti liver kidney microsomal antibody; antinuclear antibody; anti-smooth muscle antibody; immunoglobulin levels
Tyrosinemia	Urinary succinylacetone level
Galactosemia	Urine nonglucose reducing substances, galactose-1-phosphate uridyl transferase level
Miscellaneous	
Hemophagocytosis	Triglyceride, ferritin, fibrinogen and bone marrow biopsy
Paracetamol poisoning	Plasma levels of paracetamol

Table 11.28: Monitoring of children with acute liver failure

Clinical examination	Pulse rate, respiratory rate, blood pressure, temperature (q 4 hr)
	Intake-output charting (q 6 hr)
	Liver span, neurological monitoring, grading of coma (q 12 hr)
Biochemical tests (at diagnosis, repeat as shown)	Blood sugar, electrolytes, pH, bicarbonate, lactate (q 6–12 hr)
	Prothrombin time (INR) (daily)
	Complete blood counts, CRP (twice a week)
	Transaminases, GGTP, alkaline phosphatase, lactate dehydrogenase, total and conjugated bilirubin (twice a week)
	Creatinine, calcium, phosphate (twice a week)
	Monitor as needed: Evidence of infection on chest X-ray, blood and urine cultures; blood ammonia

and ventilation is beneficial in subjects with stage 3 hepatic encephalopathy or more. The hemodynamics need to be assessed and supported.

Raised intracranial pressure is managed with mannitol 20% (0.5 to 1 g/kg with target osmolality not crossing 320 mOsm/kg) or hypertonic saline (3% to 30%). The target serum sodium should be 145–155 mEq/l to maintain hypertonicity. The head end is kept at 30° elevation in neutral position. Hyperventilation to decrease cerebral edema should be transient. Monitoring intracranial pressure has not been convincingly shown to improve outcomes. Lactulose has not been shown to improve hepatic encephalopathy and outcome. Bowel decontamination by oral nonabsorbable antimicrobials (to decrease ammonia load and to decrease infections) has been tried in ALF but does not alter the survival. Recently N-acetyl cysteine has shown some promise in the early stages of nonparacetamol poisoning ALF. Phenytoin may be used for treating seizures. Normal maintenance intravenous fluids containing dextrose are given and blood glucose is monitored to prevent and treat hypoglycemia. Electrolyte imbalances should be identified and treated early.

Prophylactic antimicrobial regimens have not been shown to improve outcome or survival in patients with ALF. Empirical antibiotics are recommended in circumstances with high-risk of sepsis, i.e. surveillance cultures reveal significant isolates, advanced hepatic encephalopathy, refractory hypotension, renal failure or presence of systemic inflammatory response syndrome (temperature >38°C or <36°C, leukocyte count >12,000 or <4,000/mm^3, tachycardia). Empirical antibiotics are recommended for patients listed for transplantation, because infections result in delisting and these patients need immunosuppression in postoperative phase. Antimicrobials with coverage against gram-positive and gram-negative organisms (cefotaxime with cloxacillin) along with antifungals are used. Aminoglycosides are avoided to prevent renal dysfunction. Close monitoring and early detection of infection is essential. Coagulopathy does not necessarily warrant transfusion of fresh frozen plasma unless bleeding manifestations are clinically evident or an invasive intervention is planned or INR is >7. Proton pump inhibitions are used for stress ulcer prophylaxis.

In spite of adequate supportive care, the mortality in ALF is as high as 60–70%. Early identification of children who would benefit only from liver transplantation is essential. The King's college criteria are one of the commonly used criteria to identify adult patients requiring liver transplantation. However, application of these criteria in developing countries seems to be limited due to variation in etiology other than paracetamol induced liver failure. Young age (≤3.5 yr), bilirubin ≥16.7 mg/dl, prolonged prothrombin time (>40 seconds) and signs of cerebral edema predicted mortality in an Indian study. Table 11.29 lists the specific therapy for common etiologies of ALF.

Suggested Reading

Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010;376:190–201

Polson J, Lee WM. AASLD position paper: the management of acute liver failure. Hepatology 2005;41:1179–97

Shanmugam NP, Bansal S, Greenough A, et al. Neonatal liver failure: etiologies and management. Eur J Pediatr 2011;170:573–81

Srivastava A, Yachha SK, Poddar U.Predictors of outcome in children with acute viral hepatitis and coagulopathy. J Viral Hepat 2012;19:e194–201

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Table 11.29: Specific treatment of conditions causing pediatric acute liver failure

Neonatal hemochromatosis	Antioxidants; chelation; prenatal intravenous immunoglobulin in combination with postnatal exchange transfusion
Tyrosinemia	Nitisinone (NTBC); restriction of phenylalanine and tyrosine in diet
Galactosemia	Galactose and lactose free diet
Hereditary fructose intolerance	Fructose free diet
Mitochondrial cytopathies	Coenzyme Q10, vitamin E, carnitine
Amanita poisoning	Penicillin G, silibinin and N-acetyl cysteine
Herpes simplex	High dose acyclovir (60 mg/kg/day) for 21 days
Acetaminophen poisoning	N-acetyl cysteine (*see* Chapter 26)

CHRONIC LIVER DISEASE

Chronic liver disease (CLD) refers to a spectrum of disorders characterized by ongoing chronic liver damage and a potential to progress to cirrhosis or end stage liver disease. Although a 6-month duration cut off is used for defining chronicity related to hepatitis B and C, it does not apply to the other causes as irreversible liver damage may have already taken place before symptoms of liver disease are recognized.

Cirrhosis is a diffuse liver process characterized by cell injury (necrosis) in response to inflammation/injury and fibrosis and regeneration (nodule formation). When the disease is silent, the patient may have hepatosplenomegaly and abnormal liver function tests and it is termed as compensated cirrhosis. When the patient develops jaundice, gastrointestinal bleed, ascites and/or hepatic encephalopathy, it is known as decompensated cirrhosis.

Etiology

The main causes of CLD in children are listed in Table 11.30. In India, ~25% of CLD is due to metabolic causes (Wilson disease being the commonest), 8–15% are due to hepatitis B and 2–4% due to autoimmune causes. Nearly 40% patients do not have a known etiology, and are labeled cryptogenic.

Clinical Features

The presentation depends on the etiology and pace of disease progression. Patients may present with insidious onset disease with failure to thrive, anorexia, muscle weakness and/or jaundice or abruptly with massive gastrointestinal bleed, acute onset jaundice, along with altered sensorium and ascites. Sometimes the patient may be asymptomatic and child is noticed to have hepatosplenomegaly or elevated transaminases on investigations

Table 11.30: Causes of chronic liver disease

Viral hepatitis	Hepatitis B (common), hepatitis C (uncommon)
Autoimmune liver disease	Autoimmune hepatitis (common), autoimmune sclerosing cholangitis
Metabolic	Wilson disease, glycogen storage disease*, progressive familial intrahepatic cholestasis*, galactosemia*, NASH related, tyrosinemia*, Indian childhood cirrhosis* (rare), cystic fibrosis, hereditary fructose intolerance, alpha-1-antitrypsin deficiency
Venous obstruction	Budd-Chiari syndrome, veno-occlusive disease, constrictive pericarditis, congestive heart failure
Biliary	Biliary atresia*, choledochal cyst*, primary sclerosing cholangitis, Caroli disease
Rare causes	Niemann-Pick disease, Gaucher disease; cystic fibrosis; drug induced (valproate, carbamazepine)

NASH nonalcoholic steatohepatitis
*Causes in infants and young children <5 yr of age

for some unrelated illness. Clinical features on examination that suggest presence of CLD are:

Characteristics of liver. The liver may be firm to hard, nodular or have irregular margins in cirrhosis. Differential left lobe enlargement is a feature of CLD. A small, non palpable shrunken liver is a feature of post necrotic cirrhosis.

Stigmata of CLD. These include spider angiomata, palmar erythema, clubbing, leukonychia, muscle wasting, delayed puberty and gynecomastia. Testicular atrophy and parotid enlargement are present in adults with alcoholic liver disease, but not in children.

Portal hypertension. Splenomegaly, ascites, tortuous veins over abdominal wall, i.e. caput medusa; esophageal varices with/without gastric varices on endoscopy.

Features of hepatic encephalopathy. Asterixis, constructional apraxia or altered sensorium (Table 11.26) may be seen.

Evaluation

Evaluation of patients with suspected CLD is two pronged: (i) determine etiology of CLD and (ii) assess degree of liver dysfunction and presence of complications (Table 11.31). Based on clinical and laboratory features, liver damage is graded using scores like the CHILD score and pediatric end stage liver disease (PELD) score. Complications of CLD are: (i) hepatic encephalopathy; (ii) portal hypertension with variceal bleeding, portopulmonary hypertension and hepatopulmonary syndrome; (iii) ascites and spontaneous bacterial peritonitis; (iv) hepatorenal syndrome; (v) coagulopathy; (vi) nutrition

Table 11.31: Investigations for chronic liver disease

Common investigations	
Liver function tests	Low albumin, reversal of albumin-globulin ratio and prolonged prothrombin time High conjugated bilirubin suggests liver dysfunction or obstruction Raised transaminases suggest hepatocellular injury; raised alkaline phosphatase and gamma glutamyl transpeptidase suggest biliary disease
Ultrasonography	Nodular liver, mass lesion, dilated portal vein and collaterals, ascites, splenomegaly
Upper GI endoscopy	Portal hypertension: esophageal or gastric varices
Liver biopsy	Breaking of lamina limitans and lobular inflammation; nodule formation and loss of architecture in cirrhosis; may also aid in diagnosis of specific diseases
Specific to etiology	
Viral markers	HBsAg, HBeAg, anti-HBe, anti-HCV, HBV DNA, HCV RNA
Autoimmune hepatitis	Anti-smooth muscle, anti-liver kidney microsomal, antinuclear antibodies
Wilson disease	Ceruloplasmin, KF ring; 24 hr urine copper; liver copper
Alpha-1-antitrypsin deficiency	Serum alpha-1-antitrypsin levels; PI type
Galactosemia	Positive nonglucose reducing substances in urine; galactose-1-phosphate uridyl transferase assay
Cystic fibrosis	Sweat chloride test; genetic analysis
Tyrosinemia	Urinary succinylacetone level
Budd-Chiari syndrome	Doppler ultrasonography for hepatic vein, inferior vena cava
Sclerosing cholangitis	Magnetic resonance cholangiopancreatography; liver biopsy
Storage disorders	Bone marrow, fundus examination; liver biopsy

KF Kayser-Fleischer

failure; (vii) increased risk of infections; and (viii) hepatocellular carcinoma.

Hepatic Encephalopathy

Hepatic encephalopathy refers to neuropsychiatric abnormalities that result from liver dysfunction. It is a principal manifestations of CLD and can be graded (Table 11.26). Various factors like gastrointestinal bleed, infection, use of sedatives, dehydration due to aggressive diuresis, constipation and electrolyte imbalance can precipitate encephalopathy. Identification and reversal of the precipitating event is of importance. As ammonia is an important putative metabolite, efforts are targeted towards reducing its production and absorption and facilitating its excretion. Oral antibiotics and synthetic disaccharides have been shown to be effective in minimizing ammonia production in these patients. Neomycin was used in the past but it has serious side effects of deafness and renal toxicity. Rifaximin is a new drug with a better safety profile. Nonabsorbable disaccharides like lactulose and lactitol reach the colon intact and then are metabolized by bacteria into variety of small molecular weight organic acids. It acts by acidifying fecal contents and trapping the diffusible ammonia as ammonium ion in the fecal stream along with alteration in colonic flora (loss of ammonia producing bacteria). In infants and children, protein intake should not be restricted to the point of causing growth failure or compromising overall nutritional status and a target range of 1–2 g/kg/day is often recommended. Vegetable proteins, which are rich in branched chain amino acids are preferred over animal proteins.

Nutrition Failure

Children with end-stage liver disease are at risk for developing nutritional compromise, which increases the disease related morbidity. The etiology of failure to gain weight in children with end-stage liver disease is multifactorial, due to a combination of decreased caloric intake, increased energy expenditure, malabsorption of macro and micronutrients and altered physiologic anabolic signals. Children with CLD also have reduced levels of liver-derived insulin like growth factor 1, which mediates the anabolic action of growth hormone and thus a growth hormone resistant state that negatively impacts growth.

Clinical recognition of malnutrition in infants and children with end-stage liver disease relies on careful monitoring for clinical features like growth failure, loss of muscle mass, delayed motor development or signs of fat-soluble vitamin or essential fatty acid deficiencies (skin rash, peripheral neuropathy, rickets/fractures or bruising). The presence of ascites, edema and organomegaly makes weight an unreliable indicator of nutrition in a child with CLD. So height monitoring, along with assessment of other anthropometric markers of body fat and muscle mass like triceps skin fold and mid-arm circumference should be used.

All patients need increased caloric intake ~120–150% of their estimated daily requirements. Formulas containing medium-chain triglycerides are used to maximize fat absorption in the setting of severe cholestasis. Daily supplements of vitamins and other nutrients like calcium and iron need to be given. For patients who cannot meet the needs by oral feeding, nasogastric tube feedings should be started.

Patients with CLD are especially vulnerable to viral and bacterial infections. Careful attention must be given to ensure that all infants and children with CLD receive entire recommended routine childhood vaccinations.

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Hepatorenal Syndrome

Hepatorenal syndrome is a functional renal impairment as changes are reversible after liver transplant. It is defined as progressive renal insufficiency in absence of other known causes (prerenal, nephrotoxic drugs) of renal failure in patients with severe liver disease.

Suggested Reading

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Leonis MA, Balistreri WF. Evaluation and management of end-stage liver disease in children. Gastroenterology 2008;134:1741–51

Ascites

Ascites is the pathologic accumulation of fluid within the peritoneal cavity and it can occur at any age and also *in utero*. The main causes of ascites are given in Table 11.32. Sometimes a large intra-abdominal cyst, i.e. cystic lymphangioma, omental or ovarian cyst can masquerade as ascites; this is known as pseudoascites.

Evaluation. History and examination, imaging studies and paracentesis are required for ascertaining the etiology. Patients present with increased abdominal girth and weight gain. Physical examination reveals abdominal distension, bulging flanks, shifting dullness, fluid thrill and puddle sign. The liver and spleen may be difficult to palpate in patients with tense ascites. Dilated abdominal collaterals and caput medusae may be seen in ascites due to liver disease, while collaterals in flanks and on the back suggest inferior vena cava block. Elevated jugular venous pressure suggests a cardiac origin, e.g. constrictive pericarditis.

Table 11.32: Causes of ascites

Common
Cirrhosis and portal hypertension
Budd-Chiari syndrome
Nephrotic syndrome
Protein losing enteropathy: intestinal lymphangiectasia
Tubercular ascites
Constrictive pericarditis
Cardiac failure
Chylous: lymphatic obstruction, thoracic duct injury
Uncommon
Pancreatic: Pancreatitis, pancreatic duct injury
Urinary: Obstructive uropathy, bladder rupture
Intestinal perforation
Hepatobiliary: Bile duct perforation, veno-occlusive disease
Serositis: SLE, eosinophilic enteropathy
Peritoneal dialysis, ventriculoperitoneal shunt
Infections: Parvovirus, syphilis, cytomegalovirus
Others: Epidemic dropsy

Ultrasound is a sensitive imaging technique for the detection of ascites. Free fluid layers in the dependent regions, i.e. the hepatorenal recess (Morrison pouch) and the pelvic cul-de-sac which is detected on ultrasound. Abdominal paracentesis is a simple test for determining the etiology. Diagnostic paracentesis should be done when ascites is first detected, at the time of hospitalization, or when there is clinical deterioration with unexplained fever, abdominal pain or diarrhea. Ultrasound guided tap is warranted in children with loculated ascites.

Investigations. Ascitic fluid should be evaluated for total and differential cell count, albumin level and culture. Serum albumin is done to calculate the serum to ascites albumin gradient (SAAG), i.e. the concentration of albumin in serum minus its concentration in ascitic fluid.

High gradient ascites (SAAG ≥1.1 g/dl) suggests portal hypertension and is seen in cirrhosis, fulminant hepatic failure, Budd-Chiari syndrome and portal vein thrombosis.

Low gradient ascites (SAAG <1.1 g/dl) occurs in absence of portal hypertension in conditions such as peritoneal carcinomatosis, tuberculous peritonitis, pancreatic ascites, biliary leak ascites, nephrotic syndrome and serositis.

Elevated ascitic fluid level of amylase indicates pancreatitis or intestinal perforation. Polymicrobial infection is consistent with intestinal perforation, whereas monomicrobial infection suggests spontaneous bacterial peritonitis. Uroascites is present when the concentration of urea and creatinine are higher in the ascitic fluid than in serum. Elevated ascitic bilirubin indicates perforation of the biliary tree or upper intestine. Chylous ascites, indicated by its milky appearance, is characterized by high concentration of triglycerides.

Treatment

Small amounts of ascitic fluid that do not produce symptoms or clinical sequelae may require little or no treatment. Tense ascites causing respiratory compromise, severe pain, or other major clinical problems should be treated promptly. Treatment largely depends upon the cause, e.g. antitubercular therapy for tubercular ascites, diuretics for chronic liver disease and surgery for bile duct or bowel perforation.

Ascites with Liver Disease

In liver disease, ascites represents a state of excess total-body sodium and water. The main postulated pathogenetic mechanisms include: (i) *Underfilling theory:* Primarily there is inappropriate sequestration of fluid within the splanchnic vascular bed as a consequence of portal hypertension that produces decrease in effective circulating blood volume. This activates the plasma renin, aldosterone and sympathetic nervous system, resulting in renal sodium and water retention. (ii) *Overfill theory:* Primary abnormality is inappropriate renal retention of sodium and water in the absence of volume depletion. Basis of this theory is that

patients with cirrhosis have intravascular hypervolemia rather than hypovolemia. (iii) *Peripheral arterial vasodilation:* The chief cause of ascites is splanchnic vasodilation, which leads to decrease in effective arterial blood volume. Progressive deterioration of liver functions, portal hypertension, splanchnic arterial vasodilatation and reduced plasma oncotic pressure due to low serum albumin contribute to development of ascites.

Management

For patients with ascites related to liver disease, mobilization of ascitic fluid is accomplished by creating a negative sodium balance until ascites has diminished or resolved; then the sodium balance is maintained so that ascites does not recur. Oral diuretic therapy consists of single morning dose of spironolactone (0.5–3 mg/kg) along with furosemide (0.5–2 mg/kg), that facilitates maintenance of normokalemia. If weight loss and decrease in abdominal girth are inadequate the doses of both spironolactone and furosemide should be increased simultaneously. Along with diuretic therapy patients should be on a sodium restricted diet. One gram of table salt contains 17 mEq of sodium and one gram of sodium approximates 44 mEq of sodium. Restriction of sodium in diet is limited to 1–2 mEq/kg/day for infants and children and 1 to 2 g/ day (44 to 88 mEq of sodium/day) in adolescents.

If the ascites is massive or the patient is having respiratory discomfort, large volume paracentesis should be done preferably under cover of albumin infusion. Patients who are resistant to above therapy can be treated with transjugular intrahepatic portosystemic shunting (TIPS) as a temporary measure till orthotopic liver transplantation is done.

Spontaneous Bacterial Peritonitis (SBP)

This refers to bacterial peritonitis not associated with gut perforation or any other secondary cause. Presence of >250 polymorphonuclear cells/mm^3 with a positive culture of ascitic fluid is diagnostic. Patients present with rapid onset abdominal distension, fever, malaise and abdominal pain with tenderness on abdominal examination. About 10% of SBP cases may be asymptomatic. Third generation cephalosporins, for a total of 5 to 7 days are recommended for treatment. Longterm administration of oral norfloxacin 5–7.5 mg/kg once a day in patients with cirrhosis and ascitic protein content of <1 g/dl or prior episode of SBP is recommended. Despite advances in supportive care, bacterial peritonitis is an indicator of poor prognosis.

Suggested Reading

Giefer MJ, Murray KF, Colletti RB. Pathophysiology, diagnosis and management of pediatric ascites. J Pediatr Gastroenterol Nutr 2011; 52:503–13

Portal Hypertension

The portal vein is formed by the splenic and the superior mesenteric veins. Normal portal pressure is between 5–10 mm Hg and portal hypertension is an increase in portal pressure of >12 mm Hg. It is a common clinical situation in children and occurs due to increased portal resistance and/or increased portal blood flow. The presence of esophageal varices on endoscopy is the most definite evidence of portal hypertension. The causes of portal hypertension may be either intrahepatic or extrahepatic (prehepatic and posthepatic) (Table 11.33).

The spectrum of portal hypertension in children from developed *vs.* developing world is different. In the former, intrahepatic causes of portal hypertension are most common whereas in India, extra hepatic portal venous obstruction (EHPVO) is the commonest cause (50–75%) followed by cirrhosis (25–35%); uncommon causes are congenital hepatic fibrosis, non cirrhotic portal fibrosis and Budd-Chiari syndrome. Portal hypertension results in development of portosystemic venous channels at different sites giving rise to esophageal, gastric or colonic varices. Neonatal umbilical sepsis, umbilical vein catheterization, dehydration, peritonitis or hypercoagulable state may be the precipitating factors for EHPVO.

Clinical Features

The age of presentation ranges from 4 months to adults. A majority of patients with EHPVO present with upper gastrointestinal bleeding and splenomegaly. Hematemesis and melena occurs due to esophageal or gastric variceal bleeding. The bleed may be recurrent and is well tolerated without development of postbleed hepatic encephalopathy. Splenomegaly alone is the presentation in 10–20% cases.

Patients with portal hypertension due to cirrhosis have jaundice, ascites, hepatosplenomegaly and less often, upper gastrointestinal bleeding. In Budd-Chiari syndrome, patients present with ascites and hepatomegaly. Tortuous prominent back veins are seen in Budd-Chiari syndrome with inferior vena cava block.

Investigations

The diagnosis of portal hypertension is made by the following investigations:

i. Ultrasound and Doppler study. The vascular anatomy is defined and any block in portal, splenic or hepatic veins can be detected. Increased size of portal vein is

Table 11.33: Causes of portal hypertension

Prehepatic	Portal venous thrombosis, extrahepatic portal venous obstruction (cavernous transformation of portal vein), isolated splenic vein thrombosis
Intrahepatic	Liver cirrhosis (common), congenital hepatic fibrosis, veno-occlusive disease, noncirrhotic portal fibrosis, schistosomiasis, nodular regenerative hyperplasia
Posthepatic	Budd-Chiari syndrome (hepatic vein or inferior vena cava obstruction), constrictive pericarditis

suggestive of intrahepatic portal hypertension. Presence of collaterals, ascites, splenomegaly and liver abnormalities (altered echotexture, size and space occupying lesions) are also seen.

ii. Endoscopy can reveal varices in esophagus, stomach and congestive gastropathy.

iii. Colonoscopy is useful in children with lower GI bleeding as it can show presence of rectal varices or colopathy.

iv. Selective CT or MR portovenography are useful for delineation of vascular anatomy.

v. Liver function tests are deranged in subjects with cirrhosis. Hemogram may show anemia, leukopenia and thrombocytopenia that suggests hypersplenism.

Complications

The most common complication is GI bleeding secondary to esophageal varices. Hypersplenism usually is not symptomatic. The enlarged spleen is prone to splenic infarcts and accidental rupture with trauma. Other complications like ascites and hepatic encephalopathy occur frequently in children with cirrhosis.

Hepatopulmonary syndrome. The triad of chronic liver disease or portal hypertension, alteration of arterial oxygenation (defined as widened age corrected alveolar arterial oxygen gradient with or without arterial hypoxemia) and evidence of intrapulmonary vascular dilatations defines hepatopulmonary syndrome. Patients with hepatopulmonary syndrome present with dyspnea, platypnea (dyspnea induced in upright position and relieved by recumbency) and orthodeoxia (arterial deoxygenation accentuated in upright position and relieved by recumbency). Examination shows clubbing and cyanosis. Contrast echocardiography is the most sensitive test to demonstrate intrapulmonary shunting. The only established effective therapy is liver transplantation.

Portopulmonary syndrome. This is defined as pulmonary arterial hypertension (pulmonary artery pressure >25 mm Hg) associated with severe portal hypertension. Most patients of portopulmonary syndrome have underlying cirrhosis but it can also develop in noncirrhotic portal hypertension. Symptoms include dyspnea and syncope; echocardiography is required for diagnosis.

Management

This is based on two goals: (i) management of complications like upper gastrointestinal bleeds and ascites, discussed elsewhere in the chapter; and (ii) definitive management that depends on the etiology of portal hypertension. The prognosis is better for children with EHPVO than those with cirrhosis where liver transplantation is the ultimate therapy.

Suggested Reading

Yachha SK. Portal hypertension in children: An Indian perspective. J Gastroenterol Hepatol 2002;17:S228–31

Budd-Chiari Syndrome

Budd-Chiari syndrome is caused by the occlusion of the hepatic veins and/or the suprahepatic inferior vena cava. Right heart failure and sinusoidal obstruction syndrome (formerly known as veno-occlusive disease) impair hepatic venous outflow and share features with Budd-Chiari syndrome, but are grouped separately as its etiology and treatment is different. Budd-Chiari syndrome is considered *primary* when obstruction of the hepatic venous outflow tract is result of an endoluminal venous lesion (thrombosis or web). It is considered *secondary* when the obstruction originates from a lesion outside the venous system (tumor, abscess, cysts). The lesion can obstruct outflow by invading the lumen or by extrinsic compression.

The majority of patients with Budd-Chiari syndrome are primary and present with a chronic course; only a small number of patients present with acute or fulminant forms. Acute disorder presents clinically with abdominal pain, ascites, hepatomegaly and rapidly progressive hepatic failure. The chronic form is characterized by hepatomegaly abdominal distension and portal hypertension. In inferior vena cava block, the back veins become prominent, dilated and tortuous with flow from below upwards.

Doppler ultrasound and venography confirm the diagnosis. Investigations should be done to look for presence of hypercoagulable states. Treatment is directed towards restoring the patency of hepatic vein/inferior vena cava by radiological means (angioplasty, stenting or trans-jugular intrahepatic portosystemic shunt) or surgery (mesoatrial shunt, mesocaval shunt). Orthotopic liver transplant is reserved for patients with end stage liver disease or fulminant failure.

Suggested Reading

Plessier A, Valla DC. Budd-Chiari syndrome. Semin Liver Dis 2008; 28:259–69

Wilson Disease

Wilson disease is an inborn error of metabolism due to toxic accumulation of copper in liver, brain, cornea and other tissues. It occurs worldwide with an estimated prevalence of 1 in 30,000–50,000 and is one of the major causes of CLD in Indian children.

Clinical Presentation

The age of presentation can vary from 4 to 60 yr. Manifestations are more likely to be hepatic in early childhood and neurological in adolescents or adults. The spectrum of hepatic manifestations include all forms of chronic or acute liver disease, i.e. asymptomatic hepatomegaly, chronic hepatitis, portal hypertension, cirrhosis, 'viral hepatitis' like illness and sometimes acute liver failure. Neurological abnormalities are varied and may present as clumsiness, speech difficulties, scholastic deterioration, behavioral problems, convulsions and choreoathetoid and dystonic movements. Most of these patients have past or

concurrent history of biochemical evidence of liver disease. Due to the slow and nonspecific evolution of neurological signs, it sometimes takes 1–2 yr to manifest from onset of symptoms. Other presentations are with bony deformities (knock knees) suggestive of resistant rickets, acute or recurrent hemolysis and failure to thrive. In view of the diverse presenting features, a high index of suspicion is the key to diagnosis.

Investigations

No single test is diagnostic by itself; a group of tests is done to make the diagnosis. Serum ceruloplasmin is decreased (<20 mg/dl) in most patients. In symptomatic patients, the 24 hr urinary copper excretion is more than 100 µg/day. Kayser-Fleischer (KF) ring indicates long-standing disease and severe copper overload. KF rings are most common in children with neurological (96%) than hepatic (60%) and asymptomatic (10–20%) Wilson disease. Hepatic copper is the single best predictive marker and is considered to be the gold standard, with values usually above 250 µg/g dry weight of liver. Liver biopsy is required for hepatic copper estimation. Mutational diagnosis is difficult because of the occurrence of more than 200 mutations, each of which is rare. Mutational diagnosis is helpful in screening family members of an index patient homozygous for this mutation.

Diagnosis

Wilson disease is strongly suggested by the presence of any two of the following: low ceruloplasmin, high urinary copper and presence of KF ring. However, hepatic copper content should be estimated if diagnosis is in doubt.

Treatment

Foods with high copper content like organ meats (liver), chocolates and nuts should be avoided. Continuous life long pharmacotherapy is essential for management. Treatment entails two aspects: (i) *Induction therapy* aims to reduce copper to subtoxic threshold. This phase usually takes 4 to 6 months (as indicated by urinary copper <500 µg/day and nonceruloplasmin copper <25 mg/dl). D-Penicillamine or trientine is often used as chelation therapy. Ammonium tetrathiomolybdate is the therapy of choice in neurological Wilson disease, but is not easily available in India. (ii) *Maintenance therapy* aims to maintain a slightly negative copper balance so as to prevent its accumulation and toxicity. Penicillamine and trientine have been used for this phase for long periods. Zinc, in view of its low cost and safety profile, can be used for maintenance therapy especially if there are penicillamine side effects and in asymptomatic siblings.

D-Penicillamine and trientine. Large urinary excretion of copper (2 to 5 mg/day) is observed in the initial months of therapy, falling to 0.1–0.5 mg/day in the maintenance period. Penicillamine has many adverse effects like skin rash, bone marrow depression, nephrotic syndrome or neurological deterioration. Trientine has been used as an alternative chelating agent especially for children intolerant to penicillamine. Trientine is increasingly used as first line drug with good efficacy and few side effects; both medications are given at a dose of 20 mg/kg/day in two divided doses.

Zinc. Zinc has been used as acetate, sulphate or gluconate salts. Zinc acts by inducing intestinal cell metallothionein, which binds copper to form mercaptides. The metallothionine, with copper is held in the intestinal cells until it is sloughed out. However zinc is a slow acting drug that takes longer time to achieve a negative copper balance and is therefore effectively used as maintenance therapy.

Liver transplantation is indicated in children with Wilson disease who present as acute liver failure or have decompensated cirrhosis unresponsive to medical therapy.

Suggested Reading

Roberts EA, Schilsky ML; American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology 2008;47:2089–11

Autoimmune Liver Disease

Autoimmune liver disease is characterized by hypergammaglobulinemia, presence of circulating autoantibodies, necroinflammatory histology (interface hepatitis, portal plasma cell infiltration) on biopsy and response to immunosuppressive agents. The condition is common in girls. In children, autoimmune liver disease consists of autoimmune hepatitis, autoimmune sclerosing cholangitis and *de novo* autoimmune hepatitis after liver transplantation. The following two types of autoimmune hepatitis are recognized:

Type 1. Presence of antinuclear antibody and/or anti smooth muscle antibody; constitutes 60–70% cases.

Type 2. Presence of antiliver kidney microsomal antibody (LKM); accounts for 20–30% cases.

Clinical Presentation

Children can present in one of the following ways:

i. Acute viral hepatitis like presentation (40%) with malaise, nausea, vomiting and jaundice. It may progress to acute hepatic failure particularly in children with type II disease.
ii. Insidious onset liver disease (30–40%) with progressive fatigue, relapsing or prolonged jaundice lasting for months to years.
iii. Chronic liver disease and its complications (10–20%) with splenomegaly, ascites, variceal bleeding or hepatic encephalopathy.

Diagnosis

Autoimmune liver disease is a diagnosis of exclusion, based on the following criteria:

i. Positive autoantibodies
ii. Raised gammaglobulins and IgG levels

iii. Typical histology on liver biopsy
iv. Absence of known etiology, e.g. viral hepatitis, Wilson disease, drug hepatotoxicity or biliary disease
v. Response to immunosuppression confirms the diagnosis.

Management

Steroids and azathioprine are the primary immunosuppressive agents while cyclosporine and mycophenolate mofetil are second line drugs. The endpoint of therapy is normalization of transaminases and histological inflammatory activity with treatment. A majority of patients including those with cirrhosis respond to medical therapy. Liver transplantation is required for patients with end stage liver stage who are either refractory or intolerant to immunosuppressive therapy. Patients presenting with acute liver failure need liver transplantation, as they are less likely to respond to medical treatment. A high index of suspicion and timely diagnosis of autoimmune liver disease is crucial.

Suggested Reading

Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? Semin Liver Dis 2009;29:297–306

Chronic Hepatitis B Infection

Hepatitis B virus (HBV) infection is a worldwide heath problem and may result in AVH, ALF, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). The epidemiology, natural history and evaluation for the infection are discussed in Chapter 10. The age at time of HBV infection affects the outcome, with >90% of infected neonates becoming chronic carriers as compared to 20–25% children infected in preschool age and only 5% adults.

Clinical Features

Chronic HBV infection is defined as persistence of HBsAg for >6 months. Three potentially successive phases have been described in the natural course of chronic HBV infection:

i. Immunetolerant phase is characterized by active viral replication and minimal liver damage. In this phase, serum HBsAg and HBeAg are positive, serum HBV DNA levels are high (in millions), anti-HBe is negative and serum ALT levels are normal.
ii. Immune clearance phase occurs years after immunetolerant phase and is characterized by effort of clearing the chronic HBV infection by the host. In this serum HBV DNA levels are reduced and ALT levels increase. Serum HBsAg and HBeAg are positive and anti-HBe is negative. The patient may become symptomatic in this phase with ALT flares.
iii. Inactive carrier phase or nonreplicative phase follows HBeAg seroconversion, i.e. HBeAg is negative and anti-HBe is positive. It is characterized by very low serum HBV DNA levels (<2,000 IU/ml), HBsAg positivity and normal ALT. It may lead to resolution of infection where serum HBsAg becomes undetectable and anti-HBs is present.

Most children with early acquired HBV infection spontaneously clear HBeAg by 15–30 yr of age. Majority of the children with chronic HBV infection are asymptomatic during first two decades of life. Cirrhosis develops in 3–10% and hepatocellular carcinoma (HCC) in 1–4% of children with chronic HBV infection.

Management

The recommendations for management of children with chronic HBV include: (i) detailed examination and liver function tests; (ii) serology tests: HBeAg, anti-HBe, HBV DNA (quantitative by PCR). HCV RNA and HIV testing to rule out coinfection in high-risk groups (e.g. following multiple transfusions); (iii) consideration for liver biopsy for grading and staging of liver disease prior to initiation of treatment; and (iv) identifying and treating patients that merit therapy for hepatitis B. The ideal drug for treatment of chronic HBV infection in children is one that is cheap, safe, orally administered, given at all ages for long duration without any risk of viral resistance and capable of interrupting viral replication to undetectable levels. But no such drug is currently available. Only three drugs are licensed for use in children and they include interferon and oral antivirals [lamivudine and adefovir (for children >12 yr of age)].

Children in the nonreplicative phase do not require treatment and there is no effective therapy for patients in the immune-tolerant phase. Treatment is helpful for children in immune-clearance phase with active liver disease and raised transaminases as delayed loss of HBeAg is a risk factor for virus replication and favors development of cirrhosis and hepatocellular carcinoma. Therefore, an attempt at shortening the highly replicative phase by treatment is likely to be beneficial and forms the basis of therapy in children.

The aim of treatment is to achieve sustained loss of HBV DNA, HBeAg seroconversion (HBeAg negative and anti HBe positive), normal transaminases and improved liver histology and thereby reduced risk of cirrhosis and HCC. Correct patient and therapy selection is the key to successful management. The other aspects of managements include:

i. Followup of all infected children for disease flares and surveillance for hepatocellular carcinoma should be ensured. Risk of cancer in HBV infected subjects is 100 fold more than in HBV negative patient. Alpha-fetoprotein and abdominal ultrasound are used to screen for hepatocellular cancer.
ii. Educating the child or adolescent regarding avoidance of other hepatotoxic factors, e.g. obesity, alcohol and intravenous drugs is essential

iii. One should screen all family members of HBsAg positive patient for HBsAg. Vaccination of negative members against HBV and evaluating other HBsAg positive members for liver disease is required.

Prevention of Chronic HBV Infection

Prevention is the most effective method of successfully controlling HBV infection and its complications. The hepatitis B vaccine is highly immunogenic with seroconversion rates of >90% after three doses. Antibody titers (anti-HBs) of >10 mIU/ml signify a response and are protective. The dose in children and adolescents (aged less than 18 yr) is 0.5 ml (10 µg). It is given in 3 doses at 0, 1 and 6 months as an intramuscular injection in the deltoid/anterolateral thigh. For prevention of perinatal infection in HBsAg positive mother, the baby should be given Hepatitis B Immune Globulin (HBIG) along with hepatitis B vaccine within 12 hr of birth, using two separate syringes and separate sites for injection. The dose of HBIG is 0.5 ml IM. The other two doses of hepatitis B vaccine may be given at 1 and 6 months or at 6 and 14 week to piggy back it with the DPT vaccination. The efficacy of prophylaxis with both HBIG and hepatitis B vaccine is 90–95%. All infants born to HBsAg positive mothers should be tested for HBsAg and anti-HBs antibodies at 9–15 months of age to identify HBV infested (HBsAg positive, anti-HBsAb negative) and protected (HBsAg negative, anti-HBsAb positive) children.

Universal infant vaccination, adequate screening of blood products and use of sterile syringes is a must for controlling chronic HBV infection as prevention is always better and more feasible than cure especially in HBV infection.

Suggested Reading

Jonas MM. Treatment of chronic hepatitis B in children. J Pediatr Gastroenterol Nutr 2006;43: S56–S60

Lok ASF, Mc Mahon BJ. Chronic hepatitis B (AASLD Practice guidelines). Hepatology 2007;45:507–39

Murray KF, Shah U, Mohan N, et al. Chronic Hepatitis Working Group. Chronic hepatitis. J Pediatr Gastroenterol Nutr 2008;47:225–33

Hepatitis C

HCV is an enveloped, single-stranded positive-sense RNA virus of the flavivirus family. Based on phylogenetic analysis of HCV sequences, 6 major HCV genotypes are recognized, designated 1 to 6, with multiple subtypes within each viral genotype. In India non-1 genotype is more prevalent.

Epidemiology

Worldwide prevalence of chronic HCV infection is estimated at 3%, with 150 million chronically infected people. Routes of transmission of HCV are similar to HBV. Mother-to-infant transmission of HCV is the main mode of transmission in children. Hepatitis C affects 4–10% of children born to infected mothers, and 80% of them develop chronic infection. Children are considered infected if the serum HCV RNA is positive on at least two occasions.

Clinical Presentation

Most children with chronic hepatitis C virus infection are asymptomatic or have mild nonspecific symptoms, with persistent or intermittently elevated or even normal serum transaminases. Hepatomegaly may be present. Severe liver disease may develop 10–20 yr after onset of infection, with a less than 2% overall risk during the pediatric age.

The natural course of HCV infection in children is not clearly understood, but overall advanced liver disease is rare during childhood. In cases with vertical transmission spontaneous clearance of infection may be seen by 5 to 7 yr of age. Children with transfusion-acquired infection may have higher rates of spontaneous HCV clearance than those with vertically acquired HCV infection.

Evaluation

Diagnosis is made by testing for anti-HCV antibody and if positive, confirmed by the presence of HCV RNA. The presence of antibody shows that the patient has been exposed to the virus but does not discriminate between active or resolved infection. The absence of anti-HCV antibody usually indicates that the patient is not infected. The diagnosis of chronic HCV infection is made on the basis of persistently detectable HCV RNA for ≥6 months.

Treatment

Combination of interferon (thrice a week of standard IFN subcutaneously or once a week of pegylated IFN) and oral ribavirin (15 mg/kg maximum) daily for a period of 24 weeks for genotype 2 and 3 and 48 weeks for genotype 1 and 4 is the standard therapy for chronic HCV infection. The US FDA has recently approved combined pegylated-IFN-α 2b plus ribavirin for treatment in children >3 yr of age. The addition of polyethylene glycol (PEG) increases the half-life of IFN, reduces its volume of distribution and leads to more sustained plasma levels with better viral suppression and allowing once weekly usage. In children the rate of sustained virological response (6 months after completion of drug treatment) indicating resolution of chronic infection varies from 50% in genotype 1 patients, to 90% in genotypes 2 or 3 patients. Multi-transfused thalassemic children with hepatitis C virus infection can also be treated with IFN and ribavirin with a response rate of 60–72%. However, ribavirin induced hemolysis increases the transfusion requirement during treatment in these children. A frequently overlooked but critical component of the management of children with HCV is to provide information about the virus, including ways to prevent its spread. Adolescents, in particular, need to understand that alcohol accelerates progression of HCV-related liver disease and should abstain from its consumption. The importance of avoiding high-risk behavior such

as sharing of intravenous injection needles also needs to be discussed.

Suggested Reading

Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management and treatment of hepatitis C: an update. Hepatology 2009;49:1335–74

Murray KF, Shah U, Mohan N, et al. Chronic Hepatitis Working Group. Chronic hepatitis. J Pediatr Gastroenterol Nutr 2008;47:225–33

Metabolic Liver Disease

Metabolic diseases account for up to 15–20% of chronic liver disease in Indian children with Wilson disease being the most frequent and alpha-1-antitrypsin deficiency being rare. The etiology of metabolic liver diseases can be classified based on the primary substrate (Table 11.34).

Clinical Features

The clinical features are secondary to hepatocyte injury with development of cirrhosis, storage of lipids or glycogen, or metabolic effects secondary to hypoglycemia or hyperammonemia. Clinical signs and symptoms of most metabolic liver diseases are similar and indistinguishable from those seen in acquired hepatic disorders due to other causes. Presentations can be broadly subdivided into:

Table 11.34: Causes of metabolic liver disease

Carbohydrate metabolism
Galactosemia*
Glycogen storage disease* types I, III, IV, VI
Hereditary fructose intolerance
Protein metabolism
Tyrosinemia*
Urea cycle defects
Lipid metabolism
Gaucher disease*
Niemann-Pick type C*
Wolman disease
Bile acid metabolism
Benign recurrent intrahepatic cholestasis
Progressive familial intrahepatic cholestasis* I, II, III
Bilirubin metabolism
Gilbert syndrome*
Crigler-Najjar syndrome type I and II*
Dubin-Johnson syndrome*
Rotor syndrome
Metal metabolism
Wilson disease*
Neonatal hemochromatosis
Indian childhood cirrhosis
Miscellaneous
Alpha-1-antitrypsin deficiency
Cystic fibrosis

*Common disorders

i. Isolated unconjugated hyperbilirubinemia, e.g. Gilbert syndrome, Crigler-Najjar syndrome types I and II.
ii. Conjugated hyperbilirubinemia, e.g. progressive familial intrahepatic cholestasis, cystic fibrosis, bile acid synthesis defects.
iii. Severe liver dysfunction with ascites and coagulopathy, e.g. galactosemia, neonatal hemochromatosis, tyrosinemia.
iv. Hepatomegaly, hepatosplenomegaly, e.g. glycogen storage disease, lysosomal storage disorders.
v. Reye like illness, e.g. mitochondrial hepatopathies, urea cycle defects.
vi. Chronic liver disease or acute liver failure, e.g. Wilson disease.

The settings in which metabolic liver disease should be suspected include: (i) recurrent episodes of rapid deterioration with minor illnesses; (ii) recurrent unexplained encephalopathy, hypoglycemia, acidosis and hyperammonemia, as in mitochondrial hepatopathies, urea cycle defects, organic acidurias; (iii) consanguinity, sib deaths or positive family history, as in Wilson disease; (iv) specific food intolerance or aversions in childhood, e.g. sugars in hereditary fructose intolerance, protein in urea cycle defects; (v) rickets and unusual urine odors, e.g. tyrosinemia; (vi) developmental delay and multisystem involvement, e.g. mitochondrial hepatopathies; and (vii) fatty liver on ultrasonography or liver biopsy.

Diagnosis

Apart from the high index of suspicion, investigations include complete blood count, arterial blood gases with lactate, electrolytes, glucose, ammonia; plasma and urine amino acids and organic acids; urine for ketones and sugars. Samples of urine and plasma, skin biopsy and liver biopsy are frozen for future evaluation. Liver biopsy provides information about the extent of damage and estimation of abnormal material (copper, iron or glycogen) and enzyme assay. Confirmation of the diagnosis requires specific tests like enzyme assay and genetic mutation analysis depending on the suspected etiology.

Management

Management is two pronged; specific treatment of underlying disease and therapy for liver damage. Supportive therapy includes measures like provision of optimal nutrition with vitamin supplementation, antioxidants, correction of hypoglycemia, coagulopathy and ascites, vaccination against infections like hepatitis B and monitoring for hepatocellular carcinoma in high-risk groups like tyrosinemia. Specific therapy is most important and should be given whenever available and affordable, e.g. chelation therapy for Wilson disease and dietary modification for galactosemia. Liver transplantation might be offered to a select group of metabolic liver disorders, in absence of significant multisystem disease.

Glycogen Storage Disorders

Glycogen storage disorders are important metabolic disorders manifesting in childhood with varied clinical picture ranging from asymptomatic hepatomegaly (type VI) to hypoglycemia (type I, III) and decompensated end-stage liver disease (type IV).

Type I glycogen storage disease (von Gierke disease) Inability to convert glucose-6-phosphate to glucose in the liver results in inability to mobilize glycogen. Depending on whether this is due to glucose-6-phosphatase deficiency or translocase deficiency, it is classified as type 1A or 1B.

Hepatomegaly, doll-like facies, hypoglycemia, seizures, growth retardation, hyperuricemia, hypertriglyceridemia and lactic acidosis are main manifestations. Hypoglycemia is more marked after first few months of life as the frequency of feeding decreases. Liver adenoma might develop with risk of bleeding and malignant transformation.

Hepatomegaly and nephromegaly is appreciated on imaging. Platelet dysfunction may be present. Neutropenia is specific to type 1B. There is mild transaminase elevation. Liver biopsy shows hepatocytes with vacuolated cytoplasm and glycogen accumulation (PAS stain positive, diastase sensitive) along with microvesicular steatosis; fibrosis is absent. Definite diagnosis depends on measuring enzyme activity in the liver or mutational analysis.

Management hinges on providing a constant source of glucose in the form of slowly digested complex carbohydrates. This is achieved by frequent daytime feeding, supplementation of uncooked corn starch both in day and specifically at night. As the child grows into adolescence, longer periods of fasting may be tolerated. Since the metabolism of other carbohydrates also yield glucose-6-phosphate, galactose and fructose also need to be restricted. Strict metabolic control with dietary therapy is the key to avoiding complications.

Type III glycogen storage disorder There is a deficiency of debranching enzyme manifesting as hepatosplenomegaly, hypoglycemia, fibrosis in the liver and elevation in transaminases. While hypoglycemia and hepatosplenomegaly improve, 80–85% develop a myopathy in type III a disease while the other 15% (type III b) have only liver involvement. These cases are managed with diet similar to that in type I GSD, except that high protein diet is preferred and there is no need to restrict galactose and fructose.

Type IV glycogen storage disorder In type IV GSD there is a deficiency of branching enzyme resulting in deposition of an amylopectin like structure in the liver. The presentation is with chronic liver disease, portal hypertension and hepatic decompensation. Most children are symptomatic by 3 yr of age. Treatment is largely supportive and liver transplantation is required for patients with advanced disease.

Suggested Reading

Clayton P. Inborn errors presenting with liver dysfunction. Semin Neonatol 2002;7:49–63

Mayatepek E, Hoffmann B, Meissner T. Inborn errors of carbohydrate metabolism. Best Pract Res Clin Gastroenterol 2010;24:607–18

Nonalcoholic Fatty Liver Disease (NAFLD)

This is a common cause of liver disease in children and is closely associated with obesity and insulin resistance. The prevalence is increasing with the expanding prevalence of childhood obesity. NAFLD is a clinicopathological diagnosis characterized by macrovesicular steatosis in hepatocytes, in absence of other causes of chronic liver disease. It ranges from simple steatosis (macrovesicular steatosis in hepatocytes without inflammation) to non-alcoholic steatohepatitis (NASH, macrovesicular steatosis in hepatocytes associated with inflammation and fibrosis) to cirrhosis of liver and hepatocellular carcinoma. Insulin resistance and hyperinsulinemia is regarded as essential to the disease mechanism. Hyperinsulinemia is a response to energy dense diet (rich in saturated fats, sugars and refined carbohydrates). This diet elicits hyperinsulinemia, provides exogenous free fatty acids and drives the liver towards lipogenesis. An important environmental factor is *physical inactivity*. Various metabolic and genetic disorders that are associated with fatty liver disease in children are shown in Table 11.35.

Clinical presentation Most children are asymptomatic. Some have vague abdominal pain; examination shows generalized obesity, cutaneous striae and hepatomegaly. Splenomegaly is uncommon. Acanthosis nigricans, a velvety brown-to-black pigment in skin folds and axillae, typically associated with hyperinsulinemia can be found in 30–50% patients.

Investigations Typical biochemical abnormalities in NASH include moderately raised serum aminotransferases (with ALT more raised than AST). Metabolic abnormalities include hypertriglyceridemia, elevated fasting serum insulin and hyperglycemia. Other disorders, which may cause fatty liver can be eliminated on basis of clinical and

Table 11.35: Cause of fatty liver disease in children

Metabolic	Nonalcoholic fatty liver disease*, Alstrom syndrome, Bardet-Biedl syndrome, polycystic ovary syndrome, lipodystrophy syndromes, Prader-Willi syndrome, galactosemia*, hereditary fructose intolerance*, glycogen storage disease*
Drugs	Amiodarone, perhexiline, methotrexate, prednisolone, calcium channel blockers
Others	Craniopharyngioma, hypothalamic disorders, acute starvation, jejuno-jejunal bypass, total parenteral nutrition*

*Common conditions

biochemical findings. The diagnosis of NAFLD is suspected when there is raised serum ALT or evidence of fatty liver on radiological studies. Liver histology is required for diagnosis of NASH. Children with NASH have a histologic picture of periportal inflammation, mononuclear inflammatory infiltrate, minimal ballooning of hepatocytes and few Mallory bodies.

Treatment The first step in treating NAFLD is to identify it. Besides height and weight, waist circumference provides highly informative data and is a surrogate for visceral obesity. The treatment has two goals: to reverse liver disease and to promote healthy growth. Lifestyle changes aimed at weight reduction are essential. Dietary changes and increased physical activity lead to diminished insulin resistance. Vitamin E, ursodeoxycholic acid and metformin are given to target insulin resistance and oxidant stress. The role of bariatric surgery has not been established for childhood obesity. Prevention of over-weight and obesity in children is the best strategy to overcome the problem of NAFLD.

Suggested Reading

Barshop NJ, Sirlin CB, Schwimmer JB, Lavine JE. Review article: epidemiology, pathogenesis and potential treatments of pediatric non alcoholic fatty liver disease. Aliment Pharmacol Ther 2008;28:13–24

Marion AW Fatty liver disease in children Arch Dis Child 2004; 89:648–52

Drug Induced Liver Disorders

Medications are an important cause of liver dysfunction in children. A wide spectrum of liver diseases from acute liver failure to acute and chronic hepatitis and portal hypertension may be precipitated by drugs. The mechanism may be a predictable direct hepatotoxicity or more commonly an idiosyncratic drug reaction. Drug induced liver disorders may mimic all forms of liver disease. A reliable diagnosis is made only after detailed history and exclusion of other causes of liver dysfunction. Anti-tubercular drug therapy is an important cause, followed by anti-convulsants (phenytoin and carbamazepine). Patients with hypersensitivity features like skin rash, fever, lymphadenopathy and eosinophilia have a better outcome than those without hypersensitivity. Treatment is by timely suspicion and withdrawal of the offending drug.

Suggested Reading

Devarbhavi H, Karanth D, Prasanna KS, Adarsh CK, Mallikarjun P. Drug induced liver injury with hypersensitivity features has a better outcome: a single center experience of 39 children and adolescents. Hepatology 2011;54:1344–50

Hepatic Manifestations of Systemic Diseases

Apart from disorders that directly involve the liver, a number of disorders affecting other organ systems also have hepatic manifestations. While in some disorders these manifestations may be benign, in others the hepatic manifestations might significantly affect the outcome.

Ischemic Hepatitis

Severe shock may lead to hypoperfusion of the liver. This shock may be the result of sepsis, acute cardiogenic shock or severe intraoperative hypoperfusion as in cardiac surgery. It usually manifests as an elevation of transaminases to high levels. The degree of hepatic injury depends on the duration and severity of shock. Thus, coagulopathy as evidenced by prolonged prothrombin time and encephalopathy may result. Jaundice is a late manifestation.

Cardiac Disorders

Apart from an acute cardiogenic shock or intraoperative hypoperfusion in cardiac surgery, liver involvement may be seen as a result of congestion in right heart failure or as part of syndromes that involve both the liver and the heart. Chronic right heart failure may lead to hepatomegaly, splenomegaly and over long periods result in cardiac cirrhosis. Alagille syndrome, caused by syndromic paucity of intralobular bile ducts results in infantile cholestasis; patients also show peripheral pulmonary stenosis, tetralogy of Fallot and atrial or ventricular septal defects. In biliary atresia, splenic malformation syndrome anomaly, there may be vascular malformations and congenital heart disease.

Sepsis and Systemic Infections

Gram positive and gram negative bacterial infections may result in jaundice. Up to one-third of neonatal jaundice has been attributed to sepsis. The mechanism may vary from impaired canalicular bile transport due to defective transporter polarization in hepatocytes without hepatic necrosis to elevated bilirubin load due to hemolysis in clostridium infections and hepatocellular necrosis in pneumococcal infections. Typhoid might result in elevated alkaline phosphatase, transaminases and lactate dehydrogenase. Transaminase elevation and liver dysfunction is also present in dengue hemorrhagic fever and malaria.

Immunological Disorders

Juvenile idiopathic arthritis may be associated with hepatomegaly and elevated transaminases. Systemic lupus erythematosus may be associated with hepatomegaly or autoimmune hepatitis. Transplacental transfer of auto-antibodies might lead to neonatal SLE with transient cholestasis, congenital heart block, dermatitis and hematological abnormalities.

Hemolytic Anemias

In thalassemia, the repeated transfusions and the increased iron absorption due to ineffective erythropoiesis leads to chronic iron overload, fibrosis and cirrhosis. Recurrent transfusions increase the risk of acquiring hepatitis B and hepatitis C infections. Sickle cell anemia has a similar risk of transfusion related hepatitis but more specific problems are acute hepatic crisis which is a result of ischemic insult.

These individuals are also at higher risk of pigment stones resulting in acute and chronic cholecystitis. These episodes may be difficult to differentiate from acute hepatic crisis.

Malignancies

Leukemias and lymphomas might be associated with hepatic infiltration, presenting as jaundice. Hemophagocytic lymphohistiocytosis, either familial or infection induced, presents with jaundice, hepatosplenomegaly, liver dysfunction and cytopenia. It is an important differential diagnosis for liver failure in the first few months of life. Sclerosing cholangitis may be a complication of Langerhans cell histiocytosis.

Bone Marrow Transplant

Conditioning chemotherapy and total body irradiation may lead to veno-occlusive disease manifesting as weight gain, hepatomegaly, ascites and jaundice. Other causes of liver dysfunction after bone marrow transplant include graft versus host disease (acute or chronic), sepsis, infections hepatitis and drug toxicity.

Endocrine Disorders

Uncontrolled diabetes mellitus presents with hepatomegaly and fatty changes. Hypothyroidism manifests as jaundice in the neonatal period predominantly due to impaired conjugation of bilirubin and partly due to decreased bile flow.

Celiac Disease

Elevated transaminases may be observed, which normalize with gluten free diet.

Neonatal Cholestasis

Jaundice at 2 weeks of age is a relatively common finding, seen in 2.4% to 15% newborns. While it is chiefly unconjugated hyperbilirubinemia due to breast milk jaundice, cholestatic jaundice is an uncommon but potentially serious condition that indicates hepatobiliary dysfunction. Neonatal cholestasis is defined as direct bilirubin value greater than 1 mg/dl if the total bilirubin is less than 5 mg/dl, or a value of direct bilirubin that represents more than 20% of the total bilirubin if the total bilirubin is >5 mg/dl.

The Indian Academy of Pediatrics recommends that newborn babies having jaundice beyond 14 days of age with dark colored urine with or without acholic stools should be referred to appropriate health facility for further investigations and treatment without loss of time. The causes of neonatal cholestasis according to the experience of eight centers in India are shown in Table 11.36.

Table 11.36: Etiology of neonatal cholestasis (N=1008)

Neonatal hepatitis (47%):	Idiopathic giant cell hepatitis
Infection:	TORCH, sepsis malaria, urinary infection
Metabolic (4%):	Galactosemia, alpha antitrypsin deficiency, TPN related, tyrosinemia, storage disorders, hemochromatosis
Other causes (2%):	Inspissated bile plug syndrome, recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis, hypothyroidism, Down syndrome
Obstructive (38%):	Biliary atresia (34%), Choledochal cyst (4%)
Ductal paucity *(3%):*	Syndromic variety (Alagille syndrome), Nonsyndromic variety
Unknown *(6%)*	

Clinical Features

Neonatal cholestasis is characterized by high colored urine along with jaundice. A subset of patients present with signs of coagulopathy like skin or intracranial bleeds (seizures, irritability and bulging fontanel). Hepatomegaly or hepatosplenomegaly is common. Early decompensation is a feature in patients with an underlying metabolic disorder. In a sick infant, one should consider the diagnosis of galactosemia, tyrosinemia, hemochromatosis, herpes and sepsis. Patients with biliary atresia and choledochal cyst are otherwise healthy looking. Bilateral cataract and *E. coli* sepsis is typical of galactosemia, whereas rash (maculopapular or petechial), fever, chorioretinitis, microcephaly and lethargy are suggestive of congenital infections. Triangular facies, pointed chin, prominent ears, cardiac murmurs and butterfly vertebrae are seen in Alagille syndrome. Splenohepatomegaly with cherry-red spot on fundus examination suggests storage disorder.

Diagnosis

Neonatal cholestasis has multifactorial etiology (Table 11.36). Stool color is an important sign in the differential diagnosis. These infants need a detailed investigative workup based on a rational approach so as to avoid unnecessary and costly investigations. The etiology and algorithm of evaluation is different in a 'sick' and 'not sick' infant with cholestasis as shown in the flowchart below (Fig. 11.15).

In an infant with pale stools, HIDA scan is not of discriminatory value as both biliary atresia and severe intrahepatic cholestasis show a nonexcretory pattern, i.e. no activity in intestine at 24 hr. Priming with UDCA or phenobarbitone for 3 days before HIDA scan improves the diagnostic efficacy of HIDA. Liver biopsy is an accurate (90–95%) test for differentiating biliary atresia from other causes of neonatal cholestasis. In biliary atresia, portal tract expansion, ductular proliferation and fibrosis is seen, whereas in neonatal hepatitis, there is alteration in lobular architecture, focal hepatocellular necrosis and giant cells formation. Laparotomy and peroperative cholangiography may be required in an infant with equivocal biopsy findings and no excretion on HIDA scan, to confirm the diagnosis of biliary atresia.

In an infant with pigmented stools, ultrasound of abdomen and liver biopsy is done to determine etiology and specific

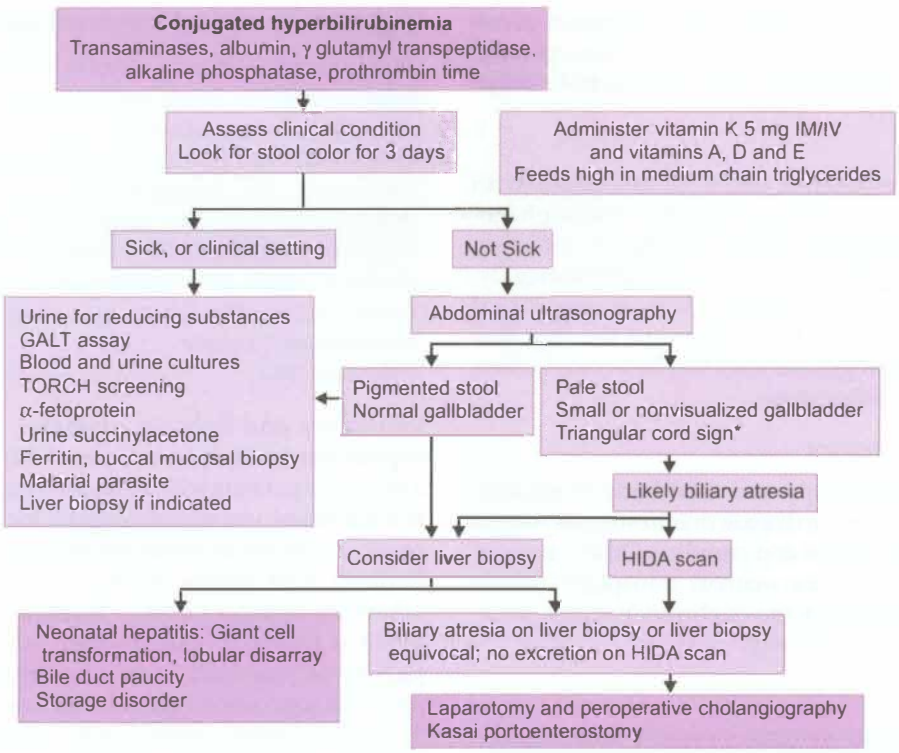

Fig. 11.15: Evaluation of a patient with neonatal cholestasis. GALT galactose-1-phosphate uridyl transferase; HIDA hydroxy iminodiacetic acid *echogenic area in porta hepatitis.

treatment is done according to the cause. A detailed metabolic workup is required for infants with conditions like progressive familial intrahepatic cholestasis types I and II, tyrosinemia and bile acid synthesis defects.

Management

Delayed diagnosis leads to problems of undernutrition, coagulopathy, pruritus, portal hypertension, ascites and hepatic encephalopathy. The management is begun as soon as the child is seen, parallel to investigations.

General management This includes the following:

i. *Nutritional.* Adequate caloric intake (125–150% of RDA based on ideal body weight) with medium chain triglyceride supplementation is necessary. Breastfeeding should be continued and supplementation with high MCT formulae should be done; 2–3% calories should come from essential fatty acids. Nasogastric feed is offered to anorexic children. Supplementation of fat soluble and water soluble vitamins is done (Table 11.37). In addition, these infants require supplements of calcium, phosphorus and magnesium.

ii. For infants with pruritus, urodeoxycholic acid (UDCA, 10–20 mg/kg/day), rifampicin (10 mg/kg/day) and cholestyramine (250 mg/kg/day) are used. UDCA is the first agent and others are used in patients with persistent symptoms.

iii. Management of other complications like ascites, gastrointestinal bleeding and hepatic encephalopathy is discussed in respective sections in the chapter.

Table 11.37: Multivitamin preparations for neonatal cholestasis

Drug	*Dose*	*Side effects*
Vitamin K	2.5–5 mg on alternate day or 5 mg IM/IV daily for 3 days and then monthly	None
Vitamin D	Oral 2500–5000 IU/day or 30,000 IU IM at diagnosis and then monthly	Hypercalcemia Nephrocalcinosis
Vitamin A	Oral 2500–15,000 IU/day or 30,000 IU IM at diagnosis and then 10,000 IU monthly	Hepatotoxicity, hypercalcemia, pseudotumor cerebri
Vitamin E	Aquasol E 50–400 IU/day tocopherol polyethylene glycol 1000 succinate: 15–25 IU/kg/day (if available)	Potentiation of vitamin K deficiency, coagulopathy, diarrhea
Water soluble vitamins	Twice the recommended daily allowance	None

Specific management This is available only for some etiologies as follows:

i. Biliary atresia is managed by Kasai procedure (hepatoportoenterostomy). The best results are obtained if it is done early (<60 days of age) and at centers with expertise. Liver transplantation is indicated in children who fail to drain bile after Kasai procedure or have progressed to end stage cirrhosis either despite surgical treatment or due to late diagnosis.
ii. Choledochal cyst: excision of cyst and hepaticojejunostomy.
iii. Herpes simplex: intravenous acyclovir.
iv. Bacterial sepsis: intravenous antibiotics.
v. Toxoplasmosis: pyrimethamine and sulfadiazine with folinic acid.
vi. Galactosemia: lactose free diet.
vii. Hemochromatosis: IV immunoglobulins (IVIG) with exchange transfusion may be useful.

There is considerable delay in referral of patients with neonatal cholestasis to higher centers in India. This results in delayed etiologic diagnosis, missed opportunity for corrective biliary atresia surgery in first 60 days and liver decompensation in patients with metabolic etiology.

Suggested Reading

Consensus report on Neonatal cholestasis syndrome. Indian Pediatrics 2000;37:845–51

Guideline for the evaluation of cholestatic jaundice in infants: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2004;39:115–28

Roberts EA. Neonatal hepatitis syndrome. Semin Neonatol 2003; 8:357–74

Liver Transplantation

Liver transplantation is possible for a number of disorders. The graft is obtained either from the cadaver or can be a split graft (left lateral graft or left lobe) from a living donor. Auxiliary liver transplantation is another method where native liver is not removed and a liver graft from the donor is surgically placed in addition to the native liver. This is usually done for Crigler-Najjar type I or acute liver failure.

The main indications for liver transplantation are biliary atresia, fulminant hepatic failure and chronic liver disease secondary to multiple causes and hepatic tumors. Careful selection of a blood group compatible donor is necessary, including detailed evaluation of liver functions and viral serologies. The recipient's diseased liver is removed and the new liver is transplanted, ensuring vascular and biliary anastomoses. Patients require lifelong immunosuppression using corticosteroids, tacrolimus and mycophenolate mofetil initially and later maintenance therapy with tacrolimus. Rejection and infection are major complications following transplantation. Five-year patient survival rate exceeds 80%.

Suggested Reading

Kamath BM, Olthoff KM. Liver transplantation in children: Update 2010. Pediatr Clin N Am 2010;57:401–14

12 Hematological Disorders

Tulika Seth

Hematopoiesis

The stem cells from which endothelial cells and hematopoietic cells develop are called hemangioblasts. Stem cells that give rise to only blood cells, called pluripotent stem cells, divide to form two colony forming units (CFU), including the common myeloid precursor for granulocytes, erythrocytes, monocytes and megakaryocytes (CFU-GEMM) and the common lymphoid precursor (CFU-L) which differentiates into lymphocytes. Two cell lines arise from the CFU-GEMM, the progenitor for erythrocytes and megakaryocytes (CFU-EMk) and that for granulocytes and monocytes (CFU-GMo). Each of these further develop into specific lineages, e.g. CFU-GMo gives rise to granulocyte lineages for eosinophils (CFU-Eo), neutrophils (CFU-N), and basophils (CFU-Baso) and a lineage for monocytes (CFU-Mo). The CFU-L differentiates to form to B lymphocytes, natural killer (NK) cells, and T lymphocytes. The sequential development of hematopoietic cells is driven and regulated by local growth factors and cytokines.

ANEMIA

Anemia is present when the hemoglobin level is more than two standard deviations below the mean for the child's age and sex (Tables 12.1 and 12.2). According to the third National Family Health Survey (NFHS3), 79% of Indian children have anemia, including 71% of urban children and 84% of those in rural areas.

Physiological Adaptations

Anemia results in a decrease in the oxygen-carrying capacity of blood with compensatory physiological

Table 12.2: Cutoffs for hemoglobin and hematocrit proposed by the World Health Organization to define anemia

Age group	*Hemoglobin (g/dl)*	*Hematocrit %*
Children, 6 mo to 5 yr	<11.0	<33
Children, 5–11 yr	<11.5	<34
Children, 12–13 yr	<12.0	<36
Non-pregnant women	<12.0	<36
Men	<13.0	<39

Source: WHO 1997

Table 12.1: Hemoglobin and hematocrit in infancy and childhood

	Hemoglobin (g/dL)		*Hematocrit (%)*	
Age	*Mean*	*–2 SD*	*Mean*	*–2 SD*
Birth (cord blood)	16.5	13.5	51	42
1–3 days (capillary)	18.5	14.5	56	45
1 weeks	17.5	13.5	54	42
2 weeks	16.5	12.5	51	39
1 mo	14.0	10.0	43	31
2 mo	11.5	9.0	35	28
3–6 mo	11.5	9.5	35	29
0.5–2 yr	12.0	10.5	36	33
2–6 yr	12.5	11.5	37	34
6–12 yr	13.5	11.5	40	35
Girls 12–18 yr	14.0	12.0	41	36
Boys 12–18 yr	14.5	13.0	43	37

Values two standard deviations below the mean (–2 SD) indicate the lower limit of normal

adjustments. When the enhanced release of oxygen from hemoglobin and increase in blood flow to the tissues is insufficient to meet requirements, tissue hypoxia develops. Blood volume is maintained by an increase in plasma volume and redistribution of blood flow to vital organs such as brain, muscle and heart. Increase in stroke volume causes an increase in cardiac output, which increases blood flow and improves oxygen delivery to tissues.

Evaluation for Etiology

The history provides significant clues to the etiology of anemia. Causes vary with age and anemia may be multifactorial. In infants, history should include that for maternal infections, anemia or collagen vascular diseases; prematurity; blood loss; jaundice (hemolysis due to ABO or Rh incompatibility, G6PD deficiency, sepsis) and presence of hemangiomas or cephalhematoma. Infants may have physiological anemia at 2–3 months of age. In infants and young children a dietary history is useful, including type and quantity of milk and intake of hematinics. Delayed or inadequate weaning with predominantly milk-based diet results in poor iron intake, leading to nutritional iron deficiency, usually occurring at 6 months to 2 yr of age; other causes include chronic diarrhea or cow milk allergy. Megaloblastic anemia may be nutritional, due to use of goat milk in infants and a vegetarian diet in older children. Adolescents are particularly susceptible due to increased micronutrient requirements during the growth spurt, and in girls menstruation and/or pregnancy.

History of pica, blood loss (melena, epistaxis), drug intake (e.g. anticonvulsants), chronic diarrhea, prior surgery, chronic infections, liver or renal disease and transfusions should be taken. A family history of severe anemia and/or need for blood transfusions suggests thalassemia major. History of gallstones and recurrent jaundice is noted in various types of hemolytic anemia (e.g. hereditary spherocytosis). Anemia affecting only male members of the family points to an X-linked disorder like glucose-6-phosphate dehydrogenase (G6PD) deficiency. Lack of response to iron supplements suggests thalassemia minor.

Over 70% of patients with thalassemia major present with anemia by 6 months of age. Similarly, children with Diamond-Blackfan syndrome (pure red cell aplasia) present at about 3 months of age; diagnosis is based on persistently low reticulocyte count and absence of erythroid precursors in the bone marrow. The age at presentation for Fanconi anemia varies between 3-4 yr to adulthood.

Clinical Features

The hemoglobin level at which symptoms of anemia appear, depends on the rate of development of the anemia. Symptoms occur at higher hemoglobin levels if anemia develops rapidly, as with hemorrhage. The most common and earliest symptoms include lassitude, and easy fatigability. Alternatively, children may have anorexia, irritability and poor school performance. Dyspnea on exertion, tachycardia and palpitations indicate severe anemia. Other symptoms include dizziness, headache, tinnitus, lack of concentration and drowsiness and with severe anemia, clouding of consciousness.

The most prominent and characteristic sign is pallor, detected most reliably in nail beds, oral mucous membranes and conjunctivae. Observing palmar creases and skin is insufficient as the skin creases in children lack pigmentation. Facial pallor varies with skin pigmentation and presence of edema. A mid-systolic 'flow' murmur, chiefly in the pulmonary area, is appreciated when the degree of anemia increases, reflecting increased blood flow across heart valves. Systolic bruits and postural hypotension may be noted with moderate to severe anemia. Severe anemia is characterized by a high output state with an elevated pulse pressure and a 'collapsing' pulse. Anemia may precipitate heart failure even with a normal cardiovascular system. Electrocardiographic changes, found in 30% patients with hemoglobin below 6 g/dl, include depressed ST segment and flattened or inverted T waves.

Etiological clues on examination include radial limb abnormalities (suggest bone marrow failure syndromes), splenomegaly (hemolytic anemia, malaria, kala-azar, tuberculosis or storage diseases) and lymphadenopathy and hepatosplenomegaly (malignancies or infections). Presence of petechiae or purpura indicates concomitant thrombocytopenia, while icterus suggests liver disease or hemolysis.

Investigations

A complete hemogram is required to understand whether the anemia is isolated or other cell lines are affected. Changes in the red cell indices provide significant information on the type of anemia and may precede lowering of hemoglobin (Table 12.3). The mean corpuscular volume (MCV) denotes the size of the red cells while the mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin content (MCHC) provide information on red cell hemoglobinization. Based on the MCV, anemia is classified as microcytic, normocytic and macrocytic (Figs 12.1 to 12.3). Patients with thalassemia minor or iron deficiency have low MCV, MCH and MCHC while those with megaloblastic anemia have elevated MCV. The red cell distribution width (RDW) provides an estimate of the size differences in red blood cells. Hence, a low RDW means that the red blood cells are uniform in size, while a large RDW indicates considerable variations in the cell size.

Examination of the peripheral smear reveals red cell morphology. The presence of schistocytes, polychromasia or parasites may help make the diagnosis. The reticulocyte

Table 12.3: Red cell indices and serum iron studies in normal children

Red cell indices	*Birth*	*0.5–2 yr*	*6–12 yr*	*Girls, 12–18 yr*	*Boys, 12–18 yr*
Mean corpuscular volume	108	78	86	90	88
Mean corpuscular hemoglobin	34	27	29	30	30
Mean corpuscular hemoglobin concentration	33	33	34	34	34
Red cell distribution width (RDW)*	12.8 ± 1.2%				
Serum iron	60–170 µg/dl (10–30 µmol/l)				
Serum ferritin, median (range)	100 (15–300) ng/ml (boys); 40 (15–200) ng/ml (girls)				
Total iron binding capacity	250–400 µg/dl (47–70 µmol/l)				
Transferrin saturation**	20–50%				

*RDW = standard deviation (SD) of red blood cell volume × 100/mean corpuscular volume.
**Transferrin saturation = Serum iron × 100/total iron binding capacity

count helps distinguish between anemia caused by red cell destruction and decreased production (Table 12.4). Normal reticulocyte count in newborns is 2–6% and in children 0.5–2%. However, the reticulocyte count should be corrected for the degree of anemia. This is done as follows:

$$\text{Corrected reticulocyte count} = \text{Reticulocyte count} \times \frac{\text{Actual hematocrit}}{\text{Normal hematocrit}}$$

where the normal hematocrit is 45%. The corrected reticulocyte count should be 1–2% in a healthy individual.

In patients with anemia with increased reticulocyte count, the Coomb test can help distinguish between immune and hereditary hemolytic anemia. When nutritional anemia is suspected, iron studies and levels of vitamin B12 and folic acid are determined.

Table 12.4: Reticulocyte count in evaluation of anemia

Low reticulocyte count

Congenital or acquired, aplastic or hypoplastic anemia
Transient eythroblastopenia of childhood
Pure red cell aplasia
Parvovirus B19 infection
Bone marrow infiltration by malignancy, storage disorder

High reticulocyte count

Hemolysis
Hemorrhage
Splenic sequestration
Recovery from vitamin B12, folic acid or iron deficiency
Sepsis

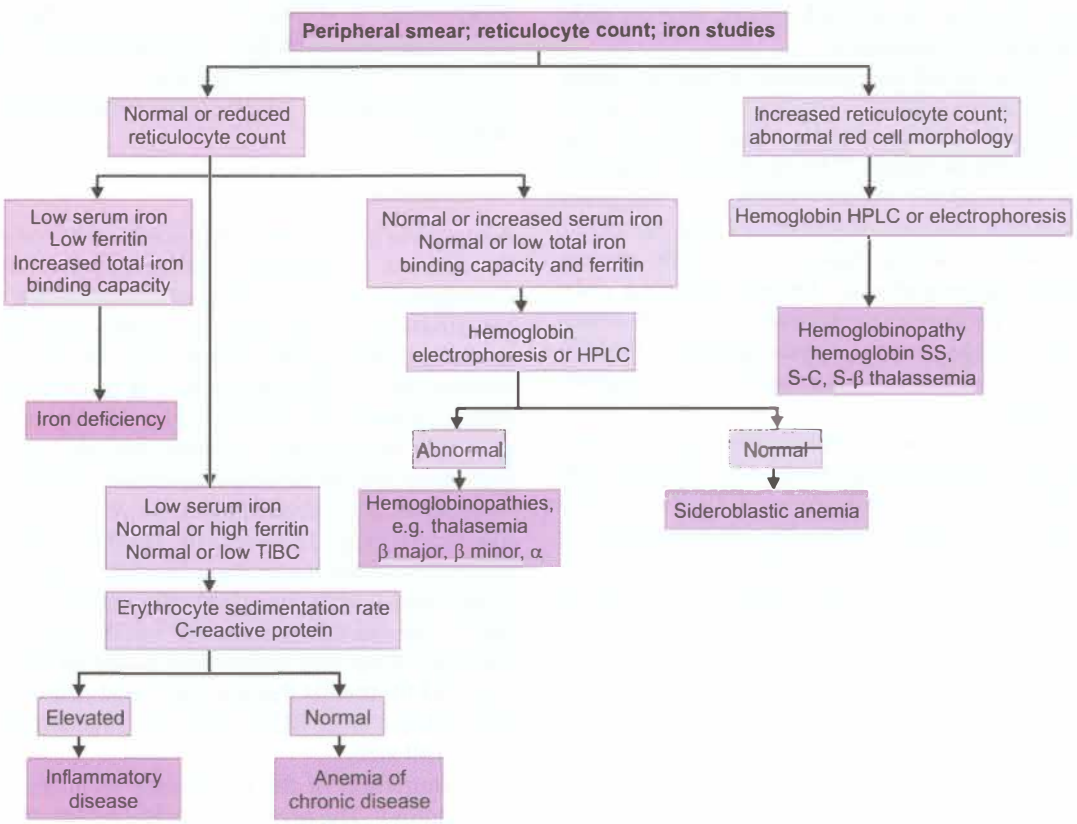

Fig. 12.1: Approach to microcytic anemia. HPLC high performance liquid chromatography

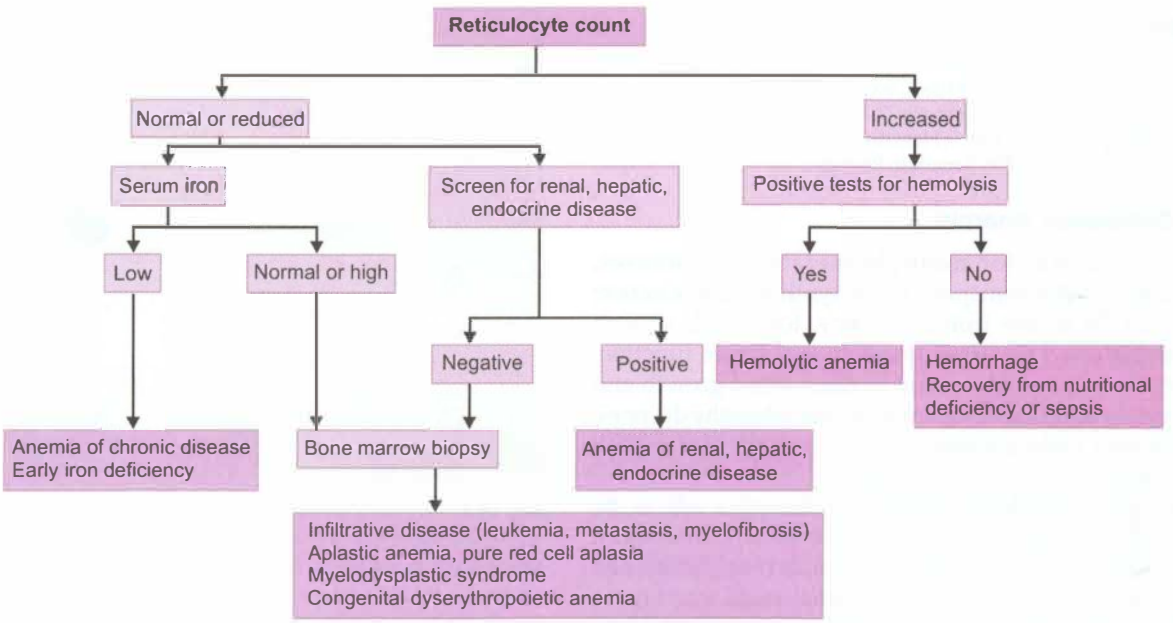

Fig. 12.2: Approach to normocytic anemia

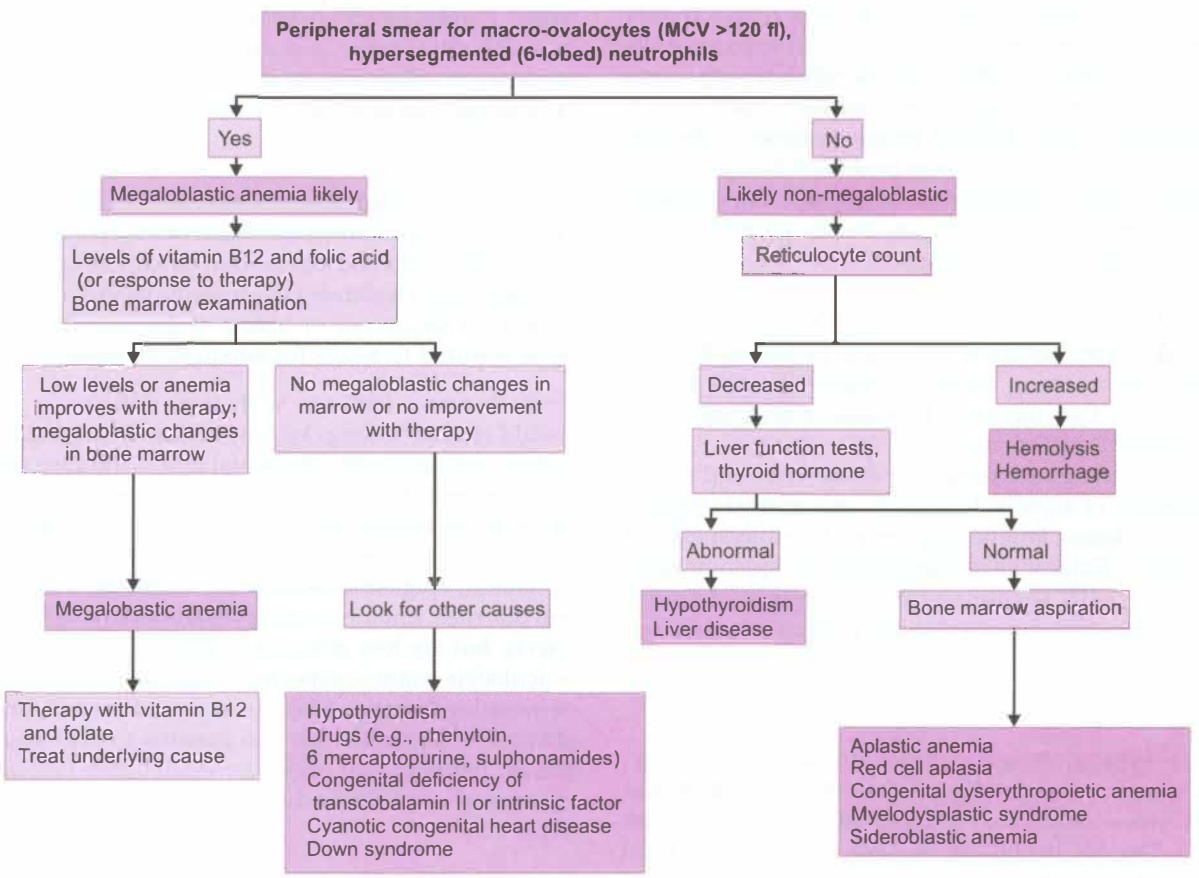

Fig. 12.3: Approach to macrocytic anemia

Suggested Reading

National Family Health Survey III, Government of India, 2007; http://www.nfhsindia.org/abt.html, accessed March 2012

Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE. (Eds.) (2009). Nathan and Oski's Hematology of Infancy and Childhood (7th Ed.). Philadelphia, PA: Saunders Elsevier

12

Iron Deficiency Anemia

Iron is essential for multiple metabolic processes, including oxygen transport, DNA synthesis and electron transport. In severe iron deficiency, low levels of iron containing enzymes affect immune and tissue function. Iron deficiency can also result in diminished growth and learning. Iron deficiency anemia occurs when the decrease in total iron body content is severe enough to diminish erythropoiesis and cause anemia.

Body iron is regulated carefully by absorptive cells in the proximal small intestine, which alter iron absorption to match body losses of iron. Iron deficiency results from diminished dietary iron absorption in the proximal small intestine or excessive losses of body iron. Iron deficiency in older children is usually caused by dietary deficiency; the absorption of iron is further impaired by dietary constituents that lower the absorption of non-heme iron, e.g. phytates, phosphates and tannates. Intercurrent infections such as hookworm infestation and malaria worsen the problem. Healthy newborns have body iron stores of 250 mg or approximately 80 parts per million (ppm); this decreases to approximately 60 ppm in the first 6 months of life, as milk is a poor source of iron. Infants consuming cow milk are more likely to have iron deficiency than breastfed infants because (i) the iron contained in cow milk has lower bioavailability; (ii) bovine milk has a higher concentration of calcium that competes with iron for absorption; and (iii) due to gastrointestinal blood loss with cow milk allergy.

Evaluation

A careful dietary history is important, including the type of milk and weaning foods in infants and the use of supplements. Pica increases the risks of lead poisoning and helminthic infections.

Clinical findings are related to the severity and rate of development of anemia. Irritability and anorexia usually precede weakness, fatigue, leg cramps, breathlessness and tachycardia. Congestive cardiac failure and splenomegaly may occur with severe untreated anemia. Angular stomatitis, glossitis, koilonychia and platynychia are noted in severe cases.

Investigations

The peripheral blood smear reveals microcytic, hypochromic red cells (Fig. 12.4) with anisocytosis and poikilocytosis and an increased red cell distribution width (RDW). The MCV and MCHC are reduced. The total number of red cells is reduced, unlike in thalassemia where it is increased. The serum level of iron and ferritin

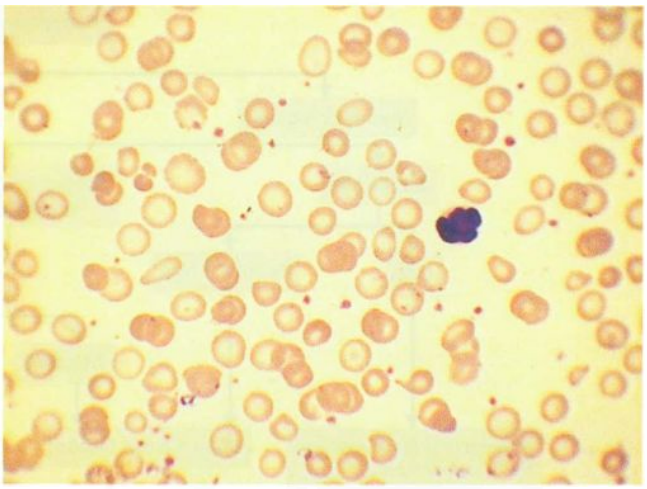

Fig. 12.4: Peripheral smear from a child with iron deficiency anemia, shows microcytosis (the red blood cells are smaller than the small lymphocyte in the field), hypochromia (central pallor >1/3rd of cell diameter), thrombocytosis, and a few ovalocytes and tear drop cells (moderate anisopoikilocytosis). Jenner-Giemsa x 1000

are reduced while the total iron binding capacity is increased (Table 12.3). The saturation of transferrin is reduced to less than 16%. The reduction in serum ferritin occurs early and correlates well with the total body iron stores. Rarely, ferritin may be falsely normal or elevated in a sick child since it is an acute phase reactant that increases in inflammatory conditions. High free erythroprotoporphyrin precedes the development of anemia.

Treatment

The cause of anemia should be identified and corrected. Hookworm infestation is the most common cause of occult gastrointestinal blood loss in rural India at all ages. Dietary counseling and treatment of causative factors are required to prevent recurrence or failure of therapy. Close follow up is required to assess for adequate response.

Oral therapy Patients with iron deficiency anemia should receive 3–6 mg/kg/day of elemental iron. Ferrous sulfate, containing 20% elemental iron, is the most effective and economical oral preparation. Absorption is best when taken on an empty stomach or in between meals. About 10–20% patients develop gastrointestinal side effects such as nausea, epigastric discomfort, vomiting, constipation and diarrhea. Enteric-coated preparations have fewer side effects, but are less efficacious and more expensive. The reticulocyte count is expected to increase within 72–96 hr of initiating therapy. After correction of anemia, oral iron should be continued for 4–6 months to replenish iron stores. Patients that show an inadequate response to therapy should be evaluated for conditions listed in Table 12.5.

Parenteral therapy The indications of parenteral iron therapy are: (i) intolerance to oral iron, (ii) malabsorption,

Table 12.5: Reasons for non-response to hematinic therapy for iron deficiency anemia

Poor compliance with therapy
Poorly absorbed iron preparation; e.g. enteric coated
Use of H_2 blockers or proton pump inhibitors that cause achlorhydria
Interaction with food and medications
Associated vitamin B12 or folic acid deficiency
Underlying hemolytic anemia, inflammation or infection
Malabsorption, e.g. celiac disease, giardiasis, *H. pylori* infection
High rate of ongoing blood loss
Alternative etiology, e.g. sideroblastic anemia

and (iii) ongoing blood loss at a rate where the oral replacement cannot match iron loss. Intravenous administration is preferred over intramuscular route. Intravenous iron sucrose is safe and effective and is commonly used for children with inflammatory bowel disease and end stage renal disease on hemodialysis. The dose is 1–3 mg/kg, diluted in 150 ml of normal saline and given as slow infusion over 30–90 min.

The total dose of parenteral iron can be calculated by the following formula:

Iron required (mg) = wt(kg) × 2.3 × (15 – patient hemoglobin in g/dl) + (500 to 1000 mg)

The total calculated dose is given as divided doses.

Blood transfusions As iron deficiency anemia is readily corrected with medication, blood transfusions should be avoided in, stable patients. Red cell transfusions are needed in emergency situations such as acute severe hemorrhage, severe anemia with congestive cardiac failure and prior to an invasive procedure. Patients with very severe anemia and congestive cardiac failure should receive transfusions at a very slow rate with hemodynamic monitoring and diuretic administration if necessary.

Suggested Reading

Kapil US. Technical consultation on strategies for prevention and control of iron deficiency anemia amongst under three children in India. Indian Pediatr 2002;39:640–7

Leijn E, Monnens LA, Cornelissen EA. Intravenous iron supplementation in children on hemodialysis. J Nephrol 2004;17: 423–6

Sachdeva HPS, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: systemic review of randomized controlled trials. Public Health Nutr 2005;8:117–32

Megaloblastic Anemia

Megaloblastic anemia is a distinct type of anemia characterized by macrocytic red blood cells and erythroid precursors that show nuclear dysmaturity. It is commonly caused by deficiency of vitamin B12 (derived from cobalamin) and/or folic acid and prevalence varies with dietary practices and socioeconomic conditions. In a study from north India, 6.8% children had folate deficiency, 32% showed vitamin B12 deficiency and combined deficiency was seen in 20%.

Pathophysiology

Megaloblastic anemia is caused by impaired nuclear maturation, usually due to lack of methyltetrahydrofolate, a folic acid derivative needed for synthesis of DNA nucleoproteins. Vitamin B12 is a cofactor in the reaction necessary for folic acid recycling. The requirement of B12 as a cofactor and its effect on hematopoiesis can be overcome by large doses of folic acid. Delay in nuclear progression leads to characteristic RBC morphology and delayed maturation. Despite active erythropoiesis, there is premature death of cells before release from the bone marrow, termed as ineffective erythropoiesis. Megaloblastic changes affect all hematopoietic cell lines with resultant anemia, thrombocytopenia and leukopenia.

Etiology

The two most common causes of megaloblastic anemia are vitamin B12 deficiency (cobalamin) and folic acid deficiency. Folate deficiency can be caused by decreased intake (infants consuming goat milk or powdered milk), increased requirements (infancy, pregnancy, chronic hemolysis, hyperthyroidism), impaired absorption (e.g. celiac disease, malabsorption, anticonvulsants), concomitant vitamin B12 deficiency and impaired conversion to biologically active tetrahydrofolate by dihydrofolate reductase (congenital deficiency, inhibition by drugs) (Tables 12.6 and 12.7). Certain drugs inhibit DNA synthesis to cause megaloblastic anemia (Table 12.6). Vitamin B12 deficiency may be caused by decreased ingestion, impaired absorption (e.g. intestinal parasites, malabsorption, inherited deficiency of intrinsic factor or post-gastrectomy, achlorhydria), or impaired utilization (e.g. congenital enzyme deficiencies) (Table 12.7). Vitamin B12 deficiency is also described in patients with HIV infection with or without AIDS. Nutritional deficiency is far more common in vegans (vegetarian ingesting little or no dairy products) and those consuming only goat milk. Anemia in infancy may relate to inadequate body stores due to maternal deficiency and/or prolonged exclusive breast-feeding, since breast milk is a poor source. *Helicobacter*

Table 12.6: Drugs that cause megaloblastic anemia

Impaired folic acid absorption: Phenytoin, phenobarbital
Impaired cobalamin absorption: Proton pump inhibitors
Interference with folate metabolism: Methotrexate, trimethoprim, pyrimethamine
Interference with cobalamin metabolism: p-Aminosalicylic acid, metformin, neomycin
Purine analogs: 6-Mercaptopurine, 6-thioguanine, azathioprine
Ribonucleotide reductase inhibitors: Hydroxyurea, cytarabine arabinoside
Pyrimidine analogs: Zidovudine, 5-fluorouracil

Table 12.7: Metabolic causes of megaloblastic anemia

Inborn errors of cobalamin metabolism
Congenital intrinsic factor deficiency
Deficiency of R-binders of vitamin B12 and/or transcobalamin II
Cobalamin malabsorption due to defect in intestinal receptor (Imerslünd-Grasbeck syndrome)
Methylmalonic aciduria
Homocystinuria
Inborn errors of folate metabolism
Congenital folate malabsorption
Dihydrofolate reductase deficiency
N^5-methyl tetrahydrofolate homocysteine methyltransferase deficiency
Other inborn errors
Hereditary orotic aciduria
Lesch Nyhan syndrome
Thiamine responsive megaloblastic anemia

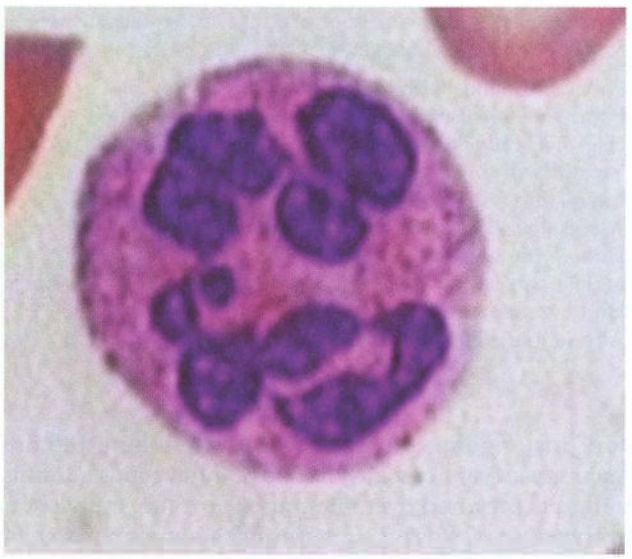

Fig. 12.5: Peripheral smear of a 12-yr-old girl with megaloblastic anemia showing hypersegmented polymorphonuclear cell. Note that the nucleus has more than 5 lobes

pylori infections are implicated in vitamin B12 malabsorption amongst adults.

Clinical Manifestations

A careful dietary history is essential to the diagnosis of megaloblastic anemia. History should include that for malabsorption, infestations and for intake of medications. Folate deficiency can occur during prolonged parenteral nutrition and through losses during hemodialysis. Patients with pernicious anemia may have history of autoimmune disorders.

Anemia, anorexia, irritability and easy fatigability are clinical features common to other causes of anemia. Features characteristically found in megaloblastic anemia include glossitis, stomatitis and hyperpigmentation of the skin on knuckles and terminal phalanges, enlargement of liver and spleen (seen in 30–40% cases). Neurologic signs may precede the onset of anemia. Petechiae and hemorrhagic manifestations are reported in one-fourth cases. The child should be evaluated for signs of malabsorption such as weight loss, abdominal distention, diarrhea and steatorrhea. Abdominal scars from ileal resections may be present.

Neurologic examination is mandatory. The earliest neurologic signs include loss of position and vibratory sensation; other posterior and lateral column deficits may appear later. Memory loss, confusion and neuropsychiatric symptoms may occur. Neurological signs may persist despite correction of deficiency.

Laboratory Evaluation

Complete hemogram with red cell indices reveals macrocytic red cells (usually >110 fl) and cytopenias. Hypersegmented neutrophils (nucleus with 6 or more lobes) may be seen (Fig 12.5). The reticulocyte count is useful. If available, serum B12 and folate levels should be assayed. Investigations are performed if a specific underlying cause is suspected. Schilling test involves administration of vitamin B12 (1 mg of unlabeled B12 by intramuscular route to saturate hepatic receptors and 1 µg of radiolabeled crystalline B12 orally) followed by collection of 24-hr urine collection; adequate absorption is suggested by detection of >7% of administered radioactivity in the urine. Repeating the test with co-administration of intrinsic factor helps differentiate between pernicious anemia and malabsorption, the latter being more common in children. Any child with more than one abnormal hematological cell line should undergo bone marrow aspiration. This helps to rule out leukemia, myelodysplasia and aplastic anemia. In megaloblastic anemia the bone marrow is cellular and shows nuclear-cytoplasmic asynchrony in red blood cell precursors. Granulocyte precursors may also be abnormal. Serum chemistry may reveal elevated lactic dehydrogenase (LDH) and indirect bilirubin.

Differential Diagnosis

Other causes of macrocytosis to be considered in the differential diagnosis of megaloblastic anemia include aplastic anemia, other marrow failure syndromes (pure red cell aplasia, Fanconi anemia, transient erythroblastopenia of childhood), congenital dyserythropoietic anemia, chronic liver disease, hypothyroidism, cold agglutinin disease, neoplasms, myelodysplastic syndromes and HIV infection (Fig. 12.3).

Treatment

Treatment depends on the underlying cause. While evaluating for cause, therapeutic doses of folate should

be administered along with vitamin B12. While folate therapy corrects anemia, it does not correct neurological changes induced by cobalamin deficiency and results in the progression of neuropsychiatric symptoms. Folate deficiency due to dietary insufficiency or increased demands is best treated with supplements, while that induced by use of anti-folate medications requires reducing or discontinuing the administration of the implicating drug and addition of supplements. Folate is available as 5 mg tablet and overdose is not associated with any adverse effects; a dose of 1–5 mg daily is advocated for 3–4 weeks. Vitamin B12 is administered at a dose of 250–1000 µg by intramuscular route; young children should receive lower doses (250–500 µg) since tremors and extrapyramidal toxicity are reported. Therapy is given daily for 1–2 weeks and then weekly until the hematocrit is normal. Patients with pernicious anemia and malabsorption require monthly supplementation for life. Patients with neurological complications should receive 1000 µg daily for 2 weeks, then every 2 weeks for 6 months and monthly for life. The absorption of oral supplements is variable and may be insufficient in patients with malabsorption. Patients with dietary insufficiency should receive nutritional counseling; if diet cannot be altered due to social and cultural reasons, lifelong vitamin B12 supplementation is required, either as oral supplements daily or parenteral doses every 3–12 months.

Therapy is associated with improvement in hematological parameters, including reticulocytosis, decline in MCV and improvement in platelet and neutrophil counts within a few days of therapy.

Suggested Reading

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Approach to Hemolytic Anemia

The term hemolytic anemia refers to conditions in which the rate of red cell destruction is accelerated and the ability of the bone marrow to respond to anemia is unimpaired. Under maximal stimulation, the normal marrow is capable of increasing its production rate about six to eight times its basal level. Hemolytic disorders may be divided into inherited and acquired varieties (Table 12.8). This classification has a pathogenetic significance because the nature of hereditary lesions differs from that of acquired. Most intrinsic defects are inherited and the extrinsic are acquired. An exception is paroxysmal nocturnal hemoglobinuria, an acquired disorder characterized by an intrinsic red cell defect.

Clinical Features

In acute hemolysis, symptoms are related to the rate of fall of hemoglobin; patients with rapid hemolysis have an acute and severe presentation. Anemia is suggested by weakness, pallor and fatigue. Jaundice is a prominent finding of some hemolytic anemias. Red urine suggests hemoglobinuria in intravascular hemolysis. Splenomegaly is seen in autoimmune and several congenital causes of hemolytic anemias. Other useful clues to etiology are the presence of gallstones (spherocytosis), hemolytic or thalassemic facies (Fig 12.6) and leg ulcers (sickle cell anemia); however laboratory tests are still required to confirm the cause.

Table 12.8: Causes of hemolytic anemia

Acquired
Mechanical: Macroangiopathic. (Artificial heart valves, march hemoglobinuria); *microangiopathic* (disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura)
Infections, e.g. malaria, kala-azar, *Clostridium welchii*
Antibody mediated: Autoimmune hemolytic anemia (warm and cold types)
Transfusion reactions: Immediate and delayed
Hemolytic disease of the newborn
Drugs: Cefotetan, ceftriaxone
Hypersplenism
Cryopathy, e.g. cold agglutinin disease, paroxysmal cold hemoglobinuria
Physical injury, e.g. burns
Chemical injury, e.g. snake bite, lead and arsenic toxicity
Inherited
Hemoglobinopathies, e.g. thalassemia, sickle cell disease
Red cell membrane defect, e.g. glucose-6-phosphate dehydrogenase deficiency
Disorders of the cytoskeletal membrane, e.g. hereditary spherocytosis
Unstable hemoglobins
Lipid membrane defects, e.g. abetalipoproteinemia
Porphyria

Laboratory Findings

The reticulocyte count is useful in determining the rate of red cell destruction. The normal reticulocyte count value in the newborn is 3.2±1.4% and in children 1.2±0.7%.

Laboratory test findings in hemolytic anemia can be divided into three groups:

i. Increase in erythrocyte destruction (Table 12.9)
ii. Compensatory increase in the rate of erythropoiesis (Table 12.10) and
iii. Features specific to particular etiologies of hemolytic anemia.

An elevated corrected reticulocyte count may be the only manifestation of mild hemolytic anemia in a well compensated child. Hemoglobin and heme released from red cells following intravascular hemolysis bind to the proteins haptoglobin and hemopexin. These protein complexes are removed from circulation. Hence, haptoglobin and hemopexin levels are low in patients with

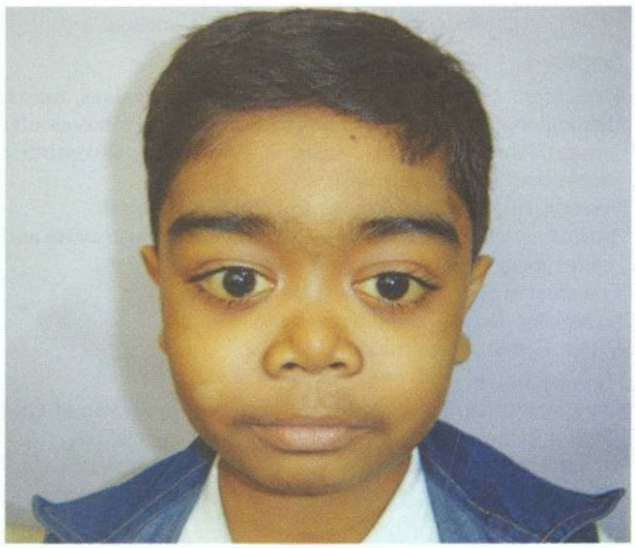

Fig. 12.6: Child with hemolytic anemia, showing hemolytic facies and icterus

Table 12.9: Laboratory signs of accelerated erythrocyte destruction

Fall in blood hemoglobin level at >1.0 g/dl per week
Increased serum level of unconjugated bilirubin
Increased urinary urobilinogen excretion
Increased serum lactate dehydrogenase
Reduced haptoglobin and hemopexin
Reduced glycosylated hemoglobin
Decreased erythrocyte life span (labeled with radioisotope ^{51}Cr)

Table 12.10: Laboratory signs of accelerated erythropoiesis

Peripheral blood
Polychromasia or reticulocytosis
Macrocytosis
Increase in nucleated red cells
Bone marrow
Erythroid hyperplasia
Iron kinetic studies
Increased plasma iron turnover
Increased erythrocyte iron turnover

intravascular hemolytic anemia. When haptoglobin is saturated, free plasma hemoglobin can be detected. The level of indirect bilirubin is an insensitive measurement of hemolysis as it is only elevated when liver function is impaired or when hemolysis is extensive.

A peripheral smear is useful in evaluation of hemolytic anemias. It may show malarial parasites; presence of bite cells may suggest glucose 6 phosphate dehydrogenase enzyme (G6PD) deficiency. Spherocytes are seen in hereditary spherocytosis, but may also be seen post transfusion. Microcytosis with many fragmented red cells may suggest thalassemia and thrombocytopenia with schistocytosis (fragmented red cells) can be seen in disseminated intravascular coagulopathy or hemolytic uremic syndrome. The Coombs test is the most important initial test to perform to define the etiology of hemolysis. A positive direct antiglobin (direct Coombs) test means that the erythrocyte is coated with IgG or C3 component of complement, and is positive in most cases of immune hemolytic anemia. However, the test may be falsely negative in 2–5% cases.

Hallmarks of intravascular and extravascular hemolysis. Following intravascular hemolysis, hemoglobin is released into the plasma (hemoglobinemia). A part of the circulating free hemoglobin is converted to methemoglobin, which binds with albumin to form methemalbumin that confers a brown color to plasma for several days following the hemolytic event. When the amount of hemoglobin exceeds the haptoglobin binding capacity it is excreted in the urine (hemoglobinuria). Some of this hemoglobin is reabsorbed in the proximal renal tubules; the loss of hemeladen tubular cells is seen as hemosiderinuria. Similar to intravascular hemolysis, unconjugated bilirubin, lactate dehydrogenase and reticulocyte count are elevated in extravascular hemolysis and haptoglobulin may be decreased. However, in extravascular destruction of red cells, there is no free hemoglobin or methemoglobin in the plasma; hence, hemoglobinemia, hemoglobinuria and hemosiderinuria are absent.

Specific tests such as hemoglobin electrophoresis, osmotic fragility, enzyme assays for G6PD and pyruvate kinase deficiency and assay for CD55/59 for paroxysmal nocturnal hemoglobinuria are based on the etiology suspected (Table 12.8).

Management

It is important to maintain fluid balance and renal output during and after acute hemolysis. Shock is managed by appropriate measures. However, blood transfusions, considered useful in acute anemia of other types, should be used cautiously when managing patients with acquired hemolytic anemias. Even with careful blood matching, transfused blood cells may undergo hemolysis, leading to an increase in the burden on excretory organs and, sometimes, thromboses.

Acute autoimmune hemolytic anemia is treated with corticosteroids (prednisone 1–2 mg/kg/day), which are tapered gradually over several months after ongoing hemolysis has resolved. Patients with chronic hemolysis require thorough investigation for etiology and treatment specific to cause.

Hereditary Spherocytosis

Patients with hereditary spherocytosis may have one of several membrane protein defects. Many of these result in instability of spectrin and ankyrin, the major skeletal membrane proteins. The degree of skeletal membrane

protein deficiency correlates with the degree of hemolysis. Membrane protein deficiency leads to structural changes including membrane instability, loss of surface area, abnormal membrane permeability and reduced red cell deformability. These defects are accentuated during depletion of metabolites, demonstrated as an increase in osmotic fragility after 24-hr incubation of blood cells at 37°C. Non-deformable erythrocytes are destroyed during passage through spleen.

Laboratory findings. Patients with hereditary spherocytosis may have a mild to moderate chronic hemolytic anemia. The red cell distribution width (RDW) is increased due to the presence of spherocytes and increased reticulocytes. The MCV is decreased and MCHC increased due to cellular dehydration.

Presentation. The age of presentation ranges from early childhood to adulthood. Patients chiefly present with jaundice of varying intensity. Splenomegaly is found in 75% patients. Gallstones are frequent, particularly in older patients and represent pigment calculi.

Management. Patients require lifelong folic acid supplementation of 1–5 mg daily to prevent folate deficient due to the high turnover of red cells and accelerated erythropoeisis. While splenectomy does not cure the hemolytic disorder, it may reduce the degree of hemolysis. It is the treatment of choice in patients with severe hemolysis and high transfusion requirement. Splenectomy is delayed or avoided in patients with mild hemolysis. Splenectomy may diminish the risk of traumatic splenic rupture in children with splenomegaly. Splenectomy is usually performed beyond 6 yr of age following immunizations against *Haemophilus influenzae* type B, *Streptococcal pneumoniae* and *Neisseria meningitidis*. Post splenectomy, patients should receive penicillin prophylaxis, to prevent sepsis, usually up to early adulthood.

As with other hemolytic anemias, patients with hereditary spherocytosis are also susceptible to aplastic crisis with human parvovirus B19. This organism selectively invades erythroid progenitor cells and causes transient arrest in red cell production. Patients usually recover in 4–6 weeks.

Abnormalities in Red Cell Glycolysis

Glucose is the primary metabolic substrate for erythrocytes. Since mature red cells do not contain mitochondria, glucose is metabolized by anerobic pathways; the two main metabolic pathways are Embden Meyerhof pump (EMP) and the hexose monophosphate shunt. The Embden Meyerhof pump pathway accounts for 90% of glucose utilization. The inability to maintain adenosine triphosphate impairs cellular functions, including deformability, membrane lipid turnover and membrane permeability, leading to shortened red cell life. The hexose monophosphate shunt is responsible for 10% of glucose metabolism. This pathway generates substrates that protect red cells from oxidant injury. A defect in this shunt causes collection of oxidized hemoglobin (Heinz bodies), lipids and membrane proteins in red cells, which result in hemolysis. The reticulocyte count is raised and bone marrow shows erythroid hyperplasia. Demonstration of autohemolysis is a useful screening test; diagnosis requires specific enzyme assays.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6- phosphate dehydrogenase (G6PD) deficiency is the most common red cell enzyme deficiency. It is an X-linked recessive disease with full expression in affected males. Many variants are identified based on differences in antioxidant reserve and enzyme levels. After an oxidant exposure, hemoglobin is oxidized to methemoglobin and denatured to form intracellular inclusions also known as Heinz bodies. These Heinz bodies get attached to the red cell membrane and aggregate intrinsic membrane proteins such as band 3. Reticuloendothelial cells detect these membrane changes as antigenic sites and ingest a part of the red cell. This partly phagocytosed cell, called 'bite' cell, has a shortened half-life.

The child may present with jaundice in neonatal period. Findings during a hemolytic crisis are pallor, icterus, hemoglobinemia, hemoglobinuria and splenomegaly. Plasma haptoglobin and hemopexin are low. The peripheral blood smear shows fragmented bite cells and polychromasia. Special stains demonstrate Heinz bodies during the initial few days of hemolysis. Diagnosis of G6PD deficiency is suggested by family history, clinical findings, laboratory features and exposure to oxidants prior to the hemolytic event (Table 12.11). Confirmation of the diagnosis requires quantitative enzyme assay or molecular gene analysis.

Management consists of supportive care during the acute crisis (hydration, monitoring and transfusions if needed) along with folic acid supplementation. Counseling to avoid intake of oxidant drugs (Table 12.11) is imperative.

Pyruvate kinase deficiency This is the most common enzyme defect in the Embden Meyerhof pump and is inherited in an autosomal recessive manner. Homozygotes present with splenomegaly, icterus and hemolytic anemia, but the clinical spectrum is variable. Folic acid supplementation is required to prevent megaloblastic

Table 12.11: Drugs that cause oxidant stress and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency

Sulfonamides: Sulfamethoxazole
Antimalarials: Primaquine, quinine
Analgesics: Aspirin, non-steroidal anti-inflammatory drugs, phenazopyridine (pyridium)
Others: Nitrofurantoin, dapsone, methylene blue, rasburicase, toluidine blue, nalidixic acid, furazolidine, quinidine

complications due to relative folate deficiency. Splenectomy is considered a therapeutic option in patients with pyruvate kinase deficiency, it does not stop the hemolytic process. The reticulocyte count increases dramatically after splenectomy.

Autoimmune Hemolytic Anemia

An autoimmune phenomenon targeting the red cells may occur in isolation, or arise as a complication of an infection (viral hepatitis B, upper respiratory tract viral infections, mononucleosis and cytomegalovirus infection), systemic lupus erythematosus (SLE) or other autoimmune syndromes, immunodeficiency states or malignancies.

Clinical features The disease usually has an acute onset, manifested by weakness, pallor, fatigue and dark urine. Jaundice is a prominent finding and splenomegaly is common. Some cases are chronic. Clinical features may suggest an underlying disease (e.g. SLE or HIV).

Laboratory findings The anemia is normochromic and normocytic and may vary from mild to severe. The reticulocyte count is usually increased. Spherocytes and nucleated red cells may be seen on the peripheral blood smear. Other features suggesting hemolysis include increased levels of lactic dehydrogenase, indirect and total bilirubin, aspartate aminotransferase and urinary urobilinogen. Intravascular hemolysis is indicated by hemoglobinemia or hemoglobinuria. Serologic studies help define pathophysiology, plan therapeutic strategies and assess prognosis. The direct antiglobulin test is positive in almost all cases. Further evaluation allows distinction into one of three syndromes.

Autoimmune hemolytic anemia due to warm reactive autoantibodies is caused by IgG antibodies against the patient's red blood cells, with specificity for Rh-like antigen. These antibodies have maximal *in vitro* antibody activity at 37°C and do not require complement for activity. The condition can occur in isolation (primary), associated with immune disorders (e.g. SLE, lymphoproliferative disease, immunodeficiency), or with use of certain drugs (e.g. penicillin, cephalosporins) due to the 'hapten' mechanism (tight binding of drug to the red cell membrane is followed by immune destruction of cells by newly formed or preexisting antibodies to the drug). Extravascular destruction of the red cells by reticuloendothelial system occurs, resulting in splenomegaly.

In contrast, patients with *cold reactive autoimmune hemolytic anemia* have antibodies, primarily of the IgM class, that require complement for their activity, have optimal reactivity in vitro at 4°C, and are specific to the i or I antigen on red cells. Detection of complement alone on red blood cells help make a diagnosis. While the condition is usually seen in adults, children may develop Donath Landsteiner hemolytic anemia, which is associated with an acute viral syndrome and is mediated by cold hemolysis. *Paroxysmal cold hemoglobinuria* is a related condition, usually identical to cold autoimmune hemolytic anemia, except for antigen specificity to P antigen and the evidence of *in vitro* hemolysis. Children may develop cold agglutinins following infections, such as mycoplasma, Epstein-Barr virus (EBV) and cytomegalovirus (CMV), in association with intravascular hemolysis.

IgG and complement associated autoimmune hemolytic anemia may occasionally occur due to warm antibody or, very rarely, due to drug associated autoimmune hemolytic anemia.

Management Medical management of any underlying disease is important. Most patients with warm autoimmune hemolytic anemia respond to prednisone 1 mg/kg, given daily for 4 weeks or till hemoglobin is stable. After initial treatment, corticosteroids may be tapered slowly over 4–6 months. While use of intravenous immune globulin (IVIG) (1 g/kg/day for 2 days) may induce remission, the response is not sustained. The rate of remission with splenectomy may be as high as 50%, particularly in warm reactive autoimmune hemolytic anemia. However, this option should be considered carefully in younger patients due to a high risk of infections with encapsulated organisms. Hence, splenectomy is withheld until other treatments have been tried. In severe cases unresponsive to conventional therapy, immunosuppressive agents such as cyclophosphamide, azathioprine and cyclosporine may be tried alone or in combination with corticosteroids. Danazol is effective in 50–60% of cases of chronic hemolytic anemia. Refractory cases may respond to rituximab (monoclonal antibody to B cell CD20) or to hematopoietic stem cell transplantation.

Patients with cold autoimmune hemolytic anemia and paroxysmal cold hemoglobinuria are less likely to respond to corticosteroids or intravenous immunoglobulin (IVIG). When associated with infections, these syndromes have an acute, self-limited course and supportive care is all that is necessary. Plasma exchange is effective in severe cold autoimmune (IgM) hemolytic anemia and may be helpful in severe cases because the offending antibody has an intravascular distribution.

Transfusion may be necessary because of the complication of severe anemia but should be monitored closely. In most patients, cross-match compatible blood will not be found and the least incompatible unit should be identified by the blood bank. Transfusions must be conducted carefully, beginning with a test dose.

Prognosis In general, children with warm autoimmune hemolytic anemia are at greater risk for more severe and chronic disease with higher morbidity and mortality rates. Hemolysis and positivity of antiglobulin tests may continue for months or years. Patients with cold autoimmune hemolytic anemia or paroxysmal cold hemoglobinuria have acute self-limited disease.

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Thalassemias

The word thalassemia is a Greek term derived from *thalassa*, which means 'the sea' (referring to the Mediterranean sea) and *emia*, which means 'related to blood'. The disease is more common in populations in the geographic belt from Southeast Asia to Africa. Thalassemias, caused by defects in the globin gene, are the most common monogenic disease. More than 200 mutations are described and the defects are inherited in an autosomal recessive manner. The carrier rates for β thalassemia in north Indians are reported to vary from 3–17% in different ethnic groups.

Pathophysiology

The major hemoglobin in humans, called HbA, constitutes approximately 90% of total hemoglobin in children beyond one year of age. A minor component, HbA_2, accounts for 2–3% of hemoglobin. The main hemoglobin in fetal life is HbF, of which only traces remain after one year. Each of these hemoglobins has two α chains that are associated with two β globin chains in HbA, δ chains in HbA_2 and γ globin chains in HbF.

Thalassemias are inherited disorders of hemoglobin synthesis that result from an alteration in the rate of globin chain production. A decrease in the rate of production of globins (α, β, δ, γ) impedes hemoglobin synthesis and creates an imbalance with normally produced globin chains. Because two types of chains (α and non-α) pair with each other at a ratio close to 1:1 to form normal hemoglobin, an excess of the normally produced type is present and accumulates in the cell as an unstable product, leading to early the destruction of the red cell. The type of thalassemia usually carries the name of the chain or chains that is not produced. The reduction may vary from a slight decrease to a complete absence. When β chains are produced at a lower rate, the thalassemia is termed β+, whereas $β^0$ thalassemia indicates a complete absence of production of β chains from the involved allele.

Presentation

Thalassemia should be considered in the differential diagnosis of any child with hypochromic, microcytic anemia that does not respond to iron supplementation. Children with β thalassemia major usually demonstrate no symptoms until about 3–6 months of age, when β chains are needed to pair with α chains to form HbA, since γ chains production is turned off. However, in some cases, the condition may not be recognized till 3–5 yr of age due to a delay in cessation of HbF production.

Severe pallor and hepatosplenomegaly are almost always present. Icterus is usually absent, but mild to moderate jaundice may occur due to liver dysfunction from iron overload and chronic hepatitis. Symptoms of severe anemia such as intolerance to exercise, irritability, heart murmur or even signs of frank heart failure may be present. Bony abnormalities, such as frontal bossing, prominent facial bones and dental malocclusion are usually present (Fig 12.6). Ineffective erythropoiesis leads to a hypermetabolic state associated with fever and failure to thrive. Hyperuricemia may be encountered.

Spectrum of Disease

β thalassemia trait. Patients have mild anemia, abnormal red blood cell indices and abnormal hemoglobin HPLC results with elevated levels of HbA_2, HbF or both. The peripheral blood film examination usually reveals marked hypochromia, microcytosis and presence of target cells. Anisocytosis, usually prominent in iron deficiency anemia, is not seen.

Thalassemia intermedia. This condition may occur due to a compound heterozygous states, resulting in anemia of intermediate severity, which usually does not require regular blood transfusions. This is primarily a clinical diagnosis and requires monitoring of the child over time to see the clinical spectrum of disease.

Thalassemia major. This condition is characterized by transfusion-dependent anemia, splenomegaly, bone deformities, growth retardation and hemolytic facies in untreated or inadequately treated individuals. Organomegaly is marked in patients receiving irregular or inadequate transfusion support. Examination of the peripheral blood smear shows severe hypochromia, microcytosis, marked anisocytosis, fragmented red blood cells, polychromasia, nucleated red cells and occasionally, immature leukocytes.

Associated variants. β thalassemia may be associated with β chain structural variants. The most significant condition in this group of thalassemic syndromes is the HbE/β thalassemias. Patients with HbE/β thalassemia may present with severe symptoms identical to that of patients with β thalassemia major, or with milder course similar to that of patients with thalassemia intermedia or minor. The variation in severity can be explained because of the difference in β globin chain production, i.e. β+ or β0, the co-inheritance of α thalassemia gene, level of HbF production and the presence of other modifying genes.

Laboratory Studies

Complete blood count and peripheral blood film examination are usually sufficient to suspect the diagnosis. In thalassemias major and intermedia, the hemoglobin

level ranges from 2–8 g/dl, MCV and MCH are significantly low, reticulocyte count is elevated to 5–8% and leukocytosis is usually present. A shift to the left reflects the hemolytic process. The platelet count is usually normal unless the spleen is markedly enlarged, causing hypersplenism. Peripheral blood film examination reveals marked hypochromasia and microcytosis, polychromatophilic cells, nucleated red blood cells, basophilic stippling and occasional immature leukocytes (Figs 12.7 and 12.8). High performance liquid chromatography (HPLC) for hemoglobin must be sent prior to the first blood transfusion. The test confirms the diagnosis of β thalassemia. Absence of HbA and elevation of HbF suggest thalassemia major; the level of HbA2 is not important for diagnosis. The presence of elevated HbA2 alone suggests the diagnosis of thalassemia trait.

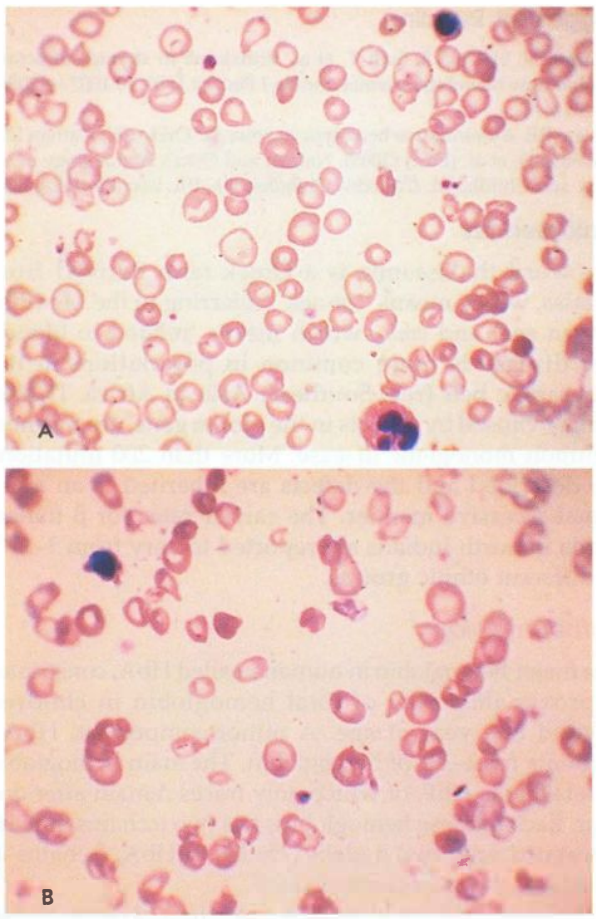
Complications and Management

Genetic counseling is needed for the couple and their family to prevent the birth of other children with thalassemia major and prenatal testing can be used to detect thalassemia major in the fetus. Carriers are relatively easy to identify and screen. Prenatal diagnosis and genetic counseling programs have led to a dramatic reduction in the frequency of births of children with thalassemia major in many countries.

The introduction of hematopoietic stem cell transplantation offers the possibility of cure in severe forms of thalassemia. However, this option is available only to a relatively small number of patients. Treatment of non-transplanted children consists of regular blood transfusions and iron-chelating agents; if both are pursued vigorously, these children survive into adulthood. Major challenges in chronic care of these children are ensuring safety of blood products and meeting the costs of life-long iron-chelating agents.

Patients with thalassemia major require medical supervision to monitor for complications and transfusion therapy. Blood transfusion should be initiated at an early age when the child is asymptomatic and attempts should be made to keep pretransfusion hemoglobin 9–10 g/dl (to promote growth and prevent deformity). Chelation therapy to deal with the accumulated iron overload is vital to prevent iron overload and organ dysfunction. A normal diet is recommended, with supplements of folic acid and small doses of vitamins C and E. Iron supplements should not be given. Drinking tea with meals has been shown to decrease absorption of iron in the gut.

Iron overload. Iron overload is the major causes of morbidity and organ toxicity. The excessive load of iron is due to increased gastrointestinal iron absorption as well as repeated transfusions. Hence, avoidance of transfusions alone will not eliminate the iron overload problem. Patients with signs of iron overload demonstrate signs of endocrinopathy caused by iron deposits, including



Figs 12.7A and B: Peripheral smears from a transfusion dependent patient with beta thalassemia major showing marked anisopoikilocytosis, microcytosis, hypochromia, polychromatophilia, nucleated red blood cells and few fragmented erythrocytes. Jenner-Giemsa x 1000

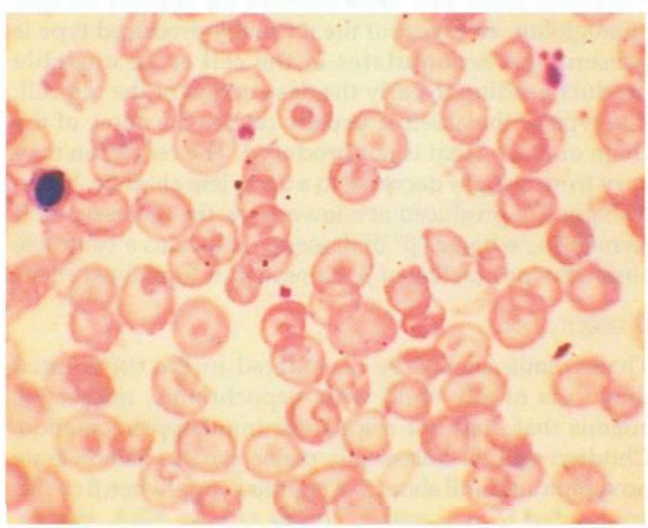


Fig. 12.8: Peripheral smear from an asymptomatic patient with hemoglobin E disease, showing microcytosis, hypochromia, target cells and nucleated red blood cells. Jenner-Giemsa x 1000

diabetes, hypothyroidism, hypoparathyroidism, decreased growth and lack of sexual maturation.

The simplest method for monitoring of iron status is by measurement of serum ferritin. However, the test may underestimate liver and cardiac iron. A liver biopsy or liver MRI and echocardiography may be useful in accurately assessing the iron status. A highly accurate and noninvasive tool to assess the heart iron status is the cardiac T2 magnetic resonance.

Chelation therapy. The introduction of chelating agents capable of removing excess iron from the body has dramatically increased life expectancy. The cost, however, has resulted in poor compliance and inadequate dosing of iron chelators in many Indian patients. The optimal time to initiate chelation therapy is dictated by the amount of accumulated iron. This usually occurs after 1–2 yr of transfusions when ferritin level is about 1000–1500 μg/l. The standard till now has been deferoxamine which must be administered parenterally because of its short half-life. Prolonged subcutaneous infusion is the most effective route. A total dose of 40–60 mg/kg/day is infused over 8–12 hours during the night for 5–6 days a week by a mechanical pump. Patients should be warned about orange discoloration of urine due to the excretion of iron-deferoxamine complex (ferrioxamine). Higher doses of deferoxamine (6–10 g) may be administered intravenously, as inpatient when serious iron overload such as cardiac failure occurs. Severe toxicity may develop if chelation therapy is started prematurely. Eye examinations, hearing tests and renal function tests are required to monitor the effects of deferoxamine therapy.

Deferiprone is an oral chelating agent which is less effective than deferoxamine in preventing organ damage. It is administered at a dose of 75 mg/day. Since the agent may cause arthritis, neutropenia and even agranulocytosis, its administration requires careful monitoring both to prevent serious complications and to assess the adequacy of chelation.

Deferasirox is another oral chelating agent that has shown efficacy similar to parenteral agent deferoxamine in maintaining or reducing liver iron. The molecule is a tridentate ligand that binds iron with a high affinity, forming a 2:1 complex that is excreted in bile and eliminated primarily via the feces. This chelator is highly selective for iron and chelates both intracellular and extracellular deposits excess in the liver, heart and reticuloendothelial system. The recommended starting dose is 30 mg/kg/day. It may cause skin rash, nausea, vomiting and renal and hepatic toxicity; hence, the serum creatinine, liver function tests and urine for proteinuria need to be monitored.

Hematopoietic stem cell transplantation Hematopoietic stem cell transplantation is the only known curative treatment for thalassemia. Poor outcome after hematopoietic stem cell transplantation correlates with the presence of hepatomegaly, portal fibrosis and inadequate chelation prior to transplant. The event-free survival rate for patients who have all three features is 59%, compared to 90% for those who do not have these features.

Reactions. After multiple transfusions, many patients develop reactions; these may be minimized by using leukocyte filters during transfusion or by using leukocyte-depleted packed red cells. Administration of acetaminophen and diphenhydramine hydrochloride before each transfusion minimizes febrile or allergic reactions. Rarely alloimmunization to red blood cell antigens can occur.

Infections. The major complications of blood transfusions are those related to transmission of infections such as hepatitis B and C and HIV. Hepatitis B vaccination and regular assessment of the hepatitis and HIV status are required.

Lactoferrin, a prominent component of the granules of polymorphonuclear leukocytes, is bacteristatic for many pathogens. The very high transferrin saturation attained in patients with iron overload compromise the bacteriostatic properties of this protein. Infection with *Yersenia enterocolitica* can occur in patients with iron overload and presents with fever and diarrhea. Treatment with trimethoprim-sulfamethoxazole and gentamicin is required. Other important infections which may occur are mucormycosis (*Rhizopus oryzae*) and *Listeria monocytogenes*.

Hypersplenism. The spleen acts as a store for nontoxic iron, protecting the body from extra iron. Hence, early removal of the spleen may be harmful. Splenectomy is justified only in hypersplenism, which is associated with excessive destruction of erythrocytes that increases the need for frequent blood transfusions, resulting in further iron accumulation. Patients who require more than 200–250 ml/kg of packed red blood cells per year to maintain hemoglobin may benefit from this procedure. This is rarely required in children receiving adequate transfusion therapy. Presplenectomy immunizations and prophylactic antibiotics have significantly decreased infections in splenectomized children. The procedure is usually delayed until the child is aged 7 yr or older.

Bone disease. The classic "hair on end" appearance of the skull, results from widening of the diploic spaces. The maxilla may overgrow, resulting in maxillary overbite and prominence of the upper incisors. These changes contribute to the classic hemolytic or 'chipmunk' facies observed in patients with thalassemia major. Osteoporosis and osteopenia may result in fractures. Such children may need treatment with calcium, vitamin D and bisphosphonates to improve bone density.

Extramedullary hematopoiesis. These occur in patients with severe anemia, e.g. thalassemias intermedia, who are not receiving transfusion therapy. The process may cause

neuropathy or paralysis from compression of the spine or peripheral nerves. Compression fractures and paravertebral expansion of extramedullary masses, which behave clinically like tumors, are more frequent during the second decade of life.

Psychosocial complications. As these children are surviving into adulthood newer problems related to employment marriage and having families, as well as the stress of chronic illness will need to be addressed.

Management of other Thalassemic States

Patients with thalassemia intermedia require monitoring to assess the need for transfusion, as persistently low hemoglobin may retard growth. Hydroxyurea at a dose of 15–20 mg/kg/day may be used to increase HbF production and reduce the need for transfusion support. This therapy is most effective in children with *XLM1* mutation.

Patients with thalassemia trait do not require medical followup after the initial diagnosis. Iron therapy should not be used unless a definite deficiency is confirmed. Genetic counseling is indicated to create awareness and prevent thalassemia major in subsequent offspring.

Suggested Reading

Nadkarni A, Gorakshakar AC, Krishnamoorthy R, et al. Molecular pathogenesis and clinical variability of beta thalassemia syndromes among Indians: Am J Hematol 2001; 68:75–80

Sarnaik SA. Thalassemia and related hemoglobinopathies. Indian J Pediatr 2005;72:319–24

Sickle Cell Anemia

Sickle cell anemia is an autosomal recessive disease that results from the substitution of valine for glutamic acid at position 6 of the beta-globin gene. Patients who are homozygous for the HbS gene have sickle cell disease. Patients who are heterozygous for the HbS gene have sickle trait. The gene frequency for sickle cell anemia in India is 4.3%, but the disease is reported chiefly from Orissa, Maharashtra, Madhya Pradesh and Jharkand. Deoxygenation of the heme moiety of sickle hemoglobin leads to hydrophobic interactions between adjacent sickle hemoglobin (HbS) molecules that aggregate into larger polymers. Sickle red blood cells are less deformable and obstruct the microcirculation, resulting in tissue hypoxia, which further promotes sickling. These red blood cells are rapidly hemolyzed and have a life span of only 10–20 days.

Clinical Features

Patients with sickle cell anemia can present with serious and varied manifestations.

Pain is the most common presentation of vaso-occlusive crisis. Presentation with pain suggests acute chest syndrome if pleuritic in nature and arthritis or osteomyelitis if joint or bone are involved. Painful crises tend to recur, precipitated by triggers such as dehydration or fever. Shortness of breath or dyspnea suggests an acute chest syndrome, while unilateral weakness, aphasia, paresthesias, visual symptoms may suggest stroke or infarct. Sudden increase in pallor, syncope or sudden pain or fullness in the left side of the abdomen mass may indicate a splenic sequestration crisis.

The usual presentations in a young child are icterus due to elevated unconjugated bilirubin, pallor and mild splenomegaly. The disease may manifest as a febrile illness since these children are prone to pneumococcal, *Salmonella* and other bacterial infections. Tachypnea suggests pneumonia, congestive heart failure, or acute chest syndrome, while hypoxia is common with acute chest syndrome. Children with aplastic crisis may present with congestive heart failure (CHF) due to severe anemia. Hypotension and tachycardia are signs of septic shock or sequestration crisis. Growth retardation and gallstones are common in children with sickle cell anemia.

Types of Crisis

Vaso-occlusive crisis. A vaso-occlusive crisis occurs when the microcirculation is obstructed by sickled red blood cells resulting in ischemic injury. The major complaint is pain, usually affecting bones such as femur, tibia and lower vertebrae. Alternatively, vaso-occlusion may present as dactylitis, hand and foot syndrome (painful and swollen hands and/or feet), or an acute abdomen. The spleen may undergo auto-infarction and is often not palpable beyond 6 yr of age. Involvement of the kidney results in papillary necrosis leading to inability to concentrate urine (isosthenuria). Other presentations include acute chest syndrome, retinal hemorrhages, priapism, avascular necrosis of the femoral head and cerebrovascular accidents.

Acute chest syndrome. This is a type of vaso-occulsive crisis that affects the lung and presents with chest pain, cough, tachypnea, dyspnea, hypoxemia, fever or a new pulmonary infiltrate. This requires urgent admission; oxygen support, antibiotics (also should cover for mycoplasma and chlamydia), intravenous fluids, bronchodilators and use of steroids may be of benefit.

Sequestration crisis. This is due to sickled cells that block splenic outflow, leading to the pooling of peripheral blood in the engorged spleen resulting in splenic sequestration.

Aplastic crisis. Aplastic crises can occur when the bone marrow stops producing red blood cells. This is most commonly seen in patients with infection or folate deficiency. This is usually self-limited and may follow viral infections of which parvovirus B19 is the most commonly implicated. Usually only supportive care and occasionally packed red blood cell transfusions are required.

Infections

Affected children have increased susceptibility to encapsulated organisms (e.g. *Haemophilus influenzae,*

Streptococcus pneumoniae). They are also at risk of other common infectious organisms such as *Salmonella*, *Mycoplasma pneumoniae*, *Staphylococcus aureus* and *Escherichia coli*.

Laboratory Studies

Anemia and thrombocytosis are commonly found. Leukocytosis occurs in patients with sickle cell anemia. However, a rise in the white blood cell count (i.e. >20,000 per mm^3) with a left shift is indicative of infection. In the peripheral smear, sickle-shaped red blood cells are found along with target cells. Presence of Howell-Jolly bodies indicates that the patient is functionally asplenic. The baseline indirect bilirubin level may be elevated because of chronic hemolysis.

If the diagnosis of sickle cell anemia has not been made, a sickling test will establish the presence of sickle hemoglobin. Hemoglobin electrophoresis is the test that can differentiate between individuals who are homozygous or heterozygous. Hemoglobin in a homozygous patient will chiefly (80–90%) be hemoglobin SS (HbSS), while carriers will have 35–40% as HbSS. This needs to be checked prior to blood transfusions.

Assessment During Acute Illness

In a sick child, a type and cross-match is required for probable transfusion. A chest X-ray and X-rays of bones may be indicated in pain crisis. Blood culture should be sent. Monitoring of oxygen saturation and arterial blood gases should be ordered in patients with respiratory distress. A major drop in hemoglobin (more than 2 g/dl) from baseline indicates a splenic sequestration or aplastic crisis. Reticulocyte count and examination of spleen size will help to differentiate between these two conditions. An electrocardiogram must be performed if symptoms of chest pain and/or pulse irregularities are noted.

Inpatient Management

Hydration and analgesia are the mainstays of treatment in a pain crisis. Narcotic analgesia is most frequently used. Hydration is corrected orally if the patient is not vomiting and can tolerate oral fluids. In severe dehydration, intravenous fluids are required. Care is taken not to overload the patient and accurate intake-output monitoring should be ensured. Blood transfusion is useful in patients in aplastic crisis and acute sequestration crisis.

Oxygen supplementation is of benefit if the patient has hypoxia. Intubation and mechanical ventilation may be required in children in whom cerebrovascular accidents have occurred, or with acute chest syndrome. Exchange blood transfusions are indicated in cases of cerebrovascular accidents and acute chest syndrome. This involves replacing the patient's red blood cells by normal donor red blood cells, decreasing HbSS to less than 30%. They may be performed in patients with acute sequestration crisis or in priapism that does not resolve after adequate hydration and analgesia.

Preventive Care

All children require prophylaxis with penicillin or amoxicillin, at least until 5 yr of age and should receive immunizations with pneumococcal, meningococcal and *Haemophilus influenzae* B vaccines. They should receive life long folate supplementation. Hydroxyurea is a cytotoxic agent which can increase HbF and reduce episodes of pain crises and acute chest syndrome and may be useful beyond 5 yr of age. Parents need to learn how to identify complications and be informed for necessity and indications for admission. Patients need to be screened regularly for development of gallstones. Genetic counseling and testing should be offered to the family.

Suggested Reading

Sachdeva A, Sharma SC, Yadav SP. Sickle cell disease. In: IAP Specialty series on Pediatric Hematology & Oncology 2006;77–96

Steinberg MH. Management of sickle cell disease. N Engl J Med 1999;40:1021–30

Aplastic Anemia

Aplastic anemia comprises a group of disorders of the hematopoietic stem cells resulting in the suppression of one or more of erythroid, myeloid and megakaryocytic cell lines. The condition may be inherited or acquired. In developed countries, bone marrow failure due to hypoplastic or aplastic anemia affects 2–6 individuals per million populations. Although precise information is lacking, the prevalence is estimated to be higher in India.

Etiopathogenesis

Hematopoietic stem cells may be deficient due to (i) an acquired injury from viruses, toxins or chemicals; (ii) abnormal marrow microenvironment; (iii) immunologic suppression of hematopoiesis (mediated by antibodies or cytotoxic T cells); and (iv) mutations in genes controlling hematopoiesis resulting in inherited bone marrow failure syndromes (Table 12.12).

Clinical Features

Physical examination in case of severe anemia reveals pallor and/or signs of congestive heart failure. Ecchymoses, petechiae, gum bleeding and nose bleeds are associated with thrombocytopenia. Fever, pneumonia or sepsis may occur due to neutropenia. Inherited bone marrow failure syndromes, usually diagnosed in childhood or as young adults, may be associated with characteristic congenital physical anomalies, positive family history or neonatal thrombocytopenia. The child should be evaluated for the stigmata of congenital bone marrow failure syndromes (Table 12.12; Figs 12.9 and 12.10). However, Fanconi anemia may be present even without any abnormal phenotypic features. History of exposure

Table 12.12: Congenital syndromes associated with bone marrow failure

Syndrome	*Inheritance*	*Associated features*	*Risk of malignancy*
Associated with pancytopenia			
Fanconi anemia	AR	Absent thumbs, absent radius, microcephaly, renal anomalies, short stature, café au lait spots, skin pigmentation	High risk of acute myeloid leukemia, myelodysplasia, oral or liver cancer
Dyskeratosis congenita	X-linked recessive, AD, AR	Dystrophic nails, leukoplakia	Skin cancer (usually squamous cell), myelodysplasia
Single lineage cytopenias			
Amegakaryocytic thrombocytopenia	AR	None	None
Diamond-Blackfan syndrome (pure red cell aplasia)	AD, AR	Short stature, congenital anomalies in one-third, macrocytosis, elevated fetal hemoglobin, raised adenosine deaminase	Leukemia, myelodysplasia, other cancers
Thrombocytopenia absent radii	AR	Absent radius	None

AR autosomal recessive; AD autosomal dominant

to toxins, drugs like chloramphenicol, environmental hazards and viral infections, e.g. hepatitis B or C, suggest an acquired aplasia.

Laboratory Studies

Hematological features of bone marrow failure include pancytopenia or bilineage involvement, noted in aplastic anemia, single cytopenia as seen in pure red cell aplasia and amegakaryocytic thrombocytopenic purpura. Single lineage cytopenias should be differentiated from transient erythroblastopenia of childhood. Peripheral blood smear reveals anemia, occasionally with macrocytosis (<110 fl), thrombocytopenia and agranulocytosis. The corrected reticulocyte count is less than 1%, indicating reduced red cell production. Bone marrow aspirate and biopsy are essential for evaluation of bone marrow cellularity (Fig. 12.11). Usually, the marrow contains very few hematopoietic cells and is replaced with fat cells and lymphocytes.

Specific tests The sucrose hemolysis test or Ham's test may be positive in patient with underlying paroxysmal nocturnal hemoglobinuria (PNH), in which red cells are lysed by patient's acidified sera, and in congenital dyserythropoeitic anemia type II, where red cells are lysed by other acidified sera but not patient's sera. Recent transfusion with packed red blood cells may give false negative results. A more specific test for PNH is the assay for two complement regulatory proteins present on red blood cells, CD55 (decay accelerating factor, DAF) and CD59 (membrane inhibitor of reactive lysis, MIRL). The

Fig. 12.9: Child with Fanconi anemia. The child had hyperpigmentation, microcephaly and microphthalmia. She also had radial ray defects and growth retardation

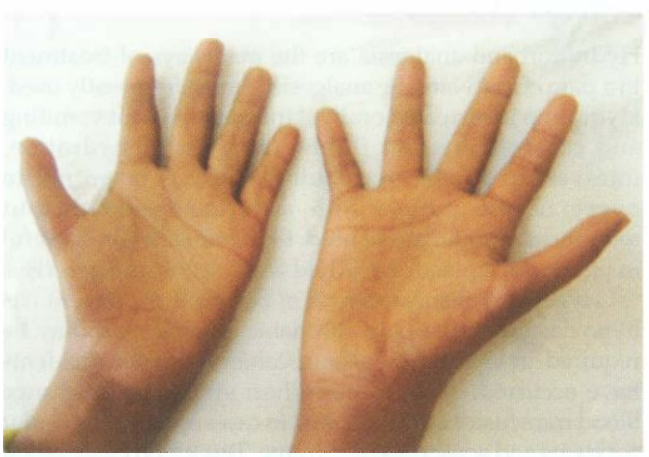


Fig. 12.10: Radial ray defects present in a wide spectrum and include absent or hypoplastic thumbs. Thenar hypoplasia may be missed unless carefully examined

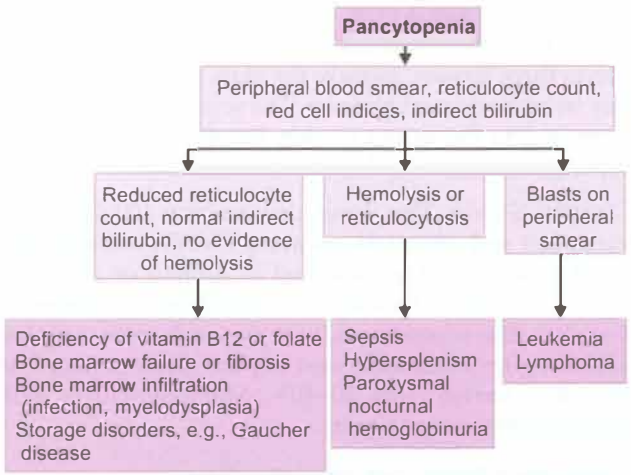


Fig 12.11: Algorithm for evaluation of pancytopenia

peripheral blood cells in Fanconi anemia show a characteristic hypersensitivity towards chromosomal breakage when incubated with DNA cross-linking agents such as mitomycin C. Chromosomal fragility is noted even in patients who lack the characteristic physical stigmata of Fanconi anemia.

Treatment

Supportive care should be instituted with packed red cells for severe anemia, platelets transfusions for severe thrombocytopenia and antibiotics for management of infections. Hematopoietic stem cell transplant (HSCT) is the only definitive therapy. Criteria for referral for HSCT include: (i) young age; (ii) severe aplastic anemia; and (iii) availability of matched sibling. Patients with severe acquired aplastic anemia who cannot undergo HSCT may benefit from infusions of antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) along with oral cyclosporine. Patients with neutropenia with infection should receive a trial of granulocyte colony stimulating factor (G-CSF). However, G-CSF should be discontinued after seven days even if neutrophil count does not improve, since its prolonged use carries the risk of malignant transformation.

Immunosuppressive therapy is contraindicated in children with Fanconi anemia. In these patients, hematopoietic stem cell transplantation is the only cure. However, these children continue to be at risk of malignancies in the future. Oral androgens have been used as palliative therapy in such patients.

Prognosis

The severity and extent of cytopenias determine prognosis. Patients with severe aplasia are at risk of high output cardiac failure due to anemia, bacterial and fungal infections due to neutropenia and severe bleeding due to thrombocytopenia. With current transplantation regimens, longterm survival in patients with severe aplastic anemia is 60–70%, with survival rates exceeding 80% in favorable subgroups.

Suggested Reading

Varma N, Varma S, Marwaha RK, et al. Multiple constitutional aetiological factors in bone marrow failure syndrome (BMFS) in patients from north India. Indian J Med Res 2006:124:51-6

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Bone marrow transplantation, more appropriately termed hematopoietic stem cell transplantation (HSCT), is life saving for several malignant and non-malignant disorders. The term 'autologous' transplant is used when stem cells are harvested from the patient and 'allogeneic' when stem cells are collected from a donor, either a human leukocyte antigen (HLA)-matched sibling or an unrelated person. The commonly used sources of hematopoietic stem cells are cytokine-mobilized peripheral blood, bone marrow and umbilical cord blood.

Indications

The indications for hematopoietic stem cell transplantation are listed in Table 12.13. In malignant disorders, the transplant serves to rescue the bone marrow from the myelotoxic effects of the high doses of chemotherapy or radiation used to cure the malignancy. In allogeneic HSCT, the immunological response of the 'graft versus cancer effect' contributes to controlling the disease. In non-malignant diseases, the abnormal marrow is destroyed and replaced by the healthy unaffected donor marrow that corrects genetic or acquired diseases of blood cells.

Allogeneic HSCT

Donor Requirement

The ideal donor for an allogeneic transplant is a HLA-identical sibling. Despite HLA identity, variations in the minor histocompatibility loci cause antigenic differences that may cause graft rejection or graft versus host disease. While transplants using partially HLA-matched siblings or an unrelated HLA-identical donors may be performed, the complications including graft versus host disease and

Table 12.13: Indications for stem cell transplantation

Malignant disorders	*Nonmalignant disorders*
Acute myeloid leukemia	Thalassemia
Chronic myeloid leukemia	Aplastic anemia
Acute lymphoblastic leukemia (high risk)	Fanconi anemia
Hodgkin disease	Immunodeficiency syndromes
Non-Hodgkin lymphoma (relapsed or refractory)	Inborn errors of metabolism
Neuroblastoma	Autoimmune diseases (rare)
Ewing sarcoma	
Myelodysplastic syndromes	
Gliomas	
Other solid tumors	

graft rejection are usually very severe. Most centers in India conduct only related transplants. Unlike other organ transplants, ABO blood group compatibility is not essential for HSCT. Successful hematopoietic transplantation causes the blood group of the recipient to change to that of the donor.

Conditioning Procedure

Myeloablative conditioning In preparation for HSCT, high doses of chemotherapy are administered to suppress the bone marrow in order to (i) eradicate malignant cells or abnormal clones; (ii) suppress the host immune responses to avoid allograft rejection; and (ii) clear a `physical space' to allow adequate growth of donor stem cells.

Non-myeloablative conditioning Alternatively, knowing that the curative potential of allogeneic HSCT is mediated in part by an immune-mediated graft-versus-tumor effect, donor T cells are used to eradicate both non-malignant and malignant cells of host origin without using myeloablative conditioning regimens. This form of conditioning suppresses the host's immunity sufficiently to allow allogenic engraftment without destroying the host marrow, and with lower toxicity.

Technical Aspects

The donor marrow is harvested under general or spinal anesthesia by repeated aspiration from the posterior iliac crests. The minimum number of marrow cells required for successful engraftment is estimated to be $1–3 \times 10^8$ cells per kilogram of recipient's body weight. When transfused through peripheral veins, the donor marrow cells home into the host marrow space and start engrafting. Engraftment is considered successful when the peripheral absolute neutrophil count exceeds $500/mm^3$ on three successive days.

After transplantation of the marrow, it takes about 2–3 weeks before engraftment occurs. During this period intensive support and protective isolation are required. Infections, predominantly bacterial and fungal infections, remain an important cause of morbidity and mortality in patients undergoing HSCT.

Until engraftment occurs, patients require multiple red cell and platelet transfusions during the 2–4 week period of pancytopenia. Patients are profoundly immune-suppressed and at risk of developing transfusion associated graft versus host disease (GVHD) after receiving cellular blood products. All cellular blood products should be irradiated prior to transfusion to inactivate the donor lymphocytes.

Graft Versus Host Disease

This unique complication may occur in allogeneic bone marrow transplant recipients in one two forms, acute and chronic.

Acute graft versus host disease (GVHD) This occurs within the first 3 months after transplant. It classically affects three tissues, namely the skin, gut and liver, and may be accompanied by fever. The severity can be graded according to the extent of skin involvement, degree of hyperbilirubinemia and severity of diarrhea.

Chronic GVHD This develops later than 100 days after transplant and often follows acute GVHD, but may also develop *de novo*. It is classified as limited or extensive chronic GVHD. Clinically, it resembles autoimmune disorders (like scleroderma) with skin rash, sicca complex, sclerosing bronchioloitis and hepatic dysfunction. The mortality varies from 20–40%. Management is with immunosuppressive agents.

Autologous Stem Cell Transplantation

Transplantation using autologous bone marrow or peripheral blood stem cells is performed similar to allogeneic HSCT, but using the patient's own stem cells for engraftment. The patient's marrow or stem cells are collected prior to chemotherapy and are subsequently used to 'rescue' the patient from the myelosuppression following the chemotherapy. The procedure is useful only for malignancies which are sensitive to chemotherapy or radiotherapy, e.g. leukemias, lymphomas, neuroblastoma and other solid tumors. Virtually all autologous stem cell transplantations are conducted using peripheral blood stem cell transplantations instead of the bone marrow since the engraftment is more rapid. The advantage of autologous transplantation over allogeneic transplants is the absence of GVHD and lower likelihood of graft rejection once engraftment occurs.

Peripheral Blood Stem Cell Transplantion

The procedure for peripheral blood stem cell transplantation is similar to bone marrow transplant except for differences in the method of collection of the stem cells and slight changes in the engraftment potential. Such transplants can be autologous or allogeneic. The peripheral blood contains a small proportion (about 0.1%) of stem cells, which can be increased by administration of colony stimulating factors such as G-CSF. For allogeneic donors, G-CSF is administered for 4 to 5 days, which results in high numbers of circulating stem cells which can be collected by a cell separator (apheresis) machine over 2–4 hours using a large-bore venous access. This process avoids hospital admission, anesthesia and pain associated with marrow aspiration. Autologous transplantation requires the stem cells to be collected in a similar fashion, but chemotherapy is required prior to the harvest to reduce tumor contamination and to yield a high proportion of stem cells.

Cord Blood Stem Cell Transplantation

Blood from the placental cord, usually discarded in clinical practice, is a useful source for allogeneic hematopoietic

stem cells. The main limitation of cord blood is the limited number of nucleated cells per unit, these being 1 log less than in a bone marrow transplant. As compared to bone marrow transplantation cord blood transplantation is associated with prolonged time to engraftment with the duration to neutrophilic engraftment being about 30 and 50 days, respectively. This, along with higher incidence of non-engraftment, leads to high transplant-related mortality. The main advantage of cord blood transplantation is a lower incidence and severity of graft versus host disease, which allows for 1 to 2 HLA antigen mismatch even in unrelated transplantation.

Suggested Reading

Copelan EA. Hematopoietic stem cell transplantation. N Engl J Med 2006;354:1813–26

DISORDERS OF HEMOSTASIS AND THROMBOSIS

Approach to a Bleeding Child

Bleeding may occur due to defects in platelets (Tables 12.14 and 12.15), coagulation disorders (Table 12.16) or dysfunctional fibrinolysis. Clinical assessment, of type of bleeding, history of antecedent events and screening tests can help identify the cause, so that specific management can be initiated.

Pathogenesis

The process of hemostasis involves platelets, vessel wall and plasma proteins in a fine balance between blood flow and local responses to vascular injury (clotting). The plasma proteins involved in hemostasis perform three processes: (i) a multiple-step zymogen pathway leading to thrombin generation; (ii) thrombin-induced formation of fibrin clot; and (iii) complex fibrinolytic mechanisms that limit clot propagation. The result of these processes is the generation of insoluble fibrin and activation of platelets to form a hemostatic plug. This process is controlled by multiple pro- and anticoagulant pathways, platelet number and function, vascular factors and other metabolic processes. The coagulation cascade is often depicted as involving two pathways, intrinsic and extrinsic (Fig. 12.12). The extrinsic pathway is the primary initiating pathway for coagulation and is measured by prothrombin time, while the intrinsic system works as a regulatory amplification loop, measured by activated partial thromboplastin time.

Table 12.14: Causes of thrombocytopenia

Idiopathic thrombocytopenic purpura
Infections: Disseminated intravascular coagulation, malaria, kala-azar, dengue hemorrhagic fever, hepatitis B and C, HIV, congenital (TORCH) infections, infection associated hemophagocytosis syndrome
Medications: Valproate, penicillins, heparin, quinine, digoxin
Thrombotic microangiopathy: Thrombotic thrombocytopenic purpura; hemolytic uremic syndrome
Malignancies: Leukemia, lymphoma, neuroblastoma
Autoimmune or related disorders: Systemic lupus erythematoses, Evans syndrome, antiphospholipid syndrome, neonatal immune thrombocytopenia
Immunodeficiency: Wiskott Aldrich syndrome, HIV/AIDS
Bone marrow failure: Thrombocytopenia with absent radii, Fanconi anemia, Shwachman-Diamond syndrome
Marrow replacement: Osteopetrosis, Gaucher disease
Others: Hypersplenism, Kasabach Merritt syndrome

Table 12.15: Qualitative disorders of platelet function

Inherited disorders
Glanzmann thrombasthenia (GP Ib deficiency)
Bernard Soulier syndrome (GP IIb-IIIa deficiency)
Gray platelet syndrome
Dense body deficiency
Acquired disorders
Medications
Chronic renal failure
Cardiopulmonary bypass

Table 12.16: Common coagulation disorders

Inherited disorders
Hemophilia A and B
von Willebrand disease
Specific factor deficiencies
Factor VII, X, XIII deficiency
Afibrinogenemia
Acquired disorders
Liver disease
Vitamin K deficiency
Warfarin overdose
Disseminated intravascular coagulation

Clinical Evaluation

The age of onset of bleeding, type of bleeding, precipitating factors (spontaneous or following dental extraction, surgery or circumcision) assist in defining the cause (Table 12.17). In case of recent onset bleeding, history of antecedent infections, rash (Henoch-Schönlein purpura, varicella), icterus (liver failure); and prodromal diarrhea or associated renal failure (hemolytic uremic syndrome) are important. Medications associated with bleeding include anticonvulsants, penicillins, warfarin, aspirin, non-steroidal anti-inflammatory medications and heparin. History of blood transfusions helps in assessing the severity of the illness. Family history is important. The sex of affected family members and details of bleeding manifestations should be noted; a disorder affecting only boys suggests an X-linked disorder such as hemophilia, while girls may have bleeding disorders in autosomal dominant conditions like von Willebrand disease. Poor wound healing and prolonged bleeding from the umbilical stump suggests factor XIII deficiency.

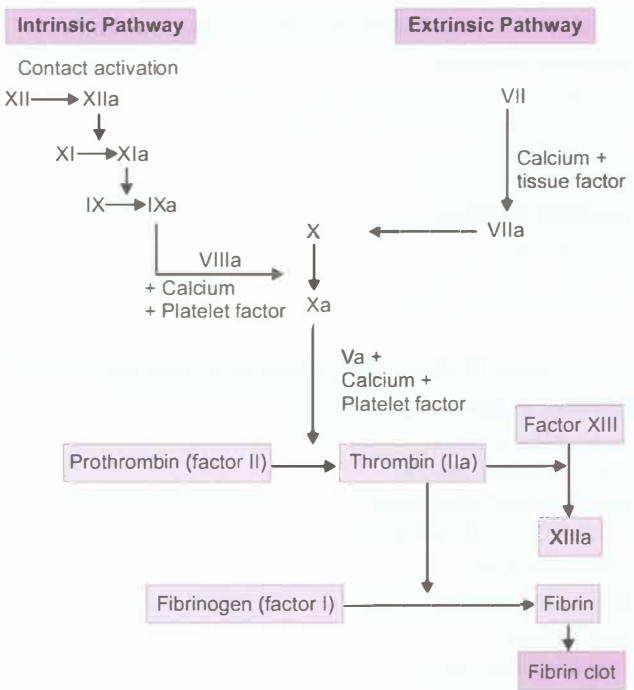


Fig. 12.12: *In vivo* coagulation cascade

Examination is done for the presence of ecchymoses (Fig. 12.13), petechia, vascular malformations (hemangioma, telangiectasia) and rashes. The presence of splenomegaly suggests the presence of infections, malignancy, collagen vascular disorders or hypersplenism rather than a primary bleeding defect. Rashes may be seen following drug exposure, due to infections, collagen vascular disorders, Langerhans cell histiocytosis and Wiskott-Aldrich syndrome.

Laboratory Investigations

A complete hemogram is done for platelet count, morphology of platelets and red cells and evidence of microangiopathic hemolysis (Fig. 12.14). Initial screening tests are prothrombin and activated partial thromboplastin time. Specific assays can be done to identify factor deficiencies; the degree of deficiency dictates the management. The activated partial thromboplastin time is used to monitor heparin therapy. Prothrombin time and its ratio to a contrast with an international normalized standard (INR) are used to assess therapeutic warfarin effect. Bleeding time is now rarely used due to problems in its reproducibility and reliability. This test is abnormal in presence of thrombocytopenia (Table 12.14) as well as in vascular abnormalities, e.g. vasculitis in Henoch Schönlein purpura and connective tissue defects like Ehlers Danlos syndrome (Table 12.18). Sick patients require evaluation for disseminated intravascular coagulopathy.

Bleeding time has been largely replaced by platelet aggregation studies for inherited and acquired platelet dysfunctions. The tests required to evaluate for von Willebrand disease are von Willebrand cofactor assay, quantitation of von Willebrand antigen, factor VIII assay, ABO blood group and electrophoretic analysis of von Willebrand multimers.

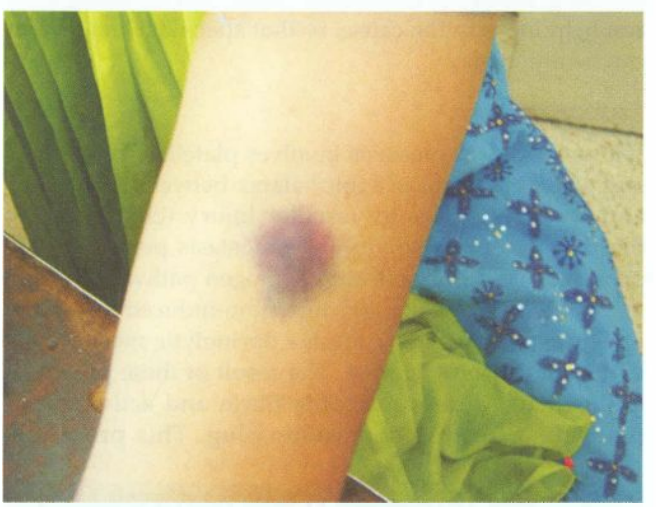


Fig. 12.13: Large ecchymotic patch on the upper limb of a young girl with von Willebrand disease

Table 12.17: Differences in bleeding patterns between platelet disorders and coagulation disorders

	Platelet disorders	*Coagulation disorder*
Site of bleeding	Skin, mucous membranes (mucosal bleeds: epistaxis, oral, gastrointestinal tract)	Soft tissues, joints, muscles (deep bleeds)
Petechiae	Yes	No
Ecchymoses	Small, superficial	Large, deep
Hemarthrosis, muscle bleeding	Extremely rare	Common
Bleeding after minor trauma	Yes	No
Bleeding after surgery	Immediate; usually mild	Delayed (1–2 days); often severe
Example	von Willebrand disease, idiopathic thrombocytopenic purpura	Hemophilia

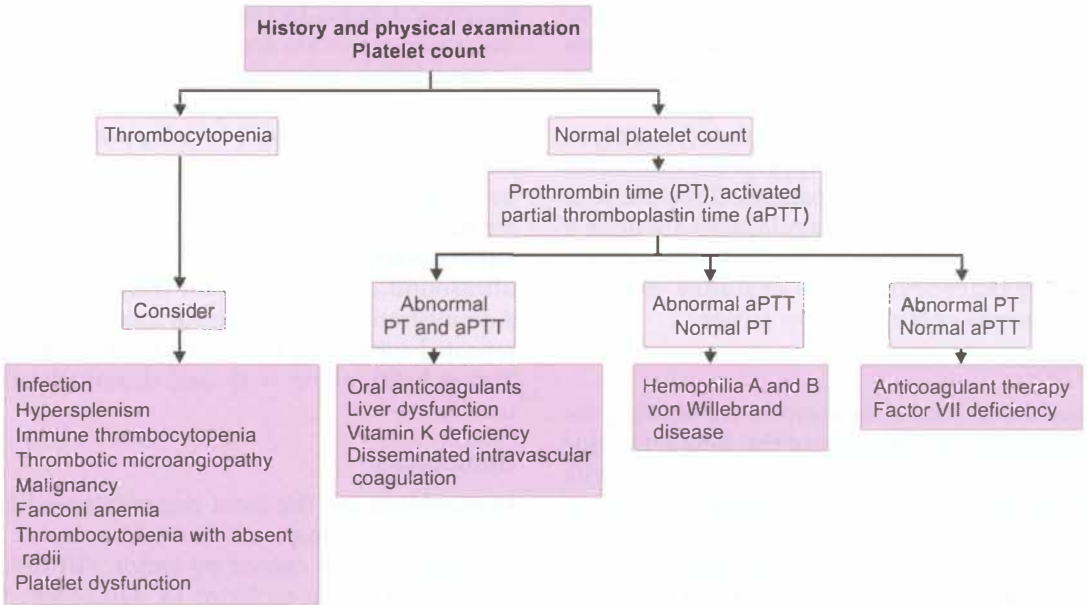


Fig. 12.14: Work up in a child with bleeding

Table 12.18: Vascular causes of bleeding

Henoch Schönlein purpura
Vasculitis in systemic lupus erythematosus
Ehler Danlos syndrome
Scurvy
Prolonged steroid use; Cushing disease
Hereditary hemorrhagic telangiectasia

Suggested Reading

Lusher JM. Clinical and laboratory approach to the patient with bleeding. Nathan and Oski's Hematology of Infancy and Childhood, 6th edn. Eds Nathan DG, Orkin SH, Ginsburg D, Look AT. Saunders, Philadelphia, 2003;1515–26

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP), renamed as immune thrombocytopenia based on evidence of autoantibody mediated consumption of platelets, is the commonest bleeding disorder presenting in children. The illness usually presents between 1 and 7 yr of age. Thrombocytopenia is termed acute if lasting less than 6 months; more than 6 months is considered chronic. It is important to correctly diagnose this entity and differentiate it from serious conditions like leukemia. The majority of children (60–75%) are likely to have acute ITP that resolves within 2–4 months of diagnosis, regardless of therapy.

Pathogenesis

ITP is proposed to be secondary to antibodies directed against the platelet glycoprotein IIb/IIIa complex. Platelets with antibodies on their surface are trapped in the spleen, where they are removed by splenic macrophages. The mechanism of production of the antibodies is not known. Recent data describes a Th1 dominant pro-inflammatory cytokine state in these individuals. Increased megakaryocyte number in the bone marrow is the hallmark of immune-mediated platelet destruction. However, a relative decrease in megakaryocyte production due to specific anti-platelet autoantibodies is also described.

Clinical Evaluation

There is often an antecedent history of febrile illness, but the patient is usually afebrile at presentation. There is a seasonal clustering of cases, the illness being more frequent during change of seasons. The child presents with sudden appearance of bruises and mucosal bleeding, epistaxis, oral oozing and prolonged bleeds with superficial trauma. The duration of symptoms is recorded to distinguish acute from chronic ITP.

Physical examination reveals the presence of petechiae and ecchymoses. Symptoms and signs depend on the platelet count. Bleeding is usually mild unless the platelet count drops below 20,000/µl. With platelet counts of 20,000–50,000/µl, petechiae and ecchymoses are observed following mild trauma. There are no dysmorphic features, bony anomalies or hyperpigmentation. The presence of lymphadenopathy or splenomegaly suggests secondary causes of thrombocytopenia rather than ITP.

Laboratory Evaluation

The complete blood count shows low platelet count; other hematological parameters are normal. A peripheral smear is done to examine for abnormal cells (such as blasts) or

malarial parasites to estimate the platelet count and to exclude spurious thrombocytopenia. Circulatory platelets are larger in size, indicating increased production. Liver and renal function tests and lactate dehydrogenase levels are done to rule out hepatitis, occult malignancy, hemolysis and hemolytic uremic syndrome. Appropriate evaluation for infection is necessary in febrile patients. Screening tests for disseminated intravascular coagulopathy are done if sepsis is suspected. Bone marrow examination shows increased megakaryocytes and excludes marrow infiltration, leukemia or bone marrow failure.

Management

Platelet transfusions should be avoided. Minimizing the risk of hemorrhage and decreasing the long term side effects of treatment are the goals of therapy. A patient with a few scattered petechiae or bruises, platelet count above 20,000/mm^3 and no mucosal bleeding only requires close observation. For children with active bleeding, treatment includes intravenous immunoglobulin 1 g/kg/day for 1–2 days, or 50–75 mg/kg of anti-D immunoglobulin in Rh positive children. Corticosteroids can be administered after the possibility of hematological malignancy has been ruled out on bone marrow examination. Prednisone is given at 1–4 mg/kg/day for 2–4 weeks and then tapered. Dexamethasone is administered at 20 mg/m^2 over 4 days every 3 weeks for 4–6 courses. If serious hemorrhage occurs, platelet transfusions may be used under cover of steroids. Therapeutic options for chronic ITP include prednisone administered at low dose on alternate days and, in refractory cases, combinations of the following options danazol, vincristine, cyclosporine, azathioprine, rituximab (anti-CD20 monoclonal antibody), splenectomy and, most recently, thrombopoietin receptor-binding agents.

Suggested Reading

Nugent D. ASH Education Book 2006. www.asheducationbook. org/cgi/reprint/2006/1/97/pdf

Sharma SK, Gupta N, Seth T, et al. Successful management of refractory chronic immune thrombocytopenia with intracranial hemorrhage by emergency splenectomy. Indian J Pediatr 2012;79:397–8

Neonatal Alloimmune Thrombocytopenia

In neonatal alloimmune thrombocytopenia, fetal platelets are destroyed by maternal antibodies against paternally inherited antigens present on fetal platelets. Antibodies are usually directed against platelet antigens HPA-1a or HPA–5b. Almost half the cases occur with the first pregnancy, without history of sensitization.

While patients with mild thrombocytopenia remain asymptomatic, hemorrhagic complications, including intracranial hemorrhage, may occur within hours of birth. A high index of suspicion is required to correctly identify this condition. As specific tests are limited, the condition is primarily diagnosed by exclusion of other etiologies of thrombocytopenia. In a sick newborn, these include sepsis, meconium aspiration and intrauterine infections; in a well looking infant, one must exclude the effect of maternal medications or maternal lupus erythematosus.

Postnatal management requires transfusion of washed maternal platelets (preferably irradiated) and close monitoring until the platelet counts normalize. The risk for neonatal alloimmune thrombocytopenia increases in subsequent pregnancies. The fetus requires serial ultrasound examinations for intracranial hemorrhage. Administration of intravenous immunoglobulin (1 g/kg repeated antenatally every four weeks) during pregnancy and at birth, along with oral dexamethasone may be useful.

Hemophilia

Hemophilias are the most common hereditary clotting defects, occurring as X-linked recessive disorders. Hemophilia A is caused by factor VIII deficiency and hemophilia B due to factor IX deficiency. The clinical manifestations of hemophilia A and B are indistinguishable and the presentation depends on the level of factor present. In mild cases, the factor level is enough to prevent spontaneous bleeds and bleeding manifests only with surgery or severe trauma. In severe cases, where the factor levels are below 1%, repeated, spontaneous and debilitating joint bleeds (Fig. 12.15) may occur, leading to severe handicaps, and intracranial bleeds may be life threatening.

Children with hemophilia should be managed at specialized centers equipped for their needs. Treatment requires appropriate factor replacement, judicious physiotherapy to prevent chronic joint disease, counseling for injury prevention and monitoring for development of factor VIII and IX inhibitors. The dose of factor replaced is targeted to the severity of bleeding manifestations. In

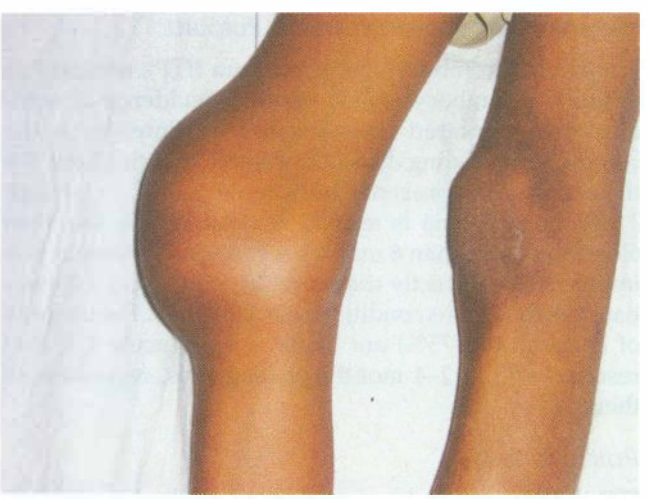


Fig. 12.15: Child with hemophilia with knee hemarthrosis with severe pain and signs of inflammation

major bleeds, e.g. intracranial hemorrhage, the target for factor level is correction to 80–100% of normal value, for hemarthroses, the target is 30–50% of normal values. One unit of factor VIII per kg body weight increases the level of factor VIII by 2%. The principles of therapy of hemophilia B are similar; except that factor IX is used for replacement, one unit of factor IX per kg raises factor level by only 0.7%. Therefore the doses of factors required are calculated as follows:

Dose of factor VIII = % desired rise in F VIII × body weight (kg) × 0.5

Dose of factor IX = % desired rise in F IX × body weight (kg) × 1.4

Hence, a patient with severe hemophilia A and hemarthroses requires 15 U/kg of factor VIII every 12–24 hours for 1–2 days, while the dose needed in a patient with intracranial bleeding is 40–50 U/kg every 12 hours for approximately 7–14 days. However, lower doses may be effective. ε-aminocaproic acid or tranexamic acid may be effective as adjunct therapy in mild cases of hemophilia.

Replacement therapy for children with hemophilia with concentrates of factor VIII or IX is expensive and often not available. Cryoprecipitate and fresh frozen plasma (FFP) can be used to control bleeding but carry the risk of transmitting HIV and hepatitis B and C. Cryoprecipitate contains factor VIII, fibrinogen and von Willebrand factor but not factor IX, and is not useful in patients with hemophilia B. When fresh plasma is frozen, it retains all factors at hemostatic levels, including labile factors V and VII.

Patients with severe hemophilia (less than 1% measurable factor level), may be given factor replacement two to three times a week to reduce the risk of bleeds. This results in less deformity and allows the child to play normally. While this is an expensive mode of treatment, it provides good quality of life. All children should receive hepatitis B immunization; vaccines can be given by the subcutaneous route and the parents should be counseled regarding injury prevention. Genetic counseling is required and families should be informed of the availability of prenatal diagnosis.

Suggested Reading

Roberts HR, Key N, Escobar MA. Hemophilia A and hemophilia B. In: Williams Hematology 8th eds Ed. Kaushansky K, Litchman MA, Beutler E, et al. McGraw-Hill Companies, New York, 2010;2009–29

Vitamin K Deficiency

Phytomenadione or vitamin K_1 plays a vital role in the production of vitamin K dependent coagulation factors, including factors II (prothrombin), VII, IX and X, and proteins C and S. Vitamin K is found in green leafy vegetables and oils (soyabean, canola) and is synthesized by colonic bacteria. Deficiency is frequent in newborns due to poor transmission of vitamin K across the placenta, its paucity in breast milk, lack of gut bacteria and prematurity of liver function. Later in life, vitamin K deficiency may follow prolonged antibiotic use, parenchymal liver disease, prolonged total parenteral nutrition and malabsorption. Bleeding due to classic vitamin K deficiency occurs in 0.25–1.7% of infants. The prevalence of late vitamin K deficiency bleeding in breastfed infants not given prophylaxis is 20 cases per 100,000 live births.

Deficiency of vitamin K dependent factors leads to prolonged prothrombin and activated partial thromboplastin time. Precise diagnosis, by measuring proteins induced by vitamin K absence (PIVKA), is usually not required. Vitamin K is administered as a single subcutaneous dose of 1 mg at birth to prevent hemorrhagic disease of the newborn. Prophylaxis with vitamin K is widely practiced and safe. Larger doses of vitamin K (2–10 mg) can be given to treat symptomatic neonates who did not receive prophylaxis or have anticoagulant overdose; this is repeated till coagulation studies are normal. Fresh frozen plasma is administered if there is overt bleeding, or liver dysfunction is suspected.

Suggested Reading

American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. Pediatrics. 2003; 112: 191–2

Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulation (DIC) is an acquired dysregulation of hemostasis. The presentation ranges from an isolated derangement of laboratory parameters to severe bleeding from multiple sites, associated with high mortality. DIC may be triggered by a variety of conditions that result in activation of the clotting cascade, deposition of fibrin in the microcirculation and consumption of platelets and clotting factors. The diagnosis of DIC is clinical (Fig. 12.16); laboratory tests provide confirmatory evidence.

Pathophysiology

There are three main pathologic processes involved.

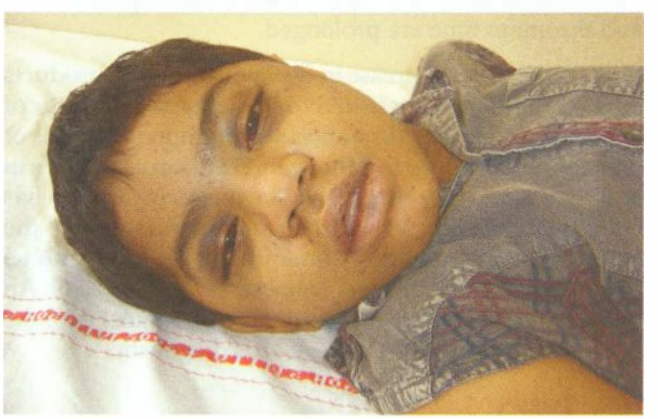


Fig. 12.16: An ill child with disseminated intravascular coagulation. Shows ecchymoses, purpura and subconjunctival hemorrhage

Initiation of fibrin deposition Thrombin generation in DIC is mediated by the extrinsic (tissue factor) pathway. The tissue factor accumulates on activated platelets by binding to platelet P-selectin which results in thrombin generation.

Amplification role of thrombin Thrombin generated amplifies inflammation and clotting by activating platelets and factors V, VIII and IX, which lead to more thrombin production. Activated factor XIII leads to it cross-linking with fibrin clots making them insoluble, while thrombin activates the fibrinolysis inhibitor, making the clot resistant to fibrinolysis.

Propagation of fibrin deposition There is suppression of fibrinolysis secondary to sustained increase in plasma levels of plasminogen-activator inhibitor. Following injury, infection or other precipitating factors, there is release of cytokines (tumor necrosis factor alpha, IL-1 and IL-6) which change the endothelium from an anticoagulant to a procoagulant surface and interfere with fibrinolysis.

As DIC continues, fibrinogen, prothrombin, platelets and other clotting factors are consumed beyond the capacity of the body to compensate and bleeding ensues. Activated protein C has an anti-inflammatory effect; it downregulates the tissue factor and decreases calcium ion flux.

Causes

The main illnesses causing disseminated intravascular coagulopathy are listed in Table 12.19. Acute DIC is usually associated with severe infections. Chronic DIC occurs due to an intermittent activation of DIC by giant hemangiomas, certain vasculitis and in some solid tumors.

Table 12.19: Disorders which cause disseminated intravascular coagulopathy (DIC)

Acute DIC	*Chronic DIC*
Medical conditions	
Septicemia or infections*	Solid tumors
Fulminant hepatic failure	Kasabach-Merritt syndrome
Heat stroke, hyperpyrexia	Liver cirrhosis
Severe burns	
Acute promyelocytic leukemia, neuroblastoma	
Snake bite	
Collagen vascular disorders	
Surgical conditions	
Severe trauma-crush injury, multiple fractures with fat emboli	Vascular tumors
	Aortic aneurysm
Major operations	
Severe renal allograft rejection	
Iatrogenic	
Hemolytic transfusion reaction; massive transfusion	Artificial surfaces
Heparin induced thrombosis	

* Includes the following infections:

Bacterial: Meningococcus, gram-negative bacteria, group B streptococus

Viral: Arboviruses, varicella, variola, rubella, paramyxoviruses, HIV, Ebola virus

Parasitic: Malaria

Mycotic: Candida, aspergillus

Rickettsial: Rocky Mountain spotted fever

Clinical and Laboratory Evaluation

DIC is characterized predominantly by bleeding manifestations in critically ill patients.

Screening tests Peripheral blood film examination and hemogram show schistocytes and thrombocytopenia. Prothrombin time, activated partial thromboplastin time and thrombin time are prolonged.

Supportive tests Increase in fibrin degradation products or D-dimers is characteristic. No single test is diagnostic of DIC. The presence of thrombocytopenia and low levels of fibrinogen (50% drop in either value) are most sensitive in making a laboratory diagnosis. A DIC scoring system has been established based on the recommendations of the Scientific Standardization Committee of the International Society on Thrombosis and Hemostasis (Table 12.20); An underlying predisposing disorder is a prerequisite for the use of this algorithm. A score of ≥5 is diagnostic.

Treatment

The underlying disease must be managed appropriately. In cases of sepsis, antibiotics are necessary. In snake bites, anti-snake venom should be administered. Tissue perfusion and respiratory function must be maintained by replacement with intravenous fluid and provision of oxygen to correct hypoxia. Coagulopathy may be compounded by vitamin K deficiency, which requires correction.

Hemostatic support (replacement therapy) In patients who have low levels of platelets, fibrinogen and other clotting factors as revealed by deranged coagulation tests, replacement of deficient components is useful. Replacement therapy is not indicated if there is no clinical bleeding and if no invasive procedures are planned. Monitoring is essential for guiding management and checking adequacy of replacement component support. The different blood components available and commonly used in DIC are: fresh frozen plasma, cryoprecipitate, platelet concentrates and packed red cells (Table 12.21). The required doses depend on rate and degree of consumption. Replacement therapy can be halted when stabilization in platelet counts and fibrinogen levels and a fall in fibrin degradation products is observed.

Heparin therapy Heparin therapy has not proved to be useful and may be harmful in most cases of acute DIC.

Table 12.20: Algorithm for diagnosis of disseminated intravascular coagulation (DIC) using the DIC score

Risk assessment

Does the patient have an underlying disorder known to be associated with disseminated intravascular coagulopathy? (If yes, proceed. If no, do not use this algorithm).

Order global coagulation tests

Platelet count; prothrombin time, fibrinogen, soluble fibrin monomers or fibrin degradation products

Score test results		Score
(a) Platelet count	>100,000/mm^3	0
	50,000–100,000/mm^3	1
	<50,000/mm^3	2
(b) Elevated fibrin-related marker (soluble fibrin monomers or fibrin degradation products)*		
	No increase	0
	Moderate increase	2
	Strong increase	3
(c) Prothrombin time		
	<3 sec	0
	>3 but <6 sec	1
	>6 sec	2
(d) Fibrinogen level		
	>1 g/l	0
	<1 g/l	1

Calculate score

Score ≥5: Compatible with overt DIC; repeat daily

Score <5: Suggestive of non-overt DIC; repeat in 1–2 days

* Values of D-dimer above the upper limit of normal are moderately elevated; values above 5 times the upper limit of normal are strongly increased.

Specific indications for such therapy include the presence of arterial or large vessel venous thrombosis. These patients should continue to receive replacement therapy with heparin during continuous monitoring of platelet counts and fibrinogen levels and prothrombin, activated partial thromboplastin and thrombin time.

Novel therapies Therapy with activated protein C and tissue factor pathway inhibitor has not been shown to be beneficial in controlled trials in children.

Suggested Reading

Levi M. Disseminated intravascular coagulation: What's new? Crit Care Clin 2005;21:449–67

Taylor FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1327–30

Thrombotic Disorders

The incidence of thrombosis is lower in children than in adults, but is associated with significant morbidity and mortality. Till 6 months of age, children have lower levels of the vitamin-K dependent coagulation factors II, IX and X as compared to adults. Levels of thrombin inhibitors, such as antithrombin, heparin cofactor II, plasminogen and proteins C and S are low at birth. Protein S level approaches adult value by the age of 3–6 months, but protein C levels remains low during childhood. In newborns compared with adults, thrombin generation is delayed and decreased, probably due to low prothrombin level. The incidence of thrombosis is maximal in infancy and during adolescence.

Table 12.21: Types of blood component therapy, their constituents and guidelines for use

Component	*Constituents*	*Indication*	*Dose*	*Precautions*
Fresh frozen plasma (FFP)	All coagulation factors as in normal plasma; contains 0.7–1.0 U/ml of factors II, V, VII, VIII, IX, X, XI, XII, XIII and 2.5 mg/ml fibrinogen	Coagulation factor deficiencies with prolonged prothrombin time; thrombotic thrombocytopenic purpura	15 ml/kg or 1 bag per 10 kg (constitutes 25–30% replacement therapy for coagulation factors)	Infuse soon after thawing; need ABO compatible units; may cause fluid overload
Cryoprecipitate	Fibrinogen 150 mg/bag, factor VIII 80-120 units/bag, factor XIII and vWD (does not contain factor IX)	Fibrinogen deficiency or consumption; factor VIII deficiency (hemophilia A), vWD disease; factor XIII deficiency	1 bag per 5 kg will raise fibrinogen levels by 70 mg/dl	
Random donor platelets (RDP)	Platelets; ≥5.5 × 10^{10} platelets per bag	Thrombocytopenia	One unit raises platelet counts by 5–10,000/mm^3; 1 unit every 10 kg raises counts by 30,000–50,000/mm^3	Infuse rapidly; do NOT refrigerate prior to transfusion
Single donor platelets (SDP)	Platelets; contains at least 3 × 10^{11} platelets	Thrombocytopenia	One collection is equivalent to approximately 6 units of random platelets	Precautions as above
Fresh blood	All components of blood	To replace acute and massive blood loss	Only to be used in severe trauma	Not a good source for platelets or coagulation factors

Clinical Evaluation

Congenital heart disease and, recent cardiac catheterization are important causes of arterial thrombosis in children. Other predisposing factors for arterial or venous thrombosis include recent surgery, trauma, use of central venous catheter, nephrotic syndrome, dehydration, sepsis and collagen vascular disorders (Table 12.22).

Limb edema, erythema and tenderness on dorsiflexion of the foot (positive Homan sign) suggest deep vein thrombosis. Signs of arterial thrombosis include diminished or absent peripheral pulses and cool extremities. Manifestations of pulmonary embolism include anxiety, breathlessness, pleuritic chest pain, fever, tachypnea and cough, and a high index of suspicion is required to make the diagnosis. Symptoms of central nervous system thrombosis include vomiting, lethargy, seizures or weakness in an extremity. Strokes may occur *in utero*; such newborns present with seizures and lethargy, while older children present with headaches or neurologic deficits such as hemiplegia. Patients with renal vein thrombosis may show flank pain and hematuria.

Laboratory Evaluation

Many clotting factors are consumed in acute thrombosis and factor levels may be fallaciously low in the acute phase. The child should be evaluated to rule out disseminated intravascular coagulopathy with complete blood count, peripheral blood smear, prothrombin time, activated partial thromboplastin time and fibrinogen level. Levels of D-dimer indicates activity of the coagulation cascade, and is a sensitive indicator of underlying DIC.

Table 12.22: Factors which increase risk of thrombosis in children

Acquired conditions
Infections: Viral, bacterial sepsis
Disseminated intravascular coagulation
Dehydration
Central venous catheter
Surgery, trauma
Cyanotic congenital heart disease
Antiphospholipid antibody syndrome
Acute lymphoblastic leukemia; therapy (L-asparaginase and steroids)
Nephrotic syndrome
Inherited prothrombotic disorders
Resistance to activated protein C
Factor V Leiden
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Prothrombin gene G20210A mutation
Elevated lipoprotein (a) level
Hyperhomocysteinemia

Color Doppler shows absence of signals in thrombosed vessels and the lumen cannot be compressed with direct pressure. However, it may not be sufficiently sensitive to detect thrombosis in vessels such as subclavian veins, superior vena cava or brachiocephalic veins. *Echocardiography* is useful for vena caval and proximal subclavian vein thrombosis. An *MRI* in conjunction with *magnetic resonance venography* is more sensitive than CT scan for the diagnosis of cerebral venous thrombosis. *Chest radiography* may reveal findings of pulmonary embolism which include small pleural effusions with wedge shaped pleural-based opacity of pulmonary infarction, but has poor sensitivity. *Ventilation-perfusion scanning* is useful in suspected pulmonary embolism. Patients with elevated levels of D-dimer and intermediate probability of pulmonary thrombosis on perfusion scan should be screened by *spiral CT*.

Management

Screening tests for hypercoagulable state should ideally be sent prior to initiating anticoagulation. Patients with respiratory distress or neurological problems should be managed in an intensive care unit. Initial therapy requires heparin (unfractionated or low molecular weight) followed by oral warfarin. Unfractionated heparin exhibits antithrombin as well as anti-Xa activity, whereas the action of low molecular weight heparin (LMWH) has primarily anti-Xa function. Close monitoring is required to prevent overdosage and risk of bleeding. The international normalized ratio (INR), is useful for monitoring oral anticoagulation with heparin and should be maintained in the range of 2 to 3. The duration of therapy depends on the risk of recurrence, which can be assessed by testing for thrombophilic states. The evaluation is best done after 3 months of the event and after stopping anticoagulants. Children with lower limb deep vein thrombosis should be fitted for compression stockings.

Recurrent Thrombosis

Recurrent thrombosis may occur due to inadequate anticoagulation therapy. The risk of recurrence is estimated at 4–5% in patients without adverse risk factors, 17–20% for those with one predisposing condition and almost 50% with two or more risk factors.

Suggested Reading

Saxena R, Kannan M, Choudhry VP. Laboratory studies in coagulation disorders. Indian J Pediatr 2007;74:649–55

Tormene D, Gavasso S, Rossetto V, Simioni P. Thrombosis and thrombophilia in children: a systematic review. Semin Thromb Hemost 2006;32:724–8.

WHITE BLOOD CELLS

Quantitative changes (more than ±2 SD) in white cell counts are the most frequently found abnormality on the

hemogram report. The differential count helps define the expanded population of cells. The percentage increase over normal range is important; very high counts are indicative of leukemoid reaction (a very high leukocyte response to infection that may be confused with leukemia) or leukemia.

The examination of the peripheral smear is very useful. The morphology of cells may reveal abnormal size, immaturity, change in nuclear-cytoplasmic ratio, inclusions and abnormal granules. Howell Jolly bodies are found with absent splenic function (asplenia, post splenectomy) and toxic granulations and shift to the left suggest sepsis. Epstein-Barr virus infection results in large monocytoid cells which can be confused for blasts on peripheral smear.

Leukocytosis

The onset and duration of illness, history of intake of medications and prior hospitalization may provide a clue to the diagnosis.

Neutrophilia

Neutrophils increase in diverse conditions, like acute bacterial infections, acute blood loss, hemolysis and diabetic ketoacidosis (Table 12. 23). Cytochemical staining for leukocyte alkaline phosphatase (LAP), an enzyme found in mature neutrophils, is useful; neutrophils granules containing LAP stain blue, resulting in a high LAP score in infections and leukemoid reaction. In chronic myeloid leukemia, neutrophils are deficient in LAP so the score is low compared to normal neutrophils.

Table 12.23: Common causes of neutrophilia

Acute
Acute bacterial infections
Epinephrine, corticosteroids, granulocyte colony stimulating factor
Hemorrhage; hemolysis
Hypoxia
Trauma, burns, exercise, heat stroke
Renal failure, diabetic ketoacidosis, hepatic failure
Hodgkin lymphoma
Chronic
Chronic myeloid leukemia
Rheumatological and inflammatory diseases
Hemolytic anemias; sickle cell anemia
Post-splenectomy
Chronic blood loss
Thyrotoxicosis
Chronic idiopathic neutrophilia
Genetic causes or syndromes
Down syndrome
Asplenia
Leukocyte adhesion defects

Monocytosis

Monocytes, the circulating tissue macrophage precursors, are important for ingestion and killing of pathogenic bacteria, e.g. *Mycobacterium tuberculosis,* and parasites, e.g. *Leishmania*. Monocytosis is noted in many infections (Table 12.24). Abnormality of macrophage activation may cause disorders like familial hemophagocytic syndrome.

Table 12.24: Causes of monocytosis

Infections: Tuberculosis, typhoid, bacterial endocarditis, brucella, kala-azar, malaria
Autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, ulcerative colitis, polyarteritis nodosa
Post-splenectomy neutropenia; hemolytic anemia
Malignancy: Lymphoma, chronic myeloid leukemia, juvenile myelomonocytic leukemia, myelodysplasia
Myxedema

Basophilia

Basophilia is usually seen during acute hypersensitivity reactions, but may be found in chronic myeloid leukemia, Hodgkin lymphoma, varicella, hypothyroidism and while on antithyroid medications.

Eosinophilia

Eosinophilia is noted in many allergic disorders systemic inflammatory conditions and malignancies (Table 12.25). Parasites which invade tissue are more likely to cause eosinophilia (e.g. *Toxocara* which causes visceral larva migrans). Sustained elevation in eosinophil count is associated with cardiac toxicity. Moderate elevation refers to an absolute eosinophil count of 1500–5000 cells/µl and severe eosinophilia is >5000 cells/µl.

Lymphocytosis

Lymphocytosis is a common feature of many infections (Table 12.26). It is important to distinguish reactive from neoplastic lymphocytosis.

Leukopenia

This is usually found in conjunction with pancytopenia, e.g. aplastic anemia, megaloblastic anemia, bone marrow replacement or infiltration (malignancy, Gaucher disease, osteopetrosis) and hypersplenism.

Neutropenia

Neutropenia may occur due to increased destruction or decreased production of neutrophils, and is usually acquired (Table 12.27) Rarely, neutropenia may be congenital, occurring as cyclic neutropenia, or as a part of inherited deficit. Transient neutropenia is common with viral infections. Severe neutropenia is present when the absolute neutrophil count is below 500 cells/µl.

Table 12.25: Common causes of eosinophilia

Acute

Allergic disorders: Asthma, atopic dermatitis, urticaria, drug hypersensitivity, pemphigoid
Parasitic infestations: Toxocara, ascaris, amebiasis, strongyloidiasis, filaria, toxoplasmosis, trichinosis, schistosomiasis, malaria, scabies
Fungal infections: Bronchopulmonary aspergillosis, coccidiomycosis
Malignancy: Hodgkin lymphoma, T cell lymphoma, acute myelogenous leukemia, myeloproliferative syndrome
Hypereosinophilic syndrome

Chronic

Allergic disorders: Pemphigus, dermatitis herpetiformis
Autoimmune disorders: Inflammatory bowel disease, rheumatoid arthritis
Myeloproliferative syndrome, hypereosinophilic syndrome
Loeffler syndrome
Immunodeficiency syndromes: Hyper IgE, Wiskott Aldrich syndrome; Omenn syndrome; graft versus host reaction
Miscellaneous: Thrombocytopenia with absent radii; renal allograft rejection; Addison disease

Table 12.26: Common causes of lymphocytosis

Infections: Infectious mononucleosis, infectious hepatitis, cytomegalovirus, tuberculosis, pertussis
Endocrine: Thyrotoxicosis, Addison disease
Malignancy: Acute lymphoblastic leukemia, lymphoma

Table 12.27: Common causes of neutropenia

Acute

Infections: Severe sepsis; tuberculosis, Shigella, brucellosis; dengue, varicella, Epstein-Barr virus, cytomegalovirus, HIV; kala-azar, malaria; rickettsia
Drugs: Sulfonamides, phenytoin, phenobarbital, penicillin, phenothiazines
Bone marrow infiltration: Leukemia, lymphoma, neuroblastoma
Hypersplenism
Chemotherapy: Busulphan, cyclophosphamide, radiation

Chronic

Aplastic anemia: Acquired; inherited (Fanconi anemia)
Autoimmune diseases: Systemic lupus erythematosus, Crohn disease, rheumatoid arthritis
Vitamin B12 or folate deficiency
Bone marrow infiltration: Myelodysplasia, chronic myelogenous leukemia, chronic idiopathic neutropenia
Paroxysmal nocturnal hemoglobinuria
Inherited disorders: Cyclic neutropenia; severe congenital neutropenia; chronic benign neutropenia; Kostmann syndrome; Schwachman-Diamond syndrome; dyskeratosis congenita; Chediak-Higashi syndrome; glycogen storage disease type 1B

Associated with immunodeficiency: Hyper IgM syndrome; HIV

Lymphopenia

Lymphopenia is noted during several infections, including viral (hepatitis, influenza) and bacterial (typhoid, tuberculosis, sepsis) illnesses. The most common infectious cause is acquired immunodeficiency syndrome (AIDS). Lymphopenia is also found in inherited immunodeficiency syndromes due to decreased production of B or T lymphocytes (severe combined immunodeficiency, isolated CD4+ lymphocytopenia, ataxia-telangiectasia and Wiskott-Aldrich syndrome. It may also occur after antithymocyte globulin treatment for aplastic anemia, use of corticosteroids, systemic lupus erythematosus and protein losing enteropathy.

Qualitative Defects

Qualititave defects in leukocytes may give rise to immunodeficiencies. The work up of most immunodeficiencies needs specialized tests for estimate of immunoglobulins, T and B lymphocyte subsets and complement and functional assays.

Chediak-Higashi syndrome is identified by its characteristic morphology showing giant lysosomes in the granulocytes and oculocutaneous albinism. Defects in *CHS1* or *Lyst* gene impair lysosomal trafficking, resulting in ineffective granulopoiesis, delayed degranulation and altered chemotaxis resulting in increased bacterial infections. In the accelerated phase, there is lymphohistiocytic infiltration of organs.

Leukocyte adhesion defect type 1 results from deficiency of CD11 and CD18 on the neutrophils, lead to defects in adhesion, chemotaxis and C3bi mediated phagocytosis. This causes delayed umbilical cord separation in the newborn and leads to repeated, severe infections and periodontitis later in life.

Chronic granulomatous disease is an X-linked, (or rarely, autosomal recessive) inherited defect of the respiratory burst pathway in the granulocytes. It manifests as infections in the lungs, skin and gastrointestinal tract with S. *aureus*, aspergillus and *Serratia marcescens*, leading to formation of deep-seated granulomatous lesions. Many other primary immunodeficiencies have quantitative defects in T, B or both lymphocyte subsets with maturation or functional defects, which lead to life threatening infections.

Otolaryngology 13

Sandeep Samant, Grant T. Rohman, Jerome W. Thompson

DISEASES OF THE EAR

Otitis Media

Otitis media is a common early childhood infection. Anatomic features that make young children particularly susceptible to ear infections include shorter, more horizontal and compliant eustachian tubes and bacterial carriage in the adenoids. Other risk factors include exposure to cigarette smoke, overcrowding, bottlefeeding, cleft palate, Down syndrome, allergy and immune dysfunction. These risk factors contribute to the pathophysiology of the two common varieties of otitis media, acute otitis media and otitis media with effusion.

Acute Otitis Media

Acute otitis media (AOM) in children tends to have a bimodal age distribution, with children between ages 6 and 24 months and 5 to 6 yr at greatest risk.

Etiology. The most common organisms causing AOM are *Streptococcus pneumoniae* and *Haemophilus influenzae*, accounting for approximately 65% cases; 15% are caused by *Moraxella catarrhalis*, *Streptococcus pyogenes* and *Staphylococcus aureus*. Respiratory viruses play an important role in initiating otitis media and may be the only pathogens in some cases, since 20% of middle ear aspirates are sterile.

Diagnosis. AOM is characterized by the rapid onset of symptoms, which may be local, e.g. otalgia or ear tugging, and/or systemic, e.g. fever or crying. Older children may report impaired hearing. History of recent upper respiratory tract infection is common. Otoscopic examination reveals a red and bulging tympanic membrane with reduced mobility as measured by either tympanometry or insufflation through the otoscope (pneumatic otoscopy). Rupture of the drum with ear discharge (suppuration) may have already occurred, in which case the ear canal contains an opaque yellow-green or reddish-brown fluid. Cleaning of this fluid usually reveals an intact drum, as the rupture is small and closes promptly after spontaneous perforation. The diagnosis of AOM is considered certain if all of the following criteria are met: (i) rapid onset; (ii) signs of middle ear effusion; and (iii) signs and symptoms of middle ear inflammation.

Treatment. Antimicrobial therapy is recommended. However, in some cases children may qualify for a trial of observation (Table 13.1). Amoxicillin should be the first-line therapy for AOM. Higher doses (80–90 mg/kg/day) may be considered where streptococcal resistance is endemic. Agents with β-lactamase resistance (e.g. amoxicillin-clavulanic acid, cefaclor, cefuroxime or newer cephalosporins) are useful second-line drugs. Initial

Table 13.1: Criteria for choice of treatment or observation in children with acute otitis media

Age	*Diagnosis certain*	*Diagnosis uncertain*
<6 mo	Antibacterial therapy	Antibacterial therapy
6–23 mo	Antibacterial therapy	Antibacterial therapy if illness severe*
≥24 mo	Antibacterial therapy if illness severe* Observation is an option if illness not severe**	Observation is an option if illness not severe**

*Severe illness is defined as moderate to severe otalgia or fever ≥39°C

*Observation is appropriate only if follow-up can be ensured; antibacterial therapy is started if symptoms persist or worsen

Adapted from guidelines of the American Academy of Pediatrics and American Academy of Family Physicians. Clinical Practice Guideline: Subcommittee on Management of Acute Otitis Media. *Pediatrics* 2004;113:1451–65

antibiotic therapy should last at least 7 days. Re-examination is indicated after 3–4 days and at 3 weeks.

Adjuvant treatment with oral and topical decongestant drugs is not necessary. Antihistaminic agents, which contribute little to the resolution of otitis media and may precipitate sinus infections due to their drying effect on mucosal secretions, are also not recommended. Tympanocentesis (aspiration of the middle ear fluid) with a bent 18-gauge spinal needle on a syringe may provide specimen for culture in patients with complicated AOM who cannot tolerate tympanostomy tube insertion. Tympanocentesis improves otalgia but does not shorten the course of the illness.

Many children present with recurrent episodes of AOM. A child that has 4 episodes of AOM in 6 months or 6 episodes in 12 months should be considered for tympanostomy tube insertion. If a child requires a second set of tympanostomy tubes, concurrent adenoidectomy is considered. No benefit from concurrent tonsillectomy has been demonstrated in patients with recurrent AOM.

Otitis Media with Effusion (OME)

Following an episode of AOM, serous or mucoid middle ear effusions may be seen. Effusions are found to persist in up to 40% of children 1 month after AOM and in 10% after 3 months. Many children with OME do not have a history of previous acute middle ear infections. Most children are asymptomatic or complain of hearing loss and ear fullness. Otalgia is not normally present. Otoscopy reveals a dull tympanic membrane with middle ear effusion (Fig. 13.1), frequently with air fluid levels or bubbles. Reduced tympanic membrane mobility on either pneumatic otoscopy or type B pattern on tympanometry confirms the diagnosis.

Since over 65% of serous middle ear effusions resolve spontaneously within 3 months, newly diagnosed effusions should be observed for this period. Antibiotic administration is not shown to resolve OME. Use of antihistamines and decongestants is not recommended. The benefit of corticosteroid administration has not been proven but a brief trial of steroids is commonly used.

If effusion persists beyond 3 months, tympanostomy tube insertion may be considered for any hearing loss >25 dB (Fig. 13.2). Other indications of tube placement in OME are speech delay, altered behavior, major sequelae such as otitic meningitis or impending cholesteatoma formation from tympanic membrane retraction. Improvement in hearing and ear discomfort is immediate. Mean time before extrusion is usually between 12 and 18 months. Insertion of longterm tubes (of T-tube design) or adenoidectomy may be considered in patients with recurrent or persistent symptomatic effusion. T-tubes have been associated with tympanic membrane perforation. Earplugs are recommended while the tubes are in place to avoid entry of water into the middle ear space.

Chronic Suppurative Otitis Media (CSOM)

Ear drainage that persists for longer than 6 weeks is generally due to chronic inflammation of the middle ear space or mastoid air cells. Chronic suppurative otitis media (CSOM) invariably presents with tympanic membrane perforation, which allows otorrhea. CSOM most often results from neglected episodes of AOM and is therefore more common in children with inadequate access to health care. It most often occurs in the first five years of life as eustachian tube dysfunction plays a central role in the pathophysiology.

Cholesteatoma, a sac of squamous epithelium extending from the tympanic membrane into the middle ear, also

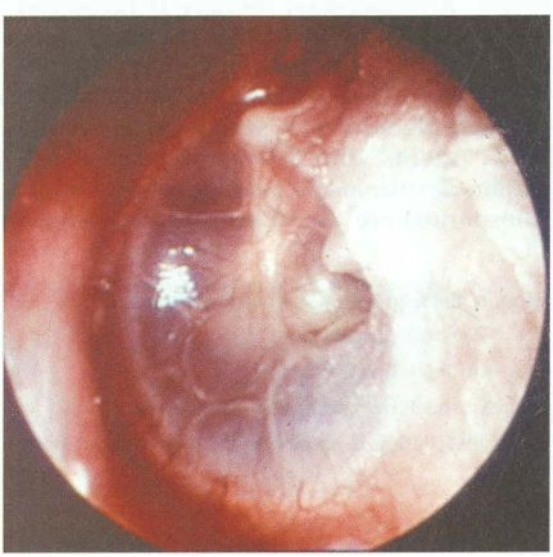


Fig. 13.1: Otitis media with effusion. Note the dull lustreless tympanic membrane. *(Courtesy:* Textbook of ENT, Hazarika)

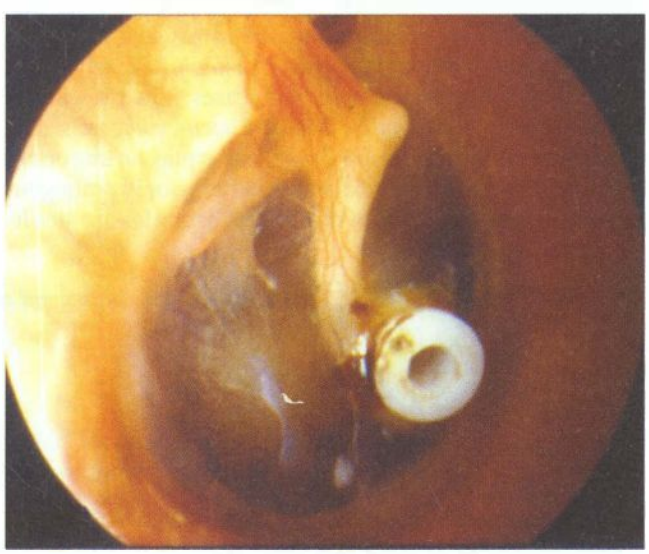


Fig. 13.2: Tympanostomy tube *in situ* in the anteroinferior quadrant of the tympanic membrane *(Courtesy:* Textbook of ENT, Hazarika)

presents with a chronically draining ear. Most cholesteatoma is acquired. It remains unclear whether a cholesteatoma arises from extension of a tympanic membrane retraction pocket, or from aberrant inward migration of normal epithelium. Rarely, it may be congenital, arising *de novo* through the eustachian tube by passage of neonatal epithelium. Though not malignant, cholesteatoma may cause serious complications by slow expansion and local destruction.

Etiology. The most commonly isolated organism is *Pseudomonas aeruginosa*; other organisms include *Staphylococcus aureus, Proteus* spp, *E. coli* and anerobes. Fungi, especially *Aspergillus* and *Candida* spp., may be important.

Diagnosis Chronic ear discharge is the hallmark of CSOM. Otoscopy reveals perforation of the tympanic membrane (Fig. 13.3). A chronically draining ear may also be seen with cholesteatoma, which is a sac of squamous epithelium extending from the tympanic membrane into the middle ear. Most cholesteatoma is acquired, although whether it arises from extension of a tympanic membrane retraction pocket, or from aberrant inward migration of the normal eardrum epithelium, remains unclear. Rarely, the cholesteatoma may be congenital, arising *de novo* in the middle ear space. Though not malignant, cholesteatoma may cause serious complications by slow expansion and local destruction. These complications are discussed further in the next section.

Treatment. Medical therapy consists primarily of topical antibiotics and aural toilet. Topical quinolones appear to be effective and safe. Complicated infections and/or any signs of systemic involvement require the use of systemic antibiotic therapy. Parents should be instructed to avoid water exposure. Secondary fungal otitis externa is a complication of topical antibiotic treatment. Otolaryngology referral is necessary to rule out cholesteatoma.

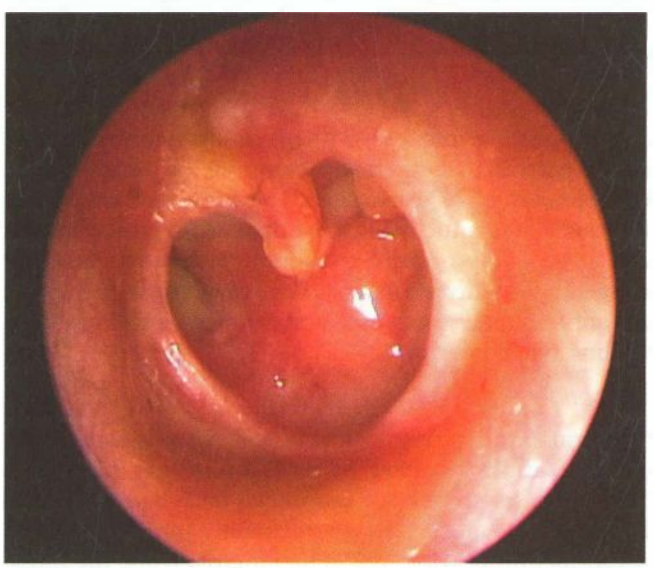


Fig. 13.3: Otoscopy in a child with chronic suppurative otitis media showing subtotal central perforation *(Courtesy:* Textbook of ENT, Hazarika)

Surgery is usually indicated for cases of CSOM that do not respond to conservative treatment. Surgical therapy involves repair of the tympanic membrane perforation (tympanoplasty) with or without mastoidectomy. If cholesteatoma is suspected, ear exploration *via* mastoidectomy and cholesteatoma removal is mandatory. The primary goal of surgical therapy for cholesteatoma is to create a 'safe ear' by removal of all cholesteatoma. Hearing preservation is a secondary goal.

Complications of Otitis Media

Untreated otitis media may cause serious complications, which are classified as either intracranial or extracranial (Table 13.2). Complications of AOM are more common in young children, while complications of CSOM with or without cholesteatoma are common in older children.

The most common complication of CSOM is hearing loss, which may affect language development and school performance. The hearing loss is usually conductive and results from middle ear edema and fluid and tympanic membrane perforation. Sensorineural hearing loss may rarely occur due to direct extension of inflammatory mediators into the inner ear.

Meningitis is the most common intracranial complication of both acute and chronic otitis media. Furthermore, AOM is the most common cause of secondary meningitis. Pneumococcal meningitis is the most common cause of acquired sensorineural hearing loss in children. The mortality rate from otitic meningitis has decreased significantly in the postantibiotic era and with the use of streptococcal vaccines.

Brain abscess is a potentially lethal complication. Unlike meningitis, which is caused more frequently by AOM, brain abscesses result almost exclusively from CSOM. Therapy with broad spectrum parenteral antibiotics is begun immediately and surgical drainage considered. Thrombosis of the sigmoid or transverse sinus is another important intracranial complication. Patients typically

Table 13.2: Complications of otitis media*

Intracranial
Meningitis
Epidural abscess
Dural venous (sigmoid sinus) thrombosis
Brain abscess
Otitic hydrocephalus
Subdural abscess
Extracranial
Acute coalescent mastoiditis
Subperiosteal abscess
Facial nerve paralysis
Labyrinthinitis or labyrinthine fistula

*Listed from most to least common

present with headache, malaise and high spiking fever in a 'picket fence' pattern. Treatment involves parenteral antibiotics and surgical drainage of the mastoid.

Acute coalescent mastoiditis. This results from the spread of infection into the mastoid bone. The entity should be differentiated from fluid effusion within mastoid air cells, which is sometimes mistakenly reported radiologically as 'mastoiditis'. Such opacification is commonly seen with AOM or OME, is readily apparent on CT and is of little clinical significance. Coalescent mastoiditis, on the other hand, presents with postauricular erythema, tenderness, and edema. The auricle is displaced inferiorly and laterally. The CT scan shows fluid and breakdown of the wall separating the mastoid air cells. Untreated, coalescent mastoiditis may spread externally, leading to the formation of subperiosteal or deep neck abscesses.

Acute coalescent mastoiditis should initially be treated with parenteral antibiotics directed against the aforementioned pathogens associated with AOM. If mastoiditis is superimposed on a chronically draining ear, coverage should be added for gram-negative and anerobic organisms. Surgery in the form of cortical mastoidectomy with tympanostomy tube insertion is indicated for cases with poor response to parenteral antibiotic therapy, presence of an abscess or an intracranial complication or acute mastoiditis in a chronic ear.

Other complications include *labyrinthine fistula* and *facial nerve paralysis*. Labyrinthine fistula, in which a cholesteatoma has eroded into the inner ear, presents with vertigo and sensorineural hearing loss. Facial nerve paralysis secondary to otitis media is treated with appropriate antibiotics and tympanostomy tube insertion. If facial nerve paralysis is secondary to cholesteatoma, mastoidectomy is indicated.

Otitis Externa

Acute otitis externa (swimmer's ear) presents with itching, pain and fullness. Erythema and edema of the ear canal and tenderness on moving the pinnae or tragus are diagnostic features. Otorrhea is common. Risk factors include swimming, impacted cerumen, hearing aid use, eczema or trauma from foreign objects (hairpins or cotton swabs). The etiologic agents of otitis externa include *P. aeruginosa, Staphylococcus, Proteus, E. coli, Aspergillus* and *Candida* spp.

Treatment consists of ear canal culture, cleaning and topical antibiotic drops. Topical antibiotics have clinical cure rates up to 80%. If edema is significant, ribbon gauze or a 'wick' may be placed in the external auditory canal to stent it open for drop delivery. Oral antibiotics are reserved for failure to improve and complications.

Otomycosis or *fungal otitis externa* is most common in humid weather and presents with pain and pruritus. These opportunistic infections are frequently seen subsequent to treatment of a bacterial infection. Examination reveals fungal spores and filaments. *Aspergillus* and *Candida* are the most common pathogens. Aural toilet and a topical antifungal (e.g. clotrimazole) are curative.

Otic furunculosis is an exquisitely painful, superficial abscess in the outer portion of the ear canal, typically from *S. aureus*. Oral antistaphylococcal antibiotics and analgesics bring about prompt relief. Incision and drainage may be necessary.

Eczematous or *psoriatic otitis externa* describes a group of inflammatory conditions in which there is drainage, pruritis and/or scaling of the ear canal skin. Underlying causes include contact dermatitis, atopic dermatitis and seborrheic dermatitis.

Malignant otitis externa is a rare invasive infection of the external auditory canal cartilage and bone. Immunocompromised children (acquired immunodeficiency syndrome, leukemia, diabetes mellitus, immunosuppression after organ transplant) are at risk. *Pseudomonas aeruginosa* is the most common etiology. Invasive fungal species, especially *Aspergillus*, are also seen. The external auditory canal is tender and facial or scalp necrosis may arise, with or without cranial nerve abnormalities. Diagnosis is confirmed with CT and MRI scan and/or scintigraphy for osteomyelitis of the temporal bone. Aggressive surgical debridement and parenteral antibiotics and/or antifungals for 4–6 weeks are required. Treatment response may be monitored with serial Gallium^{67} bone scans.

Hearing Loss

Early detection of hearing loss in children is imperative. Unrecognized early hearing loss can impede development of speech, language and cognitive skills. Separate differential diagnoses exist for deficits of both the conductive and sensorineural components of the hearing mechanism. Hearing loss in children can be classified as either *congenital* or *acquired*.

Conductive Hearing Loss

Any process that interferes with the conductive mechanism of the ear canal, tympanic membrane, or ossicles may cause a conductive hearing loss. The most common pediatric cause of conductive lost is otitis media with effusion and is typically of mild to moderate severity. Several congenital syndromes may also be associated with middle ear abnormalities, such as Apert, Crouzon and Treacher-Collins syndromes.

Sensorineural Hearing Loss

Sensorineural hearing loss is caused by a lesion of the cochlea, auditory nerve or central auditory pathway. SNHL can be *acquired* or *congenital*, both being equally common. The most common postnatal cause of acquired sensorineural hearing loss is meningitis, while the most common prenatal cause is intrauterine infection (e.g. TORCH infections, syphilis). Other causes of acquired

hearing loss include prematurity, hyperbilirubinemia, perinatal hypoxia, acquired immunodeficiency syndrome, head trauma and ototoxic medications (aminoglycosides, loop diuretics).

Congenital causes of sensorineural hearing loss are of *syndromic* and *nonsyndromic* types. Although 70% of congenital hearing loss is nonsyndromic, over 300 genetic syndromes are associated with SNHL. Common syndromes include Pendred syndrome (euthyroid goiter), Jervell and Lange-Nielsen syndrome (prolonged QT waves, syncope), Usher syndrome (retinitis pigmentosa and blindness), Alport's syndrome, branchio-oto-renal syndrome, neurofibromatosis and Waardenburg syndrome. Multiple chromosome loci and at least 65 genes associated with genetic hearing loss have been identified. Mutations in a single gene, *GJB2*, may be responsible for up to 50% of nonsyndromic congenital hearing loss. *GJB2* encodes the protein connexin 26, which is widely expressed in cells of the inner ear. Screening tests for this mutation are available.

Neonatal Screening

All neonates with risk factors for hearing loss should be screened with an oto-acoustic emission test or an auditory brainstem response. The use of clinical indicators to focus hearing screens will miss as many as 50% of all cases of impairment. Hence universal newborn hearing screen programs are now commonplace in the United States and Europe. The importance of neonatal screening cannot be overemphasized. Infants in whom treatment for hearing loss is initiated by 6 months of age are able to maintain language and social development in line with their physical development. This is in contrast to those whose hearing loss is identified after 6 months of age. A limitation of newborn screening is that some forms of early-onset hearing loss are not apparent at birth. A United States Joint Committee on infant hearing has identified 11 risk indicators that should prompt continued monitoring of hearing status even in the face of normal neonatal screens (Table 13.3).

Screening in Older Children

Clinical evaluation of hearing at routine well child assessments is critical for early detection of hearing impairment. Examination should include otoscopy with attention to middle ear pathology. Doubtful cases are referred for detailed audiologic evaluation so that timely intervention may begin.

Multiple techniques exist to assess hearing sensitivity and are selected based on the age and the abilities of the child. For younger children unable to understand instructions, visual-reinforcement audiometry is performed. Pure tone audiometry is possible in children older than 5 yr. Tympanometry may be performed in nearly all children to assess ear drum mobility.

Table 13.3: Indications for continued hearing monitoring in children with normal hearing on neonatal screening

Caregiver concern regarding hearing, speech, or developmental delay
Family history of childhood hearing loss
Neonatal intensive care for >5 days or use of any of the following, regardless of duration: Extracorporeal membrane oxygenation, assisted ventilation, exposure to ototoxic antibiotic (gentamycin, tobramycin) or loop diuretics (furosemide) and hyperbilirubinemia requiring exchange transfusion
In utero infections (CMV, rubella, syphilis, herpes, toxoplasmosis)
Findings of a syndrome associated with hearing loss
Postnatal infection known to cause hearing loss (e.g. meningitis)
Syndromes associated with progressive hearing loss (e.g. neurofibromatosis)
Neurodegenerative disorders (e.g. Hunter syndrome, Friedreich ataxia)
Head trauma
Recurrent or persistent (≥3 mo) otitis media with effusion
Chemotherapy or head radiation

Treatment of Hearing Loss

Once diagnosed, treatment of hearing loss is based on the extent of deficit and the underlying pathology. For very mild hearing loss, treatment may consist simply of preferential seating in school. For mild to moderate conductive hearing loss, treatment options include tympanostomy tubes or, if a perforation is present, tympanoplasty.

Treatment of significant sensorineural hearing loss may require the use of hearing aids from as early as 3 months of age. The development of cochlear implants has rapidly reshaped the management of childhood hearing loss. Bilateral cochlear implantation may be considered for infants as young as 12 months of age who have a profound bilateral hearing loss and may be considered even earlier if the hearing loss is due to meningitis. If a child has never had auditory stimulus (secondary to profound congenital deafness), cochlear implantation before 6 yr of age is crucial to develop the auditory cortex for sound awareness and speech development. Sign language and deaf education programs should be considered for children who are not candidates for cochlear implantation.

DISEASES OF THE NOSE AND SINUSES

Rhinitis

Allergic Rhinitis

Allergic rhinitis is an inflammatory disorder characterized by sneezing, itching, nasal obstruction and clear rhino-

rrhea. The pathophysiology involves an IgE-mediated reaction to a specific allergen. Symptoms may be seasonal ('hay fever') or perennial. Examination reveals a pale nasal mucosa, congested nasal turbinates and mucoid rhinorrhea. Conjunctival itching and redness may be present. Inhaled allergens (e.g. pollen, spores and dust mites) are common causes. Accurate diagnosis may require demonstration of eosinophilia in a nasal smear, or the use of skin/serologic tests to show specific IgE response to allergens. These tests establish the atopic etiology and help differentiate from other conditions with similar symptoms.

Treatment includes allergen avoidance, use of topical nasal steroid sprays for prevention and oral antihistamines for symptom relief. The use of oral decongestants is controversial. Topical decongestants should also generally be discouraged as they cause rebound congestion (short-term) and chemical rhinitis or rhinitis medicamentosa (longterm).

Viral Rhinitis

Viral rhinitis or common cold is the most common cause of both nasal obstruction and rhinorrhea in children. Children normally average between six and eight of these upper respiratory infections per year. Malaise, low to moderate grade fever, nasal congestion and rhinorrhea are the presenting symptoms. A number of different viruses can be responsible, including rhinovirus, influenza and adenovirus. Treatment is symptomatic and involves antipyretics, saline nasal spray. Use of oral decongestants and antihistamines are controversial. A number of developed countries recommend annual influenza vaccination in children older than 6 months. Otitis media and sinusitis are frequent complications.

Sinusitis

Sinusitis can be classified as either acute or chronic. The ethmoid and maxillary sinuses are the earliest to develop and are the ones most commonly infected in pediatric sinusitis. The frontal sinuses may become involved only after 5–6 yr of life; isolated sphenoid disease is rare. Risk factors associated with sinusitis include recurrent upper respiratory infections, allergic rhinitis, cystic fibrosis, immunodeficiency, ciliary dyskinesia, daycare attendance and exposure to tobacco smoke. Ten-fifteen percent of upper respiratory tract infections are complicated by sinusitis. A sinus infection should be considered in any child whose cold symptoms have not resolved by 7–10 days.

Etiology. The most common isolates in acute sinus infections are *S. pneumoniae, H. influenzae* and *M. catarrhalis*. The same bacteria are implicated in chronic sinusitis, as are *S. aureus,* anerobes and occasionally fungi. The adenoid pad plays an important role in the pathophysiology of pediatric sinusitis since it may serve as a bacterial reservoir for the paranasal sinuses (Fig. 13.4).

Diagnosis. Acute rhinosinusitis typically presents as an episode of upper respiratory infection with worsening of nasal discharge and cough 7 to 10 days after onset of symptoms. A severe URI with fever (>38.5°C) and purulent rhinorrhea also meets the diagnostic criteria for acute sinusitis. Chronic sinusitis is defined as symptoms of sinusitis lasting longer than 30 days. Nasal obstruction, malaise and headache may all be features of chronic rhinosinusitis. Imaging is not necessary and should be reserved for cases with complications and those being considered for surgery. CT scan is superior to plain X-rays for imaging of paranasal sinuses (Fig. 13.4).

Allergic fungal sinusitis is an increasingly recognised condition in atopic, immunocompetent patients. Older children and adolescents are most commonly affected. The cause is hypersensitivity to fungal antigens. This results in the form of chronic rhinosinusitis that requires surgical intervention.

Complications. These include orbital or intracranial spread of infection. Orbital complications most commonly result from direct extension from the ethmoids. Early orbital complications manifest as periorbital (preseptal) cellulitis. More severe complications include orbital abscess or cavernous sinus thrombosis. Ophthalmoplegia, vision loss, and toxemia indicate a life-threatening infection of the cavernous sinus. Intracranial complications (meningitis and abscesses) may also occur and are more commonly associated with frontal and sphenoid sinus infections.

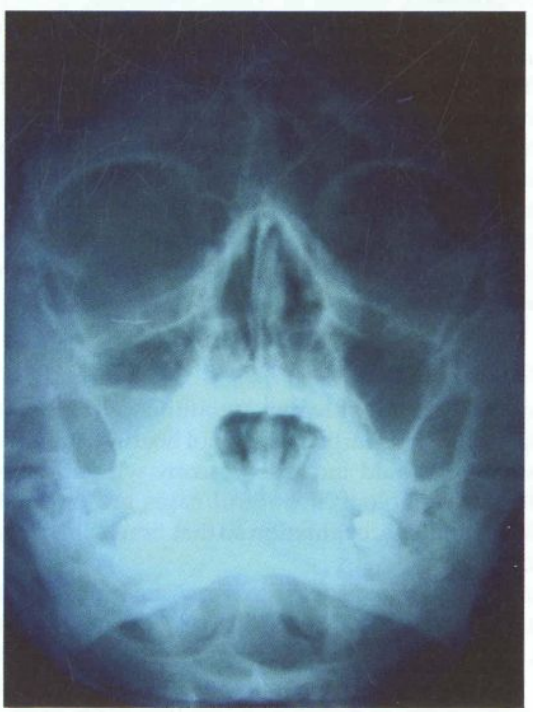


Fig. 13.4: Note the air fluid level in right maxillary sinus in a patient with maxillary sinusitis *(Courtesy:* Textbook of ENT, Hazarika)

Treatment. Although a significant number of acute sinusitis episodes will resolve spontaneously, treatment with antibiotics is preferred. Therapy with amoxicillin is recommended for 10–14 days. Longer courses and second-line antibiotic agents are indicated for refractory infections. Parenteral antibiotics are necessary for sinusitis with orbital or intracranial complications. Other adjuvant measures include oral decongestants, mucolytic agents and topical nasal saline. Topical decongestants may be used in sinusitis with complications. Antihistamines are avoided due to their drying effect.

Antibiotics are also required for chronic sinusitis. As most of these patients have already failed a course of standard-dose amoxicillin, initial therapy consists of coamoxiclav, high-dose amoxicillin or cefuroxime. The duration of treatment is longer than for acute sinusitis, typically 3 to 6 weeks. Patients with penicillin allergy may be treated with a macrolide antibiotic, although there is increasing resistance of pathogens to these agents. Topical nasal steroids are occasionally useful for treatment.

Surgical intervention for acute sinusitis is limited to those with orbital or intracranial complications. Surgery may be considered for patients with chronic sinusitis who have not responded to aggressive medical management or who show anatomical obstruction after maximal medical management and extensive medical workup with allergy testing and immune evaluation. Adenoidectomy, to remove a potential bacterial reservoir for the sinuses, must be considered in younger children. The indications for endoscopic sinus surgery include patients with sinonasal polyposis, cystic fibrosis, failure to improve despite one-month course of medical therapy and any orbital or cranial complication.

Nasal Obstruction

Causes. Chronic mouth breathing in children is generally caused by blockage of nasal airflow. The site of nasal blockage is most often in the nasopharyngeal area due to adenoid hypertrophy. Intranasal causes of obstruction include allergic rhinitis, recurrent sinusitis, nasal septum deviation, turbinate hypertrophy, nasal polyps and less commonly, neoplasms. As a rule, bilateral nasal polyps do not occur in normal children and their presence should prompt testing for cystic fibrosis. Congenital causes of nasal airway obstruction include choanal stenosis or atresia, dermoid cysts, teratomas, encephaloceles, and pyriform aperture (bony opening to the nasal cavity in the skull) stenosis.

Diagnosis. Adenoid enlargement should be suspected in children, usually older than 2 yr, who present with nasal blockage, mouth breathing, sleep disturbance and chronic nasal discharge. Examination must rule out nasal pathology such as septal deviation or polyposis. Neonates with pyriform aperture stenosis may present with a single midline maxillary incisor. A CT scan or X-ray confirms the diagnosis (Fig. 13.5).

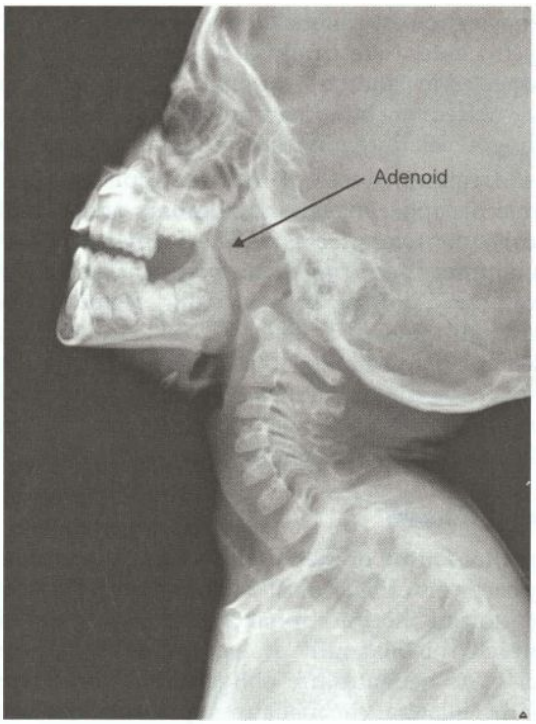


Fig. 13.5: Lateral radiograph of the neck showing adenoid hypertrophy occluding the nasopharyngeal airway in a 6-yr-old boy *(Courtesy:* Textbook of ENT, Hazarika)

Treatment. Adenoidectomy is recommended for symptomatic younger children. Pubertal growth of the midface and regression of adenoid size tend to result in relief of adenoid-related nasal obstruction in children older than 9 yr. Pyriform aperture stenosis is treated with surgical drilling of the obstructing bony plates. Treatment for sinonasal polyposis includes topical and systemic steroids for limited disease and surgical intervention for larger, obstructing polyps.

Surgery on the nasal septum should be avoided in prepubertal children, as it may lead to retardation in midface growth and saddling of the nasal dorsum. A conservative operation to correct a limited portion of the septum may be justified in a particularly symptomatic child. Turbinate hypertrophy usually responds to treatment of allergy, though electrocautery may be used in refractory cases.

Epistaxis

Bleeding from the nose occurs frequently in children. Most pediatric epistaxis occurs in the anterior portion of the nasal septum at a confluence of arterial vessels known as Little's area (Kiesselbach plexus). Local trauma, especially nose picking, is by far the most common cause of pediatric epistaxis. Reduced ambient humidity also places the patient at risk. Examination reveals prominent vessels in Little's area that bleed promptly when touched with a cotton-tipped probe. Digital pressure by pinching the nose invariably stops the bleeding. Avoidance of nose picking, application of an antibiotic ointment for lubrication and,

for refractory cases, cauterization with topical silver nitrate or electrocautery are curative. Bleeding disorders must be suspected in children with suggestive family history, a history of frequent bleeding from other sites, or any nasal bleeding which does not respond in the usual fashion.

Less frequent causes of recurrent epistaxis include juvenile nasopharyngeal angiofibroma and hereditary hemorrhagic telangiectasia. The former is a benign, vascular tumor occurring exclusively in adolescent males that can cause profuse, brisk bleeding. Hereditary telangiectasia also known as Osler-Weber-Rendu syndrome, is a genetic defect in blood vessel structure resulting in arteriovenous malformations. Patients may suffer from severe, recurrent epistaxis, as well as gastrointestinal bleeds and pulmonary hemorrhage.

Choanal Atresia

Congenital failure of the nasal cavities to open into the nasopharynx is called *choanal atresia*. It results from failed resorption of the buccopharyngeal membrane either unilaterally or bilaterally or even partial with a severe stenosis. As neonates are obligate nasal breathers for 6 months, bilateral choanal atresia presents immediately afterbirth with respiratory distress. The affected baby cycles between silent cyanosis and crying. Suckling immediately precipitates cyanosis. Bilateral atresia can present as part of the CHARGE association, consisting of coloboma, heart abnormalities, choanal atresia, retardation of growth and development, genitourinary defects and ear anomalies.

Unilateral choanal atresia is a more indolent process and may present later in childhood with unilateral nasal discharge or blockage. Atresia typically manifests when the opposite nasal passage becomes blocked due to rhinitis or adenoid hypertrophy.

Diagnosis. Inability to pass an 8 French catheter can aid in diagnosis. Flexible nasal endoscopy confirms the diagnosis. CT scan demonstrates the atretic plate thickness and differentiates between bony and membranous atresia.

Treatment. Bilateral choanal atresia requires urgent management by inserting a finger in the baby's mouth and depressing the tongue down and forward away from the back of the throat. This should be replaced with a plastic oropharyngeal airway or a McGovern open-tip nipple. Failure of these measures may necessitate intubation or tracheostomy.

Treatment of choanal atresia is surgical. The two primary approaches are transpalatal and transnasal. Transnasal endoscopic repair is often attempted first as it is less invasive. Transpalatal repair, which involves removal of the posterior hard palate, is often reserved for failed endoscopic repair. Stents are placed in the nasal passages to prevent restenosis and are typically left in place for 3 to 6 weeks postoperatively.

DISEASES OF THE ORAL CAVITY AND PHARYNX

Inflammatory Disorders

Recurrent aphthous stomatitis is a common pediatric disorder that presents as painful white ulcers of variable size on the oral mucosa. The exact etiology is unknown. The ulcers resolve spontaneously over several days. If symptomatic management does not suffice, topical steroids and rarely, systemic steroids are employed, but may require intravenous fluids for dehydration.

Herpetic stomatitis presents in children with small, painful vesicles that evolve into gray pseudomembranous mucosal ulcers. Antiviral medications may be used to hasten recovery, though the lesions usually heal spontaneously within 10–14 days. Once again intravenous fluids may be required.

Oral candidiasis (thrush) appears as small, white, curd-like lesions on the tongue and oral mucosa. In children under age 6 months or those on antibiotics, it is a benign finding. It can also be related to systemic diseases such as diabetes or immunodeficiency. Oral antifungals are effective.

Congenital Disorders

Ankyloglossia (tongue tie) is a limitation of anterior tongue mobility caused by a congenitally short lingual frenulum. This condition is not related to speech impairment.

Cleft palate may appear with or without *cleft lip* and can cause serious feeding difficulties. The etiology is multifactorial. Treatment should include staged reconstruction of the lip and palate defects and multidisciplinary management.

Micrognathia (small mandible), if severe, may displace the tongue posteriorly and cause respiratory distress in the neonate. Congenital micrognathia is most commonly seen with the Pierre Robin sequence, in which patients also have cleft palate and glossoptosis. If the micrognathia is severe, the neonate may require tracheostomy to secure the airway.

Macroglossia may be idiopathic or associated with syndromes such as Down syndrome, Beckwith-Wiedemann syndrome and neurofibromatosis. If significant, the enlarged tongue may cause drooling, speech impairment and airway obstruction.

Lingual thyroid may present as a posterior midline tongue mass and is caused by an abnormal descent of the thyroid from the tongue base *in utero*. It may present with neonatal respiratory distress and may be associated with a thyroglossal dust cyst. As lingual thyroid often represents the only functioning thyroid tissue, its removal may necessitate chronic thyroid hormone supplementation.

Sore Throat

Viral pharyngitis is very common and is caused by a number of different pathogens including adenovirus,

enterovirus, coxsackievirus and parainfluenza virus. It typically presents with nonexudative pharyngeal erythema and tender cervical adenopathy. Upper respiratory complaints (rhinorrhea, nasal obstruction, cough, fever) are common. Treatment is supportive, as this is nearly always self-limited.

Infectious mononucleosis, caused by the Epstein Barr virus, presents with sore throat, gray pharyngeal exudate and soft palate edema. Patients show significant cervical lymphadenopathy and hepatosplenomegaly. Monospot or Paul-Bunnell tests are useful screening tests (only 40% accurate) and antibody titer confirms the diagnosis. Medical treatment is supportive and may include steroids for respiratory difficulty or severe dysphagia.

Acute bacterial pharyngotonsillitis is caused by group A β-hemolytic streptococci. Less common pathogens include nongroup A. streptococcus, *S. aureus* (Fig. 13.6), *H. influenzae*, *M. catarrhalis*, diphtheria, gonococci, chlamydia and mycoplasma. Streptococcal pharyngitis presents as bilateral tonsil hypertrophy and erythema with characteristic exudate. To distinguish between viral and bacterial pharyngotonsillitis, a rapid strep test should be obtained. A negative result should be confirmed by throat culture. Treatment is with a ten-day course of penicillin VK or a first-generation cephalosporin. Both suppurative and nonsuppurative complications can result from incompletely treated streptococcal pharyngitis. Non-suppurative complications include scarlet fever, acute rheumatic fever and poststreptococcal glomerulonephritis. Suppurative complications include peritonsillar, para-pharyngeal or retropharyngeal abscesses.

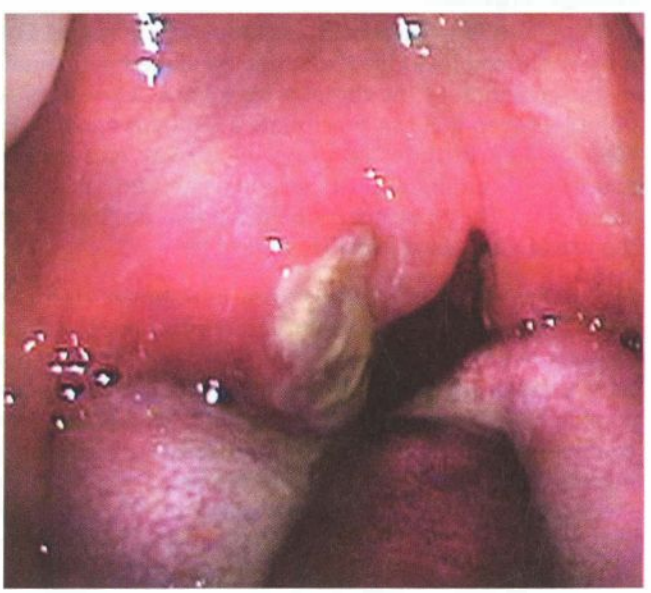


Fig. 13.6: Acute staphylococcal pseudomembranous tonsillitis with unilateral hypertrophy of the right tonsil. This condition has to be differentiated from other causes of white patch on the tonsil *(Courtesy:* Textbook of ENT, Hazarika)

Peritonsillar abscess typically presents with a muffled voice, trismus and decreased oral intake. Physical examination reveals a unilateral displacement of the affected tonsil towards the midline with a bulge in the peritonsillar region and uvular deviation to the opposite side. CT scan may aid in diagnosis. Treatment consists of incision and drainage by experienced personnel. This should be followed by a 7–10 day course of oral or parenteral penicillin or clindamycin. Steroids, to reduce pain and fever, may be considered as adjunctive therapy. Immediate tonsillectomy (Quinsy tonsillectomy) may be performed, but has increased hemorrhage risk. A single peritonsillar abscess is a relative indication for tonsillectomy. Patients with recurrent abscesses should always be considered for tonsil removal.

Pharyngeal injury may occur in children after falling with a pen, stick or other sharp object in the mouth. Examination reveals a puncture or laceration of the soft palate, tonsil, or pharyngeal wall. The most significant risk is a carotid injury. The presence of significant bleeding, neurologic findings or a puncture lateral to the exposed tonsil should prompt immediate consultation and evaluation with angiography.

Adenotonsillectomy

Removal of the tonsils and adenoids is one of the most commonly performed pediatric operations. Recurrent tonsillitis is a common indication. More than 5–6 episodes of tonsillitis in a year or significant missed time from school or work should prompt consideration for tonsillectomy. Other indications include obstructive sleep apnea, suspicion of malignancy and previous peritonsillar abscess. Surgery is performed on an outpatient basis in older children. The most significant risk of tonsillectomy is postoperative hemorrhage.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is characterized by episodic obstruction of airflow through the upper airway during sleep. Adenotonsillar hypertrophy is the most common cause for pediatric OSA. Congenital nasal masses may be responsible for neonatal OSA. Physiologic sequelae may include hypoxemia, hypercapnia and acidosis. The most severely affected patients may develop failure to thrive, right ventricular hypertrophy, pulmonary hypertension and cor pulmonale.

Patients with OSA present with noisy breathing, specifically stertor (sonorous upper airway breathing). Other symptoms include snoring, breath holding, or gasping during sleep, as well as enuresis. Daytime manifestations include morning headache, halitosis and behavioral disorders. Physical examination often reveals audible breathing with open mouth posture, hyponasal speech and tonsillar hyperplasia. Polysomnography (sleep study) remains the gold standard for diagnosis.

Adenotonsillectomy is considered first-line therapy in pediatric OSA. If the apnea hypopnea index is greater than

ten then the child should be monitored closely in the postoperative period with pulse oximetery. Surgical removal of nasal masses may be required. In the most severe cases of OSA, tracheostomy may be considered.

DISEASES OF THE LARYNX AND TRACHEA

Stridor

The term stridor refers to excessively noisy, musical breathing and is generally due to upper airway obstruction. The relationship of stridor to the respiratory cycle often provides a clue to its etiology: *Inspiratory stridor* suggests obstruction above the vocal cords (supraglottis), while *expiratory stridor* usually originates from the distal trachea (Table 13.4). *Biphasic* (inspiratory and expiratory) stridor usually originates from a subglottic or proximal tracheal lesion. Most pediatric stridor originates from supraglottic lesions.

Table 13.4: Supraglottic compared to tracheal obstruction

Supraglottic obstruction	*Tracheal obstruction*
Inspiratory stridor	Biphasic or expiratory stridor
Weak cry or voice	Normal cry or voice
Dyspnea is generally mild	May have severe dyspnea
Less pronounced cough	Deep barking, brassy cough

Evaluation of the stridorous child should include a thorough history. Physical findings include nasal flaring and suprasternal or intercostal retractions. Chest X-rays or lateral neck films may confirm diagnoses such as retropharyngeal abscess, epiglottitis, or croup. Barium esophagram or CT may rule out extrinsic vascular compression. Flexible and rigid endoscopy is generally needed to confirm the diagnosis. There are multiple causes of pediatric airway obstruction, some of which are listed below.

Infections

Croup (laryngotracheobronchitis) is a viral upper respiratory tract infection and often presents in children 1–5 yr of age with biphasic stridor, barking cough and low-grade fever. Onset of symptoms is usually over several days. Chest X-ray reveals a characteristic narrowing of the subglottic region known as the *steeple* sign (Fig. 13.7).

Most cases of croup are mild and resolve within 1 to 2 days. Conservative management should include reassurance, cool mist and oral hydration. Children with stridor at rest should be hospitalized for close observation, cool mist and supplemental oxygen. Therapy with epinephrine (1:1000 in doses of 0.1–0.5 ml/kg to a maximum dose of 5 ml), gives through a nebulizer helps in relief of symptoms. A single dose of dexamethasone (0.3–0.6 mg/kg IM) reduces overall severity during first 24 hr. Recently, inhalation of budesonide in doses of 1 mg twice a day for 2 days has shown satisfactory results.

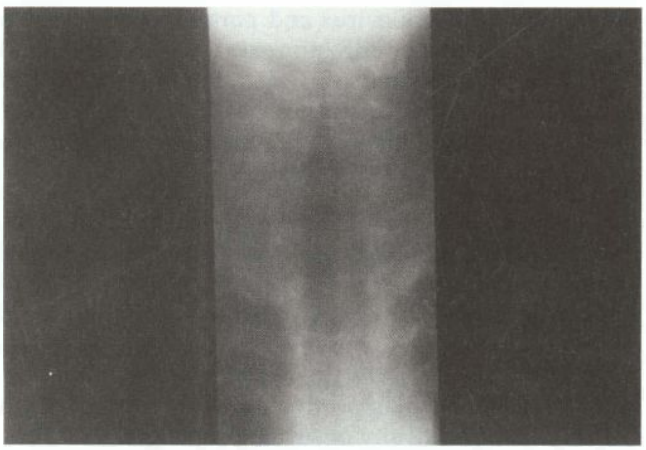


Fig. 13.7: Laryngotracheobronchitis (croup). 'Steeple sign'

Antibiotics are indicated only if the child fails to improve or if purulent secretions are present. Coverage should be directed towards *Staphylococcus* and *H. influenzae*.

Acute epiglottitis (often called *supraglottitis*), although less common than croup, typically presents with a greater degree of airway compromise. Patients typically present with acute onset (over several hours) of sore throat, marked dysphagia and high fever. Patients are often encountered leaning forward in a 'tripod' position, toxic-appearing and drooling. Unlike croup, cough is frequently absent. Lateral neck X-ray reveals a characteristic thickening of the epiglottis (*'thumbprint'* sign) or other supraglottic structures. *H. influenzae* type B is the major etiologic organism.

If epiglottitis is suspected, rapid airway management is essential and includes intubation by skilled personnel. Instrumentation of the throat with tongue depressors is not advised as this can precipitate a fatal laryngospasm. Management includes securing the airway and broad-spectrum IV antibiotics, e.g. coamoxiclav, ceftriaxone or cefuroxime. The incidence of epiglottitis has declined since the use of vaccines against *H. influenzae*.

Bacterial tracheitis is typically seen in younger children following viral upper respiratory tract infection. The child appears toxic with a brassy cough and stridor. Patients have a classic irregular tracheal wall on X-ray. Bronchoscopy is both diagnostic and therapeutic, as the purulent tracheal secretions can be visualised, cultured and mechanically debrided. Bacterial tracheitis is a relative medical emergency, as life-threatening obstruction may develop from these tracheal secretions. The responsible pathogen is usually *S. aureus*.

Retropharyngeal abscess is a potential suppurative complication of bacterial pharyngitis that may present with stridor. Patients often have high fever, reduced mobility of the neck and appear toxic. Complications of

retropharyngeal abscess include spread of infection into the mediastinum. Mediastinitis is potentially fatal. Lateral neck radiograph reveals a bulge in the posterior pharyngeal wall. Treatment is by surgical drainage and broad-spectrum parenteral antibiotics.

Congenital Causes

Laryngomalacia is the most common congenital laryngeal anomaly, accounting for up to 60% and the most common cause of infant stridor. Inspiratory stridor is the hallmark of the condition. Symptoms are typically aggravated when the child is supine or crying. Flexible endoscopy reveals partial collapse of a flaccid supraglottic airway with inspiration. If present, gastroesophageal reflux, should be managed. Laryngomalacia is generally benign and self-limited, as most cases resolve by 18 months of age. Surgical intervention is advised for either respiratory distress or failure to thrive.

Vocal cord paralysis is the second most common congenital laryngeal anomaly. *Bilateral vocal cord paralysis* usually presents with a high-pitched inspiratory stridor and cyanosis. It is usually iatrogenic by excessive stretch of the neck during vaginal delivery producing an Erb's palsy of the recurrent nerve, but can also be idiopathic. Other causes may include Arnold-Chiari malformation, hydrocephalus or hypoxia. *Unilateral vocal cord paralysis*, in contrast, may present with a mild stridor or with signs of aspiration. Iatrogenic injury during ligation of patent ductus arteriosus is a frequent cause. Tracheostomy is required to secure the airway in bilateral paralysis, though generally not in unilateral paralysis unless there is excessive aspiration.

Congenital subglottic stenosis is the third most common congenital laryngeal anomaly. It results from incomplete recanalization of the laryngotracheal tube during embryonic development. Subglottic stenosis may present as recurrent episodes of stridor and may be mislabeled as 'croup'. Many cases resolve spontaneously as the child grows, while severe cases usually require tracheostomy. Surgical excision of the stenosis may be necessary to relieve the obstruction in these cases.

Vascular ring is a great vessel anomaly that causes extrinsic compression of both the trachea and the esophagus. The child with vascular ring anomaly usually presents with dysphagia as well as stridor. Contrast swallowing studies (esophagram) or CT may reveal the diagnosis. Treatment for vascular anomalies is surgical.

Subglottic hemangioma is a benign vascular tumor that may present in the trachea. Infants usually become symptomatic between 3–6 months of life. Symptoms include biphasic stridor and a barking cough. Up to 50% may have concurrent cutaneous head and neck hemangiomas. Imaging may reveal asymmetric subglottic narrowing. The diagnosis in confirmed with endoscopy. Treatment options include primarily oral propranolol, intralesional steroids, CO_2 laser excision, tracheostomy, and open surgical excision.

Congenital saccular cyst, laryngeal web and *laryngeal atresia* are rare laryngeal anomalies. They present with airway obstruction and require surgical intervention.

Iatrogenic Causes

Acquired subglottic stenosis is the most common cause of acquired stridor. It most often results from longterm endotracheal intubation and subsequent scar formation. Minor stenosis may be observed, while more severe stenosis may be treated by a variety of surgical methods including tracheostomy, widening of the stenosis with cartilage grafts, and excision of the stenotic segment.

Laryngeal granuloma may also result from prolonged intubation. Endoscopy reveals a vocal cord granuloma. These are often amenable to endoscopic removal.

Neoplasms

Recurrent respiratory papilloma is the most common benign laryngeal tumor and presents with gradual airway obstruction. Endoscopy reveals single or multiple irregular, wart-like masses in the larynx or pharynx. The condition is caused by human papillomavirus; HPV types 6 and 11 are the most common. Transmission is believed to be vertical, from the passage of the fetus through an infected birth canal. Treatment is with CO_2 laser ablation or microdebrider excision of the papillomas. Adjunctive therapies include intralesional cidofovir and alpha-interferon. Multiple surgical procedures are usually necessary as the disease typically recurs.

Foreign Body Aspiration

Foreign body aspiration should always be considered as a potential cause of stridor and airway obstruction in children. Foreign bodies most commonly aspirated are food and coins. Conforming objects such as balloons pose the greatest risk of choking death, followed by round objects such as balls or marbles. After establishing airway patency, urgent endoscopic visualization and removal by an experienced surgeon are necessary.

Hoarseness

Vocal nodules are the most common cause of hoarseness in children and are generally caused by vocal abuse. They are seen more frequently in habitually shouting or screaming children, usually boys with siblings. The severity of hoarseness fluctuates, worsening with vocal abuse and improving with rest. Endoscopy reveals small, bilateral, opposing nodules at the junction of the anterior and middle-thirds of the vocal cord. Speech therapy is usually effective in older children. Surgery is rarely indicated.

Reflux laryngitis may result from gastric secretions spilling onto the larynx. Reflux has been implicated in numerous diseases of the head and neck, ranging from laryngitis and subglottic stenosis to chronic sinusitis and otitis media with effusion. Diagnosis is best established with 24 hr pH monitoring. Medical management is usually effective, though surgical fundoplication may be needed in severe cases.

Hypothyroid myxedema may occasionally cause an increase in vocal fold edema and present as hoarseness or stridor. Thyroid function tests should be conducted in the hoarse child with a clinical history suggestive of hypothyroidism.

Laryngotracheal cleft is a rare congenital defect in the posterior cricoid cartilage of the larynx. In its mildest form, children with this process may experience feeding difficulty, recurrent respiratory tract infection or hoarseness. In its more severe forms, the cleft may extend inferiorly between the entire trachea and esophagus. Severe clefts usually cause significant aspiration pneumonias and are often not compatible with life. The condition may be associated with hereditary conditions such as Opitz-Frias or Pallister-Hall syndromes. Management of symptomatic clefts is surgical.

DISEASES OF THE SALIVARY GLANDS

Infections

Bacterial parotid sialoadenitis is frequent in small children and presents with painful unilateral parotid swelling. Purulent material may be expressed from the parotid duct intraorally with parotid massage. Dehydration leads to staphylococcal overgrowth in the duct system. Treatment includes oral antibiotics as well as hydration, sialogogues, massage and warm compresses.

Viral parotitis is caused most often by the mumps virus. Patients generally present with painful parotid enlargement and fever. They may also present with an acute unilateral hearing loss or vestibular weakness. Systemic manifestations such as meningoencephalitis, pancreatitis and orchitis may also be present.

Tuberculosis is the most common granulomatous inflammation of the parotid. It may be limited to the salivary glands without lung involvement. *Sarcoidosis* may also present with unilateral or bilateral parotid swelling. It is usually seen with systemic symptoms and peripheral adenopathy. A variety of laboratory tests and radiological studies including chest radiograph support the diagnosis. Steroids are of value in treating xerostomia.

Human immunodeficiency virus (HIV) involvement of the parotid glands is common, presenting as bilateral intraglandular cysts. The cysts invariably recur after aspiration.

Drooling

Drooling (sialorrhea) is a common, self-limited finding in young children. However, in children with neuromuscular disorders, dysphagia and poor lip closure may result in chronic drooling. If the swallowing mechanism is also abnormal, pooled secretions may allow chronic aspiration, leading to pneumonia or other complications.

Medical therapy for drooling not controlled with speech therapy consists of drying agents such as glycopyrrolate and antihistamines. Refractory cases of sialorrhea may be treated surgically with salivary gland excision; ductal ligation or rerouting; destruction of parasympathetic fibers; or some combination of the above. At present, the preferred surgical treatment is bilateral submandibular gland excision with parotid duct ligation. Tracheostomy or separation of the trachea from the upper airway is reserved for profound and life-threatening chronic aspiration.

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Disorders of Respiratory System

14

SK Kabra

COMMON RESPIRATORY SYMPTOMS

Cough

After maximal inspiration, the air is suddenly released through the partially closed glottis, because of forceful contraction of the expiratory muscles. This produces a bout of cough. The cough reflex is controlled by a center in the medulla. Irritation of the pharynx, larynx, trachea, bronchi and pleura transmit the afferent impulses through the vagus or glossopharyngeal nerves. Efferent pathways are in the nerve supply to the larynx and respiratory muscles.

Cough is an important defense mechanism of the respiratory system and helps to bring out the infected secretions from the trachea and bronchi. Cough should not be suppressed in younger children as retention of secretions in their lungs may result in atelectasis and pulmonary complications. On the other hand, persistent cough interferes with the sleep and feeding. It fatigues the child and may result in vomiting.

Etiology

Acute cough Causes include:

i. Upper respiratory tract infection (rhinovirus, influenza virus, parainfluenza, respiratory syncytial virus, adenovirus), postnasal discharge due to sinusitis (streptococci, *Haemophilus influenzae* or *Moraxella*, usually in older children), rhinitis, hypertrophied tonsils and adenoids, pharyngitis, laryngitis and tracheobronchitis
ii. Nasobronchial allergy and asthma
iii. Bronchiolitis
iv. Pneumonia and pulmonary suppuration (*S. pneumoniae, S. aureus, H. influenzae, Klebsiella, Chlamydia, Mycoplasma*, gram-negative bacilli, viral pneumonia)
v. Measles
vi. Whooping cough and related syndromes (*Bordetella pertussis*, parapertussis, respiratory syncytial virus, adenovirus)
vii. Foreign body in the air passage
viii. Empyema

Chronic and recurrent cough Causes are as follows:

i. Inflammatory disorders of airway, such as: (a) asthma; (b) infections, e.g. viral, bacterial, chlamydia, mycoplasma, tuberculosis, parasitic infections; (c) inhalation of environmental irritants such as tobacco smoke, dust; and (d) Löeffler syndrome.
ii. Suppurative lung disease, including: (a) bronchiectasis, (b) cystic fibrosis; (c) foreign body retained in bronchi; (d) congenital malformations, sequestrated lobe, or bronchomalacia; and (e) immunodeficiency or primary ciliary dyskinesia.
iii. Anatomic lesions, tumors, tracheal stenosis or H-type tracheoesophageal fistula.
iv. Miscellaneous causes, e.g. (a) psychogenic, habit cough; (b) postnasal discharge, sinusitis; (c) gastroesophageal reflux disease; and (d) interstitial lung disease.

Expectoration

Young children are not able to expectorate and usually swallow the respiratory secretions. Older children with chronic respiratory problems may be able to bring out expectoration. Common causes of expectoration are bronchiectasis due to various causes, lung abscess, bronchitis, asthma and tuberculosis. The amount and nature of expectoration may give clue about the cause of respiratory disease. Investigations such as cell count, Gram stain and culture or stain for AFB and culture help in diagnosis and guide for treatment.

Hemoptysis

Causes of hemoptysis in children include necrotizing pneumonia, foreign body aspiration, bleeding diathesis, cavitatory tuberculosis, idiopathic pulmonary hemosiderosis, mitral stenosis, dilated cardiomyopathy and Goodpasture syndrome.

Respiratory Noises

The intensity and pitch of respiratory sounds depend on their site of origin within the respiratory tract. The pitch of the sound keeps increasing and the intensity keeps decreasing with decreasing size of the respiratory tract (Table 14.1). For example, snoring is a highly intense but low pitched sound because it results from the oropharynx. Wheeze is a high pitched, less intense sound originating from lower airway obstruction. As a rule, extrathoracic airway obstruction produce inspiratory sounds. Intrathoracic major airway obstruction produces inspiratory as well as expiratory sounds while distal airway obstruction predominantly produce expiratory sounds.

Rattling

Rattling is due to excessive secretions in the pharynx or tracheobronchial tree during breathing. It is present in asthma, bronchitis and tracheobronchial stenosis. Inhalation of gastrointestinal content into the tracheobronchial tree can also result in rattling. Some normal infants may have transient rattling but prolonged rattling is pathological.

Wheezing

Wheezing refers to high pitched whistling sounds audible without auscultation. Partial obstruction of the bronchi and bronchioles produces wheezing. Sufficient air must flow through the narrowed airway to produce the wheezing sound. This may be due to causes within the lumen or in the walls of the bronchi. The causes of wheezing are listed below.

Wheeze associated lower respiratory tract infection Wheezing is most often due to heightened sensitivity of the respiratory tract. Infections of the lower respiratory passages may cause bronchospasm in these patients. Attacks of wheezing are always preceded by a cold or acute respiratory disease. These are most frequent between 3 and 8 yr of age and become less frequent thereafter. These attacks are relieved by bronchodilators.

Bronchiolitis (*see* page 381)

Bronchial asthma (*see* page 382)

Tropical eosinophilia This is more frequent in adults than in children. It is an unusual form of infection with filariasis, e.g. *Dirofilaria imitis, W. bancrofti, B. malayi*. Clinical features simulate chronic recurrent asthma. X-ray films show fine pulmonary infiltrates with snowflake appearance. This should be distinguished from miliary tuberculosis. The leukocyte count shows eosinophilia. The patients are treated with diethylcarbamazine (10 mg/kg) in 3 divided doses orally for 2 to 3 weeks. Two or three spaced courses may be given.

Löeffler syndrome The pulmonary phase of migration of ascaris larvae may cause wheezing, pulmonary problems and eosinophilia. These features are characteristically transient.

Inhaled foreign bodies cause unilateral localized wheeze which begin suddenly. Wheezing tends to be continuous and becomes worse with crying, during excitement and with cold.

Rare causes These include pressure from enlarged mediastinal nodes or from anomalous left pulmonary artery compressing the right main bronchus.

Cystic fibrosis Recurrent wheezing, productive cough and malabsorption are usual features. Some may have history of meconium ileus in the neonatal period.

Stridor

Stridor indicates upper respiratory obstruction and is usually accompanied by hoarseness, brassy cough, dyspnea, chest retractions and restlessness. Stridor is frequent in infants and is often attributed to (i) small size of the larynx; (ii) loose submucous connective tissue around the glottic region; and (iii) rigid cricoid cartilage encircling the subglottic zone.

Acute stridor Acute upper airway obstruction occurring in the region of glottis which is produced by inflammation and edema may be life-threatening. The obstruction may either be supraglottic as in epiglottitis or subglottic as in infectious croup (Table 14.2).

Table 14.2: Stridor due to supraglottic and tracheal obstruction

Clinical features	*Supraglottic obstruction*	*Tracheal obstruction*
Stridor	Inspiratory and often less serious	Usually expiratory and more serious
Cry	Muffled	Normal
Dyspnea	Less severe	More marked
Cough	Less marked	Deep barking or brassy

Table 14.1: Respiratory sounds

Sound	*Cause*	*Character*
Snoring	Oropharyngeal obstruction	Inspiratory, low-pitched, irregular
Grunting	Partial closure of glottis	Expiratory; occurs in hyaline membrane disease
Rattling	Secretions in trachea or bronchi	Inspiratory, coarse; can be felt by placing hands over the chest
Stridor	Obstruction larynx or trachea	Inspiratory; may be associated with an expiratory component
Wheeze	Lower airway obstruction	Continuous musical sound, predominantly expiratory in nature

Chronic stridor Common causes are listed below:

Congenital laryngeal stridor. This is caused by flaccidity (laryngomalacia) or easy collapsibility of the aryepiglottic folds or epiglottis. This condition usually manifests by the end of the first week or during the second week afterbirth. The stridor is characteristically intermittent and is aggravated by crying or feeding. It is modified in sleep or by the change of posture. The loud inspiratory sound frightens the parents but the infant is relatively less symptomatic. Respiratory distress and chest retraction are absent or minimal. Feeding behavior and activity of the infant are generally normal. Breathing difficulty may be significant, if micrognathia and cleft palate are also associated. Congenital laryngeal stridor disappears spontaneously by the age of six months to one year. These infants are more prone to develop aspiration of feeds and frequent lung infection.

Congenital laryngeal or tracheal stenosis or web. Cry of the infant is weak and hoarse, breathing is labored and the air entry in lungs is reduced. In subglottic tracheal stenosis, the cry is unaffected and the stridor is both inspiratory and expiratory.

Laryngeal cysts or neoplasm. Angioma, papilloma, lymphangioma and retention cysts may be responsible for stridor.

Neurogenic stridor. Bilateral vocal cord paralysis results from brainstem injury. Unilateral paralysis is due to the involvement of the peripheral nerve. The left recurrent laryngeal nerve is more liable to injury since it has a longer course and hooks around the aorta from the front to back.

Extrinsic obstruction. Vascular rings cause intermittent stridor that becomes worse when the neck is flexed. The infant prefers to keep the head in the position of hyperextension. Other causes of external airway compression are mediastinal goiter, lymphangioma and thyroglossal duct cyst. Congenital goiters which cause respiratory obstruction and stridor are due to maternal intake of antithyroid drugs and iodides during pregnancy. Goiter of neonatal hypothyroidism and that due to defect in the synthesis of thyroid hormones are usually not so big as to cause stridor.

Miscellaneous causes. Stridor is common in infants with hydrocephalus and those with Down syndrome. Other causes include micrognathia and glossoptosis, macroglossia and diaphragmatic hernia.

Treatment The diagnosis of congenital laryngeal stridor can be established only by direct laryngoscopy. Fluoroscopy after barium swallow should be done to rule out the extrinsic causes of obstruction. Tumors and cysts require surgical excision. Corticosteroids hasten the recovery in laryngeal edema. Congenital laryngeal stridor does not require treatment. Gavage feeding is done if the respiratory distress is marked. Congenital goiter caused by the administration of antithyroid drugs or iodides to the mother during pregnancy is treated with triiodothyronine and Lugol's iodine.

Dyspnea

Tachypnea refers to abnormally rapid respiration, while dyspnea means labored or difficult breathing, usually accompanied by pain and air hunger. The causes of dyspnea range from illnesses affecting the lungs, heart and musculoskeletal system.

Epistaxis

Epistaxis or bleeding from the nose is rare in children below the age of 3 yr. It may occur due to local or systemic causes. Local causes include: (i) trauma to nose caused by nose picking, (ii) capillary malformations in the Little's area, (iii) foreign body, (iv) bleeding polyps of the septum, and (v) allergic rhinitis and nasal diphtheria. Systemic causes of epistaxis are: (i) hypertension, (ii) blood dyscrasia, (iii) emphysema, and (iv) pertussis.

Pressure on alae nasi for 10 min controls bleeding in most cases of epistaxis. In resistant cases, the nasal mucosa is plugged with gauze piece soaked in 1:10,000 solution of adrenaline hydrochloride as a temporary measure. Plugging of the nose for a prolonged period (>48 hr) should be avoided. The bleeding points should be identified and cauterized with silver nitrate solution. Nasal bleed due to systemic causes should be evaluated and treated appropriately. The child should receive treatment with iron supplements to raise hemoglobin level. Profuse bleeding is more likely to be from the posterior aspect from sphenopalatine vessels. Cauterization is ineffective in these vessels. Firm anterior and posterior packing is done. Blood dyscrasia if present should be appropriately treated.

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INVESTIGATIONS FOR RESPIRATORY ILLNESSES

Bronchoscopy

Bronchoscopy can be of two types, fiberoptic and rigid. Fiberoptic bronchoscopy is done under local anesthesia and sedation. This is used for diagnosis of structural abnormality of airways, diagnosis of foreign body and for obtaining bronchoalveolar lavage samples to identify cell type and infective etiology of lower respiratory tract. Rigid bronchoscopy can be used in place of fiberoptic bronchoscopy. This is commonly used for removal of foreign bodies from airways or obtaining biopsy from airway tumors.

Pulmonary Function Tests

Pulmonary function tests (PFT) are important tools for monitoring of a patient with chronic respiratory illness. Flow rates and lung volumes are measured. The proce-

dure requires cooperation of the patient. PFT may be performed in children above the age of 5–7 yr. Commonly used parameters include: forced expiratory volume in first second (FEV1), forced vital capacity (FVC), mid-expiratory flow rate and ratio of FEV1/FVC. Normal FEV1/FVC ratio is between 0.8 and 1.0. In obstructive diseases (asthma) the ratio is reduced. In restrictive lung diseases (interstitial lung disease), the ratio of FEV1/FVC is normal but FVC is reduced below 80% of predicted.

Blood Gas Analysis

Estimation of partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in blood along with blood pH gives a fair estimate of pulmonary functions. Arterial blood gas analysis is useful in making a diagnosis of respiratory failure as well as for monitoring children with acute and chronic respiratory failure. PaO_2 below 60 mm Hg and $PaCO_2$ over 50 mm Hg suggest acute respiratory failure.

Imaging

Noninvasive diagnostic methods include X-rays, most commonly used to diagnose pulmonary infections and computerized tomography scans, used for visualization of lymph nodes, tumors, bronchiectasis and pleural pathologies.

Sweat Chloride Test

Chloride in sweat is increased in children suffering from cystic fibrosis. Sweat chloride is estimated by quantitative pilocarpine iontophoresis. Values of sweat chloride in normal children is less than 40 mEq/l. Patients with cystic fibrosis show levels more than 60 mEq/l.

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RESPIRATORY TRACT INFECTIONS

Common Cold or Nasopharyngitis

Common cold is a frequent illness in childhood and is usually caused by infections of the upper respiratory tract with adenoviruses, influenza, rhinovirus, parainfluenza or respiratory syncytial viruses. These are spread by droplet infection. Predisposing factors include chilling, sudden exposure to cold air and overcrowding. Rhinitis could also be due to allergy.

Clinical features include fever, thin nasal discharge and irritability. Cervical lymph nodes may enlarge. Naso-pharyngeal congestion causes nasal obstruction and respiratory distress. The latter is more pronounced in young infants. Eustachian tube opening may be blocked leading to serous otitis media and congestion of tympanic membrane. In allergic rhinitis there is a clear mucoid discharge with sneezing.

Narrowing of the airway and pharyngeal irritation causes dry hacking cough. Excessive lacrimation is due to the blocked lacrimal ducts in the nose. Nasal discharge may become purulent, if secondarily infected especially in younger children. Purulent discharge does not necessarily mean secondary infection as it can result from shedding of epithelial and inflammatory cells resulting from viral infection itself. The illness usually lasts for three days but cold may persist up to two weeks.

Complications include otitis media, laryngitis, sinusitis, bronchiolitis, exacerbation of asthma and broncho-pneumonia.

Differential diagnosis include the presence of foreign body which presents with unilateral serosanguineous or purulent discharge from a nostril. The intermittent use of rifampicin may cause flu-like syndrome in some children. Drugs like reserpine and prochlorperazine cause nasal stuffiness. Clear mucoid discharge from the nose in the first few weeks of life is called snuffles. *Snuffles* of congenital syphilis is severe rhinitis with bilateral serosanguineous discharge commonly excoriating the upper lip and leaving fine scars. Nasal strictures may ulcerate leaving a flat nasal bridge.

Treatment

Relieve nasal congestion. Babies sneeze and blow out the nasal discharge, if their anterior nares are tickled by the tip of a handkerchief. Nose drops of saline may give symptomatic relief. Nasal decongestants (ephedrine, xylometozoline) may cause rebound congestion. These should not be used routinely and used only in refractory cases for limited duration. Antihistaminics are best avoided in the first six months of life, but give symptomatic relief by drying up thin secretions and relieving sneezing. Nonsedating agents, e.g. loratidine and cetirizine may be used in allergic rhinitis. Terfenadine should not be prescribed in children because of potential cardiotoxicity.

Fever is controlled by antipyretics such as paracetamol (acetaminophen). Cough syrups should not be given. If the cough is suppressed in infants and young children, mucoid secretions may be retained in the bronchi and this may predispose to spasmodic cough, wheezing, atelectasis and suppuration.

Antibiotics are of little value in viral infections. These are used if the secretions become purulent, the fever continues to rise and if the child develops bronchopneumonia. There is no evidence that large doses of vitamin C are helpful. The children should be protected from sudden exposure to chills and kept warm during the winter months.

Acute Tonsillopharyngitis

Sore throat is due to acute inflammation of the pharynx and tonsils. Most often, it is associated with the viral infections

of the upper respiratory tract such as adenovirus, influenza, parainfluenza virus, enterovirus and Epstein-Barr virus. It may, however, be a prodrome of measles and rubella or may be caused by *S. pyogenes* especially group A beta-hemolytic streptococci. *Mycoplasma pneumoniae* and *Candida albicans* have also been incriminated.

Clinical features of tonsillopharyngitis include fever, malaise, headache, nausea and sore throat. Younger children may not complain of sore throat but often refuse to feed normally. It is difficult to distinguish the clinical syndromes due to viral or streptococcal infections. Hoarseness, cough and rhinitis are more common in viral infection. In these, the onset is gradual and there is less toxemia. In streptococcal infections, cervical lymph nodes are enlarged, the illness is acute with high fever and there is absence of nasal discharge or conjunctivitis. Tonsils are swollen and covered with exudates in both types of infections.

A possibility of acute pharyngitis due to group A beta-hemolytic streptococci may be considered in a patient who has exudates in throat, tender enlarged cervical nodes along with absence of nasal or conjuctival congestion. Throat swab culture for group A beta-hemolytic streptococci helps in the definitive diagnosis. A rapid antigen detection test (RADT) for identification of group A beta-hemolytic *Streptococcus* gives the result within 10 min and has moderate (80–90%) sensitivity and high (>95%) specificity. Enzyme immunoassays are preferred to latex agglutination tests. Testing for antistreptolysin O (ASO) and anti DNAase B antibodies is not useful.

Complications of sore throat include acute glomerulonephritis, rheumatic fever, otitis media, sinusitis and peritonsillar and retropharyngeal abscesses. The infection may spread down the tracheobronchial tree to cause tracheobronchitis and pneumonia.

Differential Diagnosis

Herpangina is an acute febrile illness due to group A Coxsackie virus. Patients have dysphagia, sore throat and papulovesicular lesions surrounded by erythema over the tongue, pharynx, anterior tonsillar pillars and soft palate. Pharynx appears congested. Diphtheria is characterized by moderate fever, severe toxemia, sore throat and membrane formation over the fauces or palate. Patients with pharyngoconjunctival fever have fever, conjunctivitis, pharyngitis and cervical lymphadenitis due to infection with adenovirus type 3. Infectious mononucleosis is characterized by lymphadenopathy, morbilliform rash, hepatosplenomegaly and sometimes, aseptic meningitis.

Treatment

Warm saline gargles are prescribed for older children. Younger children are encouraged to sip warm tea/liquids. Paracetamol is administered for fever. Soft food such as custard or rice and lentil gruel is given because swallowing is painful. Oral antihistaminics, e.g. chlorpheniramine or promethazine are useful in symptomatic relief. However, routine use of cough suppressants (e.g. dextromethorphan, codeine) and expectorants (ambroxol, guaifensin) should be avoided.

Antibiotics are not required in patients with viral infections. Patients with documented streptococcal infection (i.e. by throat culture or RADT) should receive antibiotic therapy in order to decrease the duration of symptoms, reduce morbidity and prevent complications. Options of oral treatment include (i) penicillin V 250 mg q 8–12 hr, (ii) amoxycillin 30–40 mg/kg/day, (iii) erythromycin 40–50 mg/kg/day or (iv) cephalexin 50 mg/kg/day, given for 10 days; or (v) azithromycin 10–12 mg/kg/day for 5 days. Where noncompliance is likely, a single intramuscular injection of benzathine penicillin (0.6–1.2 MU) may be given. Cotrimoxazole, which is commonly used for sinusitis and otitis media, is not an appropriate medication for sore throat.

The therapy for diphtheria is described in Chapter 10.

Recurrent Sore Throat

A detailed history is obtained and physical examination conducted. Paranasal sinuses and ears should be examined for the foci of infection. Smoky and dusty atmosphere should be avoided. Dampness in the environment and overcrowding predispose the child to recurrent upper respiratory tract infections.

Each episode of bacterial pharyngitis should be treated with adequate doses of antibiotics for at least 10 days. Presence of beta-lactamase producing bacteria in the pharynx may inactivate penicillin and lead to recurrent sore throat. This should be treated with amoxycillin plus clavulinic acid or clindamycin. In selected cases, penicillin prophylaxis may be administered for 3–6 months, especially if group A beta-hemolytic streptococcal infection is present.

Tonsillectomy is often recommended for recurrent attacks of sore throat. It does not prevent recurrence of pharyngeal infections. Tonsillectomy should be advised only if there are more than 5–6 episodes of tonsillitis in a year or tonsillar or peritonsillar abscess. It may reduce the incidence of infection with group A beta-hemolytic streptococcus. Tonsillectomy is recommended in diphtheria carriers, in presence of retention cysts in tonsils or if the tonsils are a focus of infection for suppurative otitis media. There is no indication for tonsillectomy after rheumatic fever or glomerulonephritis.

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ACUTE LOWER RESPIRATORY TRACT INFECTIONS

Acute lower respiratory tract infections are the leading cause of death in children below 5 yr of age. These include croup syndromes, bronchitis, bronchiolitis and pneumonia.

Croup

The term croup is used for a variety of conditions in which a peculiar brassy cough is the main presenting feature. Inspiratory stridor, hoarseness or respiratory distress may not always be associated with croup. The diseases include acute epiglottitis, laryngitis, laryngotracheobronchitis and spasmodic laryngitis.

Epiglottitis

Supraglottitis includes both epiglottitis and inflammatory edema of the hypopharynx. *Haemophilus influenzae* type B is the most frequent cause. Other microbes like *pneumococcus*, beta-hemolytic *Streptococcus* and *Staphylococcus* are not common etiologies. The illness usually starts with a minor upper respiratory tract illness which progresses rapidly within the course of a few hours. The child suffers from high fever and has difficulty in swallowing. The breathing becomes noisy but is generally softer than in case of laryngotracheobronchitis. The child is not able to phonate and often sits up leaning forwards with his neck extended and saliva dribbling from his chin which appears to be thrust forwards. The accessory muscles of respiration are active and there is marked suprasternal and subcostal retraction of the chest. As the child becomes fatigued, the stridor diminishes. The diagnosis of epiglottitis is made by a cautious direct laryngoscopy, wherein the epiglottis appears angry red and swollen. Injudicious attempt to examine the throat may, rarely, cause death by sudden reflex spasm of the larynx. It is therefore prudent not to force a child, panting for breath, to lie down for throat examination or to send him to the radiology department for an urgent X-ray film if the clinical diagnosis is otherwise obvious. In case these procedures are considered essential, the equipment and personnel for respiratory resuscitation should always be readily available.

Laryngitis and Laryngotracheobronchitis (Infectious croup)

These conditions are nearly always caused by viral infections, usually with parainfluenza type 1. Other viruses incriminated include respiratory syncytial and parainfluenza types 2 and 3, influenza virus, adenovirus and rhinovirus. Bacterial etiology or bacterial superinfection are unusual. In infectious croup, the onset of the illness is more gradual. Usually, there is a mild cold for a few days before the child develops a brassy cough and mild inspiratory stridor. As the obstruction increases, the stridor becomes more marked and the suprasternal and sternal recession with respiration become manifest. The child becomes restless and anxious with fast breathing due to increasing hypoxemia. Eventually cyanosis appears. As the obstruction worsens, breath sounds may become inaudible and stridor may apparently decrease. This may unfortunately be misinterpreted as clinical improvement by an unwary physician.

Spasmodic Croup

It occurs in children between the age of 1 and 3 yr. There is sometimes no preceding coryza. The child wakes up suddenly in the early hours of the morning with brassy cough and noisy breathing. The symptoms improve within a few hours. The illness may recur on subsequent days. The course is generally benign and patients recover completely. The cause is unknown. Humidification of the room in which the child is nursed is all that is necessary.

Differential Diagnosis

The syndromes of croup should be distinguished from each other and also from the croup associated with diphtheria in which a membrane is seen on laryngoscopy or occasionally with measles. Rarely the croup may result from angioneurotic edema. A retropharyngeal abscess may cause respiratory obstruction. Aspiration of a foreign body is an important cause of obstruction. It may be rarely confused with wheezing in asthma.

Management

A child with epiglottitis needs hospitalization. Humidified oxygen should be administered by hood. Face masks are not well tolerated by these children. As oxygen therapy masks cyanosis, a careful watch should be kept for impending respiratory failure. Sedatives should not be given. Unnecessary manipulation of the patient may induce laryngeal spasm. Fluids should be administered for adequate hydration of the patient by intravenous route. Antibiotics such as cefotaxime or ceftriaxone 100 mg/kg/day is recommended in patients with epiglottitis, but not in laryngotracheobronchitis or laryngitis. Endotracheal intubation or tracheostomy may be indicated if the response to antibiotics is not adequate and obstruction is worsening.

A child with acute laryngotracheobronchitis should be assessed for severity of illness on basis of general appearance, stridor (audible with or without stethoscope), oxygen saturation and respiratory distress (Table 14.3). Mild cases can be managed on ambulatory basis with symptomatic treatment for fever and encouraging the child to take liquids orally. Parents may be explained about the progression of diseases and to bring the child back to hospital in case of worsening of symptoms.

A patient with moderately severe illness may need hospitalization and treatment with nebulised epinephrine (1:1000 in doses of 0.1–0.5 ml/kg to a maximum dose of 5 ml administered through nebulizer for immediate relief of symptoms. While epinephrine acts rapidly to decrease vascular permeability, airway edema and improves

Table 14.3: Assessment of severity of acute laryngotracheobronchitis

	Mild	*Moderate*	*Severe*
General appearance	Happy, feeds well, interested in surroundings	Irritable but can be comforted by parents	Restless or agitated or altered sensorium
Stridor	Stridor on coughing; no stridor at rest	Stridor at rest; worsens when agitated	Stridor at rest; worsens when agitated
Respiratory distress	No distress	Tachypnea and chest retractions	Marked tachypnea with chest retractions
Cyanosis	Absent	Absent	May be present
Oxygen saturation in room air	>92%	>92%	<92%

airflow, the action is temporary and repeat administration may be necessary at 2–4 hr. Recent studies have shown that a single intramuscular dose of dexamethasone (0.3–0.6 mg/kg) reduces disease severity in the first 24 hr with decreased need of intubation and adrenaline nebulization and shortened duration of hospital stay. Inhalation of budesonide in doses of 1 mg twice a day for two days is useful.

Severe croup may need hospitalization, preferably in intensive care, with oxygen inhalation and need for steroids (similar to moderate severity). Worsening distress may need short term ventilation.

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Pneumonia

Pneumonia may be classified anatomically as lobar or lobular pneumonia, bronchopneumonia and interstitial pneumonia. Pathologically, there is a consolidation of alveoli or infiltration of the interstitial tissue with inflammatory cells or both.

Etiology

Viral pneumonia caused by respiratory syncytial virus, influenza, parainfluenza or adenovirus may be responsible for about 40% of the cases. In over two-thirds of the cases, common bacteria cause pneumonia. In the first 2 months, the common agents include gram-negative bacteria such as *Klebsiella*, *E. coli* and gram-positive organisms like pneumococci and staphylococci. Between 3 months and 3 yr common pathogens include *S. pneumoniae*, *H. influenzae* and staphylococci. After 3 yr of age, common bacterial pathogens include pneumococci and staphylococci. Gram-negative organisms cause pneumonia in early infancy, severe malnutrition and immunocompromised children.

Atypical organisms including *Chlamydia* and *Mycoplasma* spp. may cause community acquired pneumonia in adults and children. *Pneumocystis jiroveci*, histoplasmosis and coccidioidomycosis may cause pneumonia in immunocompromised children.

Other causes of pneumonia include ascaris, aspiration of food, oily nose drops, liquid paraffin and kerosene poisoning. The etiology remains unknown in one-third of cases of pneumonia.

Clinical Features

Risk factors for pneumonia include low birth weight, malnutrition, vitamin A deficiency, lack of breastfeeding, passive smoking, large family size, family history of bronchitis, advanced birth order, crowding, young age and air pollution. Indoor air pollution is one of the major risk factor for acute lower respiratory tract infection in children in developing countries. Onset of pneumonia may be insidious starting with upper respiratory tract infection or may be acute with high fever, dyspnea and grunting respiration. Respiratory rate is always increased.

Rarely, pneumonia may present with symptoms of acute abdominal emergency. This is attributed to referred pain from the pleura. Apical pneumonia may be associated with meningismus and convulsions. In these patients the cerebrospinal fluid is always clear.

On examination, there is flaring of alae nasi, retraction of the lower chest and intercostal spaces. Signs of consolidation are present in lobar pneumonia.

Pneumococcal Pneumonia

Respiratory infections due to *S. pneumoniae* are transmitted by droplets and are more common in the winter months. Overcrowding and diminished host resistance predisposes the children to infection with pneumococci. Bacteria multiply in the alveoli and an inflammatory exudate is formed. Scattered areas of consolidation occur, which coalesce around the bronchi and later become lobular or lobar in distribution. There is no tissue necrosis. Pathological process passes from the stage of congestion to red and gray hepatization before the final stage of resolution.

Clinical features. Incubation period is 1 to 3 days. The onset is abrupt with headache, chills, cough and high fever. Cough is initially dry but may be associated with thick

rusty sputum. Child may develop pleuritic chest pain. Respiration is rapid. In severe cases there may be grunting, chest indrawing, difficulty in feeding and cyanosis. Percussion note is impaired, air entry is diminished, crepitations and bronchial breathing may be heard over areas of consolidation. Bronchophony and whispering pectoriloquy may be observed. Meningismus may be present in apical pneumonia.

Diagnosis. The diagnosis is based on history, physical examination, X-ray findings of lobar consolidation (Fig. 14.1) and leukocytosis. Bacteriological confirmation is difficult; sputum is examined by Gram staining and culture. Blood culture may be positive in 5–10% of cases. Demonstration of polysaccharide antigen in urine and blood do not have sufficient specificity for confirming pneumococcal pneumonia as it may be also be positive in children with colonization in throat.

Treatment. Antibiotic therapy may be empiric while awaiting confirmation of etiology. While the treatment of choice for pneumococcal pneumonia is penicillin (penicillin V 250 mg q 8–12 hr orally, penicillin G 0.5 MU/kg/day IV or procaine penicillin 0.6 MU IM daily, for 7 days), amoxycillin (30–40 mg/kg/day for 7 days) with or without clavulanic acid is a useful alternative.

The need for oxygen administration should be guided by signs of respiratory distress (rapid breathing, chest retractions, nasal flare), presence of cyanosis or hypoxemia on pulse oximetry. Patients may be dehydrated, and require IV fluids. Fever should be managed with paracetamol.

Staphylococcal Pneumonia

Staphylococcal pneumonia occurs in infancy and childhood. The pulmonary lesion may be primary infection of the parenchyma; or may be secondary to generalized staphylococcal septicemia. It may be a complication of measles or influenza; other risk factors include cystic fibrosis, malnutrition and diabetes.

In infants, the pneumonic process is diffuse initially, but soon the lesions suppurate, resulting in bronchoalveolar destruction. The illness is characterized by the formation of multiple pneumatoceles. The pneumatoceles fluctuate in size and finally resolve and disappear within a period of few weeks to months. Staphylococcal abscesses may erode into the pericardium causing purulent pericarditis. Empyema in a child below two yr of age is nearly always secondary to staphylococcal infections.

Clinical manifestations. The illness usually follows upper respiratory tract infection, pyoderma or a purulent disease. The patient is toxic and sick looking. Cyanosis may be present. Progression of the symptoms and signs is rapid. Pulmonary infection may occasionally be complicated by disseminated disease, with metastatic abscesses in joints, bone, muscles, pericardium, liver, mastoid or brain.

Diagnosis. The diagnosis of staphylococcal pneumonia is suspected in a newborn or an infant with respiratory infection who has evidence of staphylococcal infection elsewhere in the body. The characteristic complications of pyopneumothorax and pericarditis are highly suggestive. Pneumatoceles are present in X-ray films (Fig. 14.2), characteristically in pneumonia due to staphylococci or *Klebsiella*. These pneumatoceles persist as thin walled asymptomatic cysts for several weeks. Staphylococci can be cultured from the blood.

Treatment. The child should be hospitalized and isolated to prevent the spread of resistant staphylococci to the other patients. Fever is controlled with antipyretics; intravenous fluids may be required. Oxygen is administered to relieve dyspnea and cyanosis.

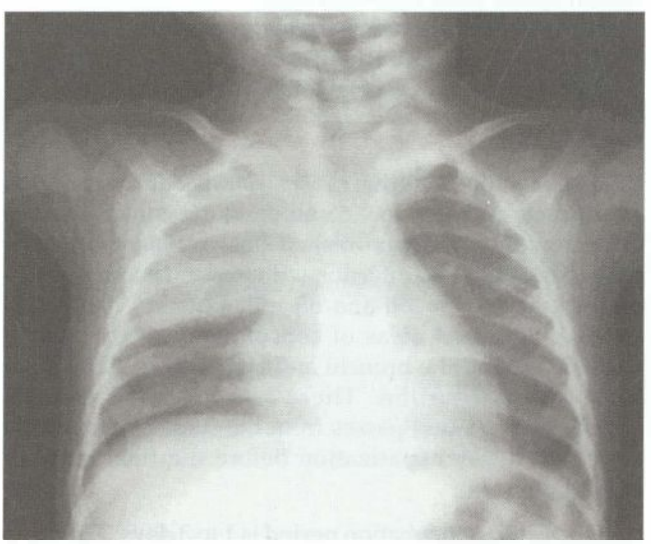

Fig. 14.1: Consolidation of right upper lobe due to infection with *Streptococcus pneumoniae*

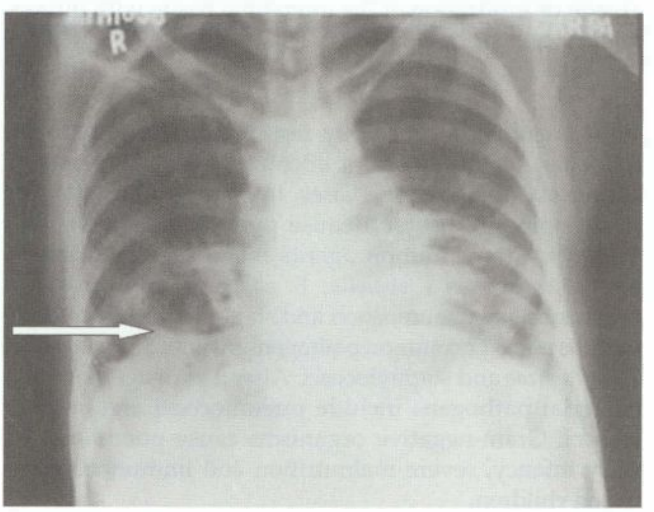

Fig. 14.2: *Staphylococcal pneumonia.* Note multiple pneumatoceles (arrow)

Empyema is aspirated and the pus is sent for culture and sensitivity. Prompt antibiotic therapy should be initiated with coamoxiclav, or a combination of cloxacillin and a third-generation cephalosporin, e.g. ceftriaxone. If the patient does not show improvement in symptoms within 48 hr, therapy with vancomycin, teicoplanin or linezolid may be necessary. Therapy should continue till all evidence of the disease disappears both clinically and radiologically, which usually takes 2 weeks in uncomplicated cases. Therapy is continued for 4–6 weeks in patients with empyema or pneumothorax. Following initial IV therapy, the remaining course may be completed with oral antibiotics.

Complications. Pneumatoceles do not require specific measures. Empyema and pyopneumothorax are treated by intercostal drainage under water seal or low pressure aspiration. Metastatic abscesses require surgical drainage. Significant pleural thickening that prevents complete expansion of the underlying lung may require decortication. Early thoracoscopic drainage of empyema helps prevent pleural thickening. Installation of streptokinase or urokinase in pleural cavity or loculated pleural effusion may also be useful.

Haemophilus Pneumonia

Haemophilus influenzae infections occur usually between the age of three months and three years and are nearly always associated with bacteremia. Infection usually begins in the nasopharynx and spreads locally or through the bloodstream. Most nasopharyngeal infections are mild and confer immunity from subsequent serious illness after the early months of life. As the infants have transplacentally transferred antibodies during the first 3 to 4 months of life, infections are relatively less frequent during this period.

Clinical features. The onset of the illness is gradual with nasopharyngeal infection. Certain viral infections such as those due to influenza virus act synergistically with *H. influenzae*. The child has moderate fever, dyspnea, grunting respiration and retraction of the lower intercostal spaces.

Complications include bacteremia, pericarditis, empyema, meningitis and polyarthritis.

Treatment. Haemophilus infection is treated with ampicillin at a dose of 100 mg/kg/day or coamoxiclav. Cefotaxime (100 mg/kg/day) or ceftriaxone (50–75 mg/kg/day) are recommended in seriously ill patients.

Streptococcal Pneumonia

Infection of the lungs by group A beta hemolytic streptococci is secondary to measles, chickenpox, influenza or whooping cough. Group B streptococcal pneumonia is an important cause of respiratory distress in newborns. Pathologically it causes interstitial pneumonia, which may be hemorrhagic. Tracheobronchial mucosa may be ulcerated and lymph nodes enlarged. Serosanguineous or thinly purulent pleural effusion is frequently associated.

Clinical feature. The onset is abrupt with fever, chills, dyspnea, rapid respiration, blood streaked sputum, cough and extreme prostration. Signs of bronchopneumonia are generally less pronounced, as the pathology is usually interstitial. X-ray film shows interstitial pneumonia, segmental involvement, diffuse peribronchial densities or an effusion.

Complications. Thin serosanguineous or purulent empyema is a usual complication. Pulmonary suppuration is less frequent. Ten percent of the patients have bacteremia. When pneumatoceles are present, the condition mimics staphylococcal pneumonia.

Treatment. Therapy for streptococcal pneumonia is carried out as outlined for pneumococcal pneumonia. The response is gradual but recovery is generally complete. Empyema is treated by closed drainage with indwelling intercostal tube.

Primary Atypical Pneumonia

The etiological agent of primary atypical pneumonia is *Mycoplasma pneumoniae.* The disease is transmitted by droplet infection, chiefly in the winter months. The illness is uncommon in children below the age of four yr, although subclinical and mild infections are reported in infants.

Primary atypical pneumonia involves the interstitial tissue with round cell infiltration. The alveolar septae are edematous and mucosa of the bronchioles is inflamed and ulcerates. Obstruction of the terminal bronchioles causes emphysema and atelectasis. Pleura may show patchy fibrinous exudates.

Clinical features. Following an incubation period of 12–14 days, patients have malaise, headache, fever, sore throat, myalgia and cough. Cough is dry at first but later associated with mucoid expectoration, which may be blood streaked. Dyspnea is unusual. There are very few physical signs, except mild pharyngeal congestion, cervical lymphadenopathy and few crepitations. Hemolytic anemia may be seen.

X-ray findings are more extensive than suggested by the physical findings. Poorly defined hazy or fluffy exudates radiate from the hilar regions. Enlargement of the hilar lymph nodes and pleural effusion are reported. Infiltrates involve one lobe, usually the lower.

Diagnosis. It is difficult to distinguish *Mycoplasma pneumonia* from viral or rickettsial pneumonia. The leucocyte count is usually normal. Cold agglutinins are elevated in many patients. *M. pneumoniae* may be cultured from the pharynx and sputum. The diagnosis is made rapidly by demonstration of IgM antibody by ELISA during the acute stage. IgG antibodies are seen on a complement fixation test after one week of illness.

Treatment. Patients are treated with macrolide antibiotics (erythromycin, azithromycin or clarithromycin) or tetracycline (for older children) for 7 to 10 days.

Chlamydia Pneumoniae

It may cause pneumonia in young infants. Clinical features include spasmodic cough. A history of purulent conjunctivitis during early neonatal period may be present.

Pneumonia Due to Gram-negative Organisms

The etiological agents are *E. coli*, *Klebsiella* and *Pseudomonas*. These organisms affect small children (<1 yr of age) or children with malnutrition and deficient immunity. *Pseudomonas* may colonize airways of patients with cystic fibrosis and causes recurrent pulmonary exacerbations. The clinical features are similar, but patients can be very sick. Signs of consolidation are minimal, particularly in infants. Constitutional symptoms are more prominent than respiratory distress. X-ray shows unilateral or bilateral consolidation. Infection with *E. coli* or *Klebsiella pneumoniae* may be associated with pneumatoceles.

Treatment. Intravenous use of third generation cephalosporins (cefotaxime or ceftriaxone, 75–100 mg/kg/day) with or without an aminoglycoside is recommended for 10 to 14 days. Ceftazidime or piperacillin-tazobactam are effective in patients with *Pseudomonas* infection.

Viral Pneumonias

Respiratory syncytial virus is the most important cause in infants under 6 months of age. At other ages, influenza, parainfluenza and adenoviruses are common. The bronchial tree or alveoli are involved resulting in extensive interstitial pneumonia. Features of consolidation are usually not present. Radiological signs consist of perihilar and peribronchial infiltrates.

Ingestion of Aliphatic Hydrocarbons

Kerosene exerts its toxic effects on the lungs and the central nervous system. It is poorly absorbed from the gastrointestinal tract. Milk and alcohol promote its absorption. It has low viscosity and less surface tension, and therefore, diffuses quickly from the pharynx into the lungs. Administration of oil apparently decreases its absorption from the gastrointestinal tract but is not recommended. Clinical features of hydrocarbon pneumonia include cough, dyspnea, high fever, vomiting, drowsiness and coma. Physical signs in lungs are minimal. X-ray film of the chest shows ill defined homogeneous or patchy opacities; occasionally features resemble miliary mottling.

Vomiting is not induced. Gastric lavage is usually avoided to prevent inadvertent aspiration. The patient is kept on oxygen. The routine use of antibiotics and/or corticosteroids is not recommended.

Löeffler Syndrome

Larvae of many nematodes, during their life cycle, enter the portal circulation, liver and then through the hepatic vein and inferior vena cava into the heart and lungs. In the lungs, the larvae penetrate the capillaries, enter the alveoli, plug the bronchi with mucus and eosinophilic material due to allergic reaction. There are fleeting patchy pulmonary infiltrations. Some cases may be due to drug reaction to aspirin, penicillin, sulfonamide or imipramine.

Clinical features include cough, low fever, feeling unwell and scattered crepitations. There is eosinophilia and X-ray lungs shows pulmonary infiltrates of varying size, which superficially resemble miliary tuberculosis. Treatment is symptomatic.

Suggested Reading

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Acute Respiratory Tract Infection (ARTI) Control Program

Acute lower respiratory tract infection (LRTI) is a leading cause of mortality in children below 5 yr of age. The etiological agent is bacterial in 50–60% children. The common bacteria causing LRTI in preschool children include *H. influenzae*, *S. pneumoniae* and staphylococci. All these agents are sensitive to antibacterials like cotrimoxazole. Hence, judicious use of cotrimoxazole in children suffering from LRTI may prevent death due to pneumonia. World Health Organization (WHO) has recommended certain criteria for diagnosis of pneumonia is children at primary health care level for control of LRTI deaths in developing countries where the infant mortality is more than 40/1000 live births. Clinical criteria for diagnosis of pneumonia include rapid respiration with or without difficulty in respiration. Rapid respiration is defined as respiratory rate of more than 60, 50 or 40 per minute in children below 2 months of age, 2 months to 1 yr, and 1 to 5 yr of age, respectively. Difficulty in respiration is defined as lower chest indrawing.

The World Health Organization recommends that, in a primary care setting, if a child between 2 months and 5 yr of age presents with cough he should be examined for rapid respiration, difficulty in breathing, presence of cyanosis or difficulty in feeding (Table 14.4). If the respiration is normal and there is no chest indrawing and difficulty in feeding, the patient is assessed to be having an upper respiratory tract infection and can be managed

Table 14.4: WHO clinical classification for treatment in children aged 2 mo to 5 yr with cough or difficult breathing

Signs, symptoms	*Classification*	*Therapy*	*Where to treat*
Cough or cold No fast breathing, chest indrawing or indicators of severe illness	No pneumonia	Home remedies	Home
Increased respiratory rate <2 mo-old: ≥60 per min 2–12 mo-old: ≥50 per min 12–60 mo-old: ≥40 per min	Pneumonia	Cotrimoxazole or amoxicillin	Home
Chest indrawing	Severe pneumonia	IV/IM penicillin	Hospital
Cyanosis, severe chest indrawing, inability to feed	Very severe pneumonia	IV penicillin + gentamicin	Hospital

at home. If the child has rapid respiration but there is no chest indrawing, he/she is suffering from pneumonia and can be managed at home with oral cotrimoxazole for 5 days.

Patients with chest indrawing are considered to have severe pneumonia and need hospitalization and therapy with parenteral penicillin. The presence of severe chest indrawing or cyanosis indicates very severe pneumonia, requiring hospital admission and therapy with IV penicillin (or ampicillin) with gentamicin and supportive care.

In children below 2 months of age presence of any of the following indicates severe disease: fever (38°C or more), convulsions, abnormally sleepy or difficult to wake, stridor in a calm child, wheezing, not feeding, tachypnea, chest indrawing, altered sensorium, central cyanosis, grunting or apneic spells and distended abdomen. Such children should be referred to hospital for admission and treated with parenteral ampicillin and gentamicin along with supportive care.

Suggested Reading

Basis for WHO recommendations on the management of pneumonia in children at first level health facilities. WHO/ARI/91.20 Geneva: World Health Organization, 1991

Bronchiolitis

This is a common, serious acute lower respiratory infection in infants. Affected infants are between the ages of 1 and 6 months, but the disease can affect children up to their second birthday. Disease usually occurs in winter and spring. Respiratory syncytial virus (RSV) is implicated in most cases. Other causative organisms include parainfluenza virus, adenovirus, influenza viruses and rarely *M. pneumoniae*. Protection against RSV is mediated by antibodies of IgG3 subclass. These antibodies have shorter half life and do not cross the placenta in substantial amount so as to offer protection to the infant. High quantities of secretory IgA antibodies to RSV are present in the colostrum and breast feeding reduces the likelihood of an infant being hospitalized with acute bronchiolitis.

Pathogenesis

The inflammation of the bronchiolar mucosa leads to edema, thickening, formation of mucus plugs and cellular debris. Bronchiolar spasm occurs in some cases. The bronchial lumen, which is already narrow in the infants, is further reduced. As airway resistance is inversely related to the fourth power of the radius, even slight narrowing of the bronchiolar lumen causes marked increase in the airway resistance, both during inspiration and expiration. During expiration, the bronchioles are partially collapsed and egress of air from the lungs is severely restricted resulting in trapping of the air inside the alveoli causing emphysematous changes. When obstruction becomes complete, the trapped air in the lungs may be absorbed causing atelectasis. Due to diminished ventilation and diffusion, hypoxemia is produced in almost all of these infants. Retention of carbon dioxide leads to respiratory acidosis. The presence of eosinophils in the blood and respiratory secretions suggest that the virus infection initiates the wheezing attack in a child who is already sensitized.

Clinical Features

A few days following an upper respiratory tract infection, breathing becomes fast and respiratory distress develops. Majority of infants has mild symptoms and recover in 3–7 days. Those with severe disease may develop retraction of lower intercostal spaces and suprasternal notch by 3–5 days.

In severe infection the infant is dyspneic and may appear cyanosed. The fever is moderately high. Accessory muscles of respiration are working. Expiration is prolonged; fine crepitations and rhonchi are auscultated. Breath sounds may be faint or inaudible in severe cases. Respiratory distress is out of proportion to the physical signs. Hyperinflation results in the liver and spleen being pushed down. When the chest becomes over inflated, the anteroposterior diameter of the chest is increased and increased resonance is noted on percussion.

X-ray chest shows hyperinflation (Fig. 14.3) and infiltrates. Diaphragm is pushed down. The lung fields appear abnormally translucent. The leukocyte count is normal or slightly elevated. A rapid test, using monoclonal antibodies, on nasopharyngeal aspirate can identify RSV.

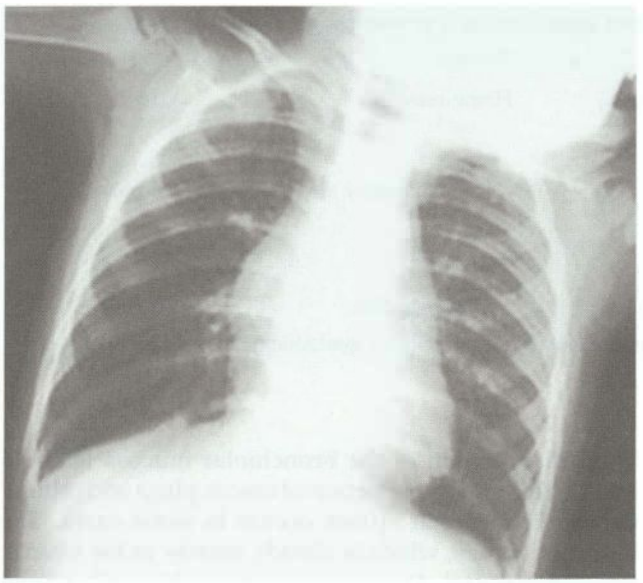

Fig. 14.3: Chest X-ray. Bronchiolitis showing hyperinflation

Course and Prognosis

Bronchiolitis is generally a self limiting illness. The symptoms subside in three to seven days. Death may occur in one percent of the severely ill patients due to respiratory failure. The relationship of acute bronchiolitis to bronchial asthma in later life is observed in about 25% cases of acute bronchiolitis. Bronchial asthma is more likely in children with personal or family history of an allergic illness.

Differential Diagnosis

Bronchial asthma. Bronchiolitis is often confused with bronchial asthma. The latter is unusual below the age of one year; a family history of asthma is usually present. Several attacks occur in the same patient with or without a preceding respiratory infection. Response to bronchodilators is more consistent in children with asthma as compared to bronchiolitis.

Congestive heart failure. Congestive heart failure is suggested, if there is cardiomegaly on X-ray film of chest, tachycardia, large tender liver, raised JVP, edema and rales on auscultation of the lungs.

Foreign bodies in trachea. These are diagnosed by the history of aspiration of foreign body, localized wheeze and signs of collapse or localized obstructive emphysema.

Bacterial pneumonia. In bacterial pneumonia, the signs of obstruction are less pronounced, fever is high and adventitious sounds in the lungs are prominent.

Treatment

Treatment of bronchiolitis is essentially symptomatic. Infants with mild disease can be cared for at home in a humidified atmosphere. If respiratory distress increases or feeding problems appear, child should be hospitalized.

In hospital, the child is nursed in a humid atmosphere preferably in sitting position at angle of 30° to 40° with head and neck elevated. Moist oxygen is given continuously even in the absence of cyanosis. Very sick infants may need a concentration of 60% oxygen given through hood. Pulse oximetry should be performed regularly to keep oxygen saturation of more than 92%. Fluids and electrolyte balance should be maintained.

Antibiotics have no role. Ribavirin, an antiviral agent has no role in the treatment of infants who were previously healthy. The medication, however, shortens the course of illness in infants with underlying congenital heart disease, chronic lung disease and immunodeficiency. Ribavirin is delivered by a nebulizer 16 hr a day for 3–5 days in such cases.

Beta$_2$-adrenergic drugs and ipratropium are not recommended for infants less than 6 months. A recent review on the use of bronchodilators in bronchiolitis suggests a beneficial effect of inhaled salbutamol with ipratropium and epinephrine. If a patient shows improvement, the bronchodilators may be given every 4–6 hourly. Continuous positive airway pressure (CPAP) or assisted ventilation may be required to control respiratory failure. Extracorporeal membrane oxygenation is effective, if respiratory failure is not controlled by mechanical ventilation.

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BRONCHIAL ASTHMA

Bronchial asthma is a disease characterized by an increased responsiveness of the airways to various stimuli. It manifests by widespread narrowing of the airways causing paroxysmal dyspnea, wheezing or cough. The diffuse obstruction to the airflow is reversible in a large majority of cases, either spontaneously or in response to treatment. Bronchial reactivity is a necessary component of asthma.

Pathophysiology

Airway obstruction in asthma is caused by (i) edema and inflammation of mucous membrane lining the airways; (ii) excessive secretion of mucus, inflammatory cells and cellular debris; and (iii) spasm of the smooth muscle of bronchi. Obstruction is diffuse but not uniform.

Asthma has been classified as atopic (IgE mediated, triggered by allergens), nonatopic (nonIgE mediated, triggered by infection), mixed, exercise induced or aspirin induced. Inhalation of an allergen leads to a biphasic response with early and late reactions ultimately causing bronchoconstriction.

Early reaction starts within 10 min of the exposure to allergen. It is characterized by release of histamine, leukotrienes, prostaglandins, platelet activating factor and bradykinin from the mast cells following the interaction of allergen with specific mast cell bound IgE. All these substances cause bronchoconstriction, mucosal edema and mucus secretion which manifests as airway obstruction. This phase is inhibited by β_2-agonist drugs.

Late phase occurs in about two-thirds of patients. It develops 3-4 hr later and peaks at 8–12 hr. The release of mast cell mediators is not prevented by premedication with β_2-agonist. However, it is inhibited by premedication with steroids suggesting that airway narrowing is mainly due to an inflammatory reaction and mucosal edema. This phase presents as clinical asthma.

Airway resistance is increased more during exhalation because airways close prematurely during expiration. Lungs are hyperinflated; elasticity and frequency-dependent compliance of the lungs is reduced. Breathing involves more work resulting in dyspnea. Perfusion of inadequately ventilated lungs causes hypoxemia.

In early stages of illness the partial pressure of CO_2 falls because of hyperventilation. When obstruction becomes more severe, alveolar hypoventilation supervenes, leading to hypercarbia and respiratory acidemia.

Pathology

Airway inflammation is considered to be the basic pathology in asthma. This is initiated by degranulation of mast cells and release of various mediators of inflammation, which damage the airways leading to epithelial shedding and mucus secretion. Inflammatory mediators also influence reactivity *via* neural mechanisms.

Triggers of Episodes of Asthma

Viral infections. Viral infections in young children and exercise in older child or adult appear to be more frequent triggers of airway narrowing. Viral infections interfere with the integrity of mucosal surfaces by opening up tight intraepithelial cell junctions and induce shedding of epithelium.

Role of exercise. Exercise induced asthma occurs in genetically susceptible individuals with hyper-reactive airways. The loss of water from the respiratory tract induces mucosal hyperosmolarity, which stimulates mediator release from mast cells.

Weather change. Sudden change in the weather might result in (i) loss of heat and water from lower airways and (ii) sudden release of airborne allergens in atmosphere, resulting in exacerbation of asthma.

Emotional factors. Emotional stress operated through the vagus nerve, initiates bronchial smooth muscles contractility.

Role of food. Allergy to food proteins or additives in food might have a minor role in the pathogenesis of asthma. These should be incriminated only on a very strong association with the illness.

Endocrine factors. Some endocrine changes including puberty may increase symptoms of asthma.

Clinical Features

The clinical features of asthma are variable. Symptoms vary from simple recurrent cough to severe wheezing. The symptoms occur with change in season, aggravated by exercise and more at night. Acute asthma may usually begin with a cold, or bouts of spasmodic coughing. In early phase of the episode, the cough is nonproductive. The patient becomes dyspneic, with prolonged expiration and wheezing. Accessory muscles of respiration are excessively used. The child sweats profusely, may develop cyanosis and becomes apprehensive and restless and appear fatigued.

In severe episodes the child may show air hunger. The chest is hyper-resonant because of excessive air trapping. As the obstruction becomes severe, the airflow decreases markedly. As a result the breath sounds become feeble. Wheezing which was earlier audible may disappear. This is an ominous sign. Absence of wheezing in the presence of cyanosis and respiratory distress should not be considered as an evidence of clinical improvement. As the child improve, the airflow increases and wheezing may reappear. With remission, the wheeze disappears.

Severe hypoxemia in asthma results in cyanosis and cardiac arrhythmias. Pulsus paradoxus indicates severe illness. Mucus plugs occluding the bronchial tree may cause collapse of small segments of the lung. Persistence of hyperinflation of the chest even after subsidence of the asthmatic attack signifies that the apparent relief from bronchospasm will be short lived. In chronic intermittent cases the chest becomes barrel shaped. Clubbing of fingers, however, is unusual.

Diagnosis

A prolonged whistling sound heard at the mouth during expiration is called a wheeze. Recurrent attacks of wheezing indicate bronchial asthma. Although intermittent attacks of coughing may be due to recurrent viral infections, the diagnosis of bronchial asthma should be considered. Cough, which is associated with asthma generally, worsens after exercise. Sputum is generally clear and mucoid but expectoration of yellowish sputum (attributed to large number of eosinophils) does not exclude he diagnosis of asthma. Chronic spasmodic cough may suggest occult asthma.

Investigations

The diagnosis of asthma is clinical in most cases, hence pulmonary function tests may not play significant role. These investigations have an important role in diagnosis of doubtful cases and in monitoring the response to treatment. The important parameters in spirometry include PEFR, FEV1, FVC and FEV25–75. All parameters are decreased in asthma. FEV1 is commonly used parameter for documentation of severity of asthma. FEV25–75 is effort independent and is probably more sensitive indicator of airway obstruction. PEFR can be measured easily with peak expiratory flow meter, while for other parameters spirometer is required. PEFR may be used as diagnostic tool in doubtful cases as well as monitoring of treatment. Abnormality in PEFR suggestive of asthma include: a diurnal variation of more than 20%, ≤80% of predicted and improvement of ≥20% after bronchodilator therapy.

Absolute eosinophil counts. Significance of eosinophilia for distinguishing between allergic, vasomotor or infectious nature of the chronic respiratory obstructive disease is limited. When eosinophilia is present, bronchial obstruction generally responds well to antispasmodic therapy and the condition is often reversible. The eosinophil count may be low in cases associated with infection. Steroid medication in asthma causes eosinopenia.

Chest X-ray film. The X-ray film of the chest shows bilateral and symmetric air trapping in case of asthma. Patches of atelectasis of varying sizes due to mucus plugs are not unusual. Main pulmonary artery is prominent due to pulmonary hypertension. Bronchial cuffing may occur due to the presence of edema fluid in perivascular and peribronchial interstitial space. Extensive areas of collapse or consolidation should suggest an alternative diagnosis. Chest X-ray film may often be normal.

Allergy test. Skin test and radioallergosorbent allergen specific IgE (RAST) have limited usefulness. Few children need skin tests to identify sensitivity to different antigens since the role of desensitization therapy is not established.

Differential Diagnosis

Bronchiolitis. Bronchiolitis always occurs within the first 2 yr, usually within the first 6 months of life. It is commoner in winter or spring months. Generally there is a single attack. Repeated attacks indicate viral infection associated wheeze or asthma. Hyperinflation of chest with scattered areas of infiltration may be seen on chest X-ray. Asthma may start at any age; more than 3 episodes are usual and wheezing is prominent. Infants diagnosed as bronchiolitis with family history of allergy, having atopic eczema or whose IgE levels are elevated are likely to develop asthma.

Congenital malformation causing obstruction, e.g. vascular rings such as aberrant right subclavian artery or double aortic arch, bronchogenic cysts and tracheomalacia should be excluded in differential diagnosis.

Aspiration of foreign body. Wheeze, if present is generally localized. The history of foreign body aspiration may be forgotten. An area with diminished air entry, with or without hyperresonance on percussion especially in children, may be due to obstructive emphysema because of a check-valve type of obstruction due to the foreign body. Most children develop frequent infections in the lung around the foreign body.

Hypersensitivity pneumonitis. An acute or chronic lung disease may be observed following inhalation of organic dust such as molds, wood or cotton dust, bird droppings, fur dust, grain or following exposure to certain chemicals or drugs such as epoxy resins, PAS and sulfonamides. In the acute form of illness, these children show from fever, chills, dyspnea, malaise, aches and pain, loud inspiratory rales (crackles) at bases of lung and weight loss. X-ray chest shows interstitial pneumonia. Bronchial markings are prominent. The levels of IgE antibodies to the specific antigen are increased. The skin test shows Arthus phenomenon with local hemorrhage, edema and local pain within 8 hr of the test. Diagnosis is established by lung biopsy.

Cystic fibrosis. Children with cystic fibrosis may present with recurrent wheezing but over a period of time they develop clubbing. There may be clinical evidence of malabsorption. X-ray film may show evidence of hyperinflation, peribronchial cuffing and pneumonia. Diagnosis is established by estimating sweat chloride levels.

Management

The effective longterm management of asthma involves:

i. Identification and elimination of exacerbating factors
ii. Pharmacological therapy
iii. Education of patient and parents about the nature of disease and the steps required to avoid acute exacerbation.

Identification and Elimination of Exacerbating Factors

Factors associated with development and precipitation of asthma include passive smoking, allergic disorders, inadequate ventilation at home leading to dampness, cold air, cold food, smoke, dust and pets in the family. Acute respiratory infection due to viruses is the commonest cause of exacerbation of asthma. The following measures help in reducing the triggers of asthma:

- The bedroom of the child should be kept clean and as free from dust as possible. Wet mopping of the floor should be done because dry dusting increases exposure of the child to house dust.

- Heavy tapestry attracts dust and therefore, light plain cloth sheets should be used as curtains in the child's room.
- Carpets, stuffed furniture, loose clothing, wall hangings, calendars and books attract lot of dust and should be cleaned periodically.
- The bed of the child should be made of light material and should be aired regularly.
- Caressing of animal pets should be discouraged, as the child may be sensitive to their fur.
- Generally, it is not necessary to restrict the diet of the child because bronchial asthma due to food allergy is unusual.
- Adolescent patients should be advised to refrain from smoking.
- Exposure to strong or pungent odors such as wet paint, disinfectants and smoke should be minimized.
- The child should avoid attics or basements, especially if these were unoccupied and closed for some days.

Pharmacotherapy

The pharmacological therapy of bronchial asthma involves use of medications that relax smooth muscle and dilate the airways and that decrease inflammation and thereby prevent exacerbations. The medications used for longterm treatment of asthma include bronchodilators, steroids, mast cell stabilizers, leukotriene modifiers and theophylline (Table 14.5).

Bronchodilators. This group of drugs provides immediate symptomatic relief. They may be short-acting and long-acting. The commonly used short-acting bronchodilators are adrenaline, terbutaline and salbutamol. All of these have quick onset of action. Adrenaline stimulates both α and β receptors, thus having cardiac side effects. Terbutaline and salbutamol are specific β_2-agonist and hence have a few cardiac side effects. Adrenaline is given subcutaneously. The other two agents can be administered by oral or inhalation or parenteral route. Inhalation route is preferred because of quick onset of action and fewer side effects.

Long-acting beta-agonists include salmeterol and formoterol. Both these drugs are specific β_2-agonist and have a longer duration of action of 12–24 hr. The onset of action is delayed by ½ –1 hr. Their safety and efficacy has been demonstrated in children above four yr of age.

Corticosteroids. Asthma is a chronic inflammatory disease of airways. Corticosteroids being potent anti-inflammatory agents, are useful for the longterm treatment. Systemic glucocorticoids used early in the treatment of acute exacerbation can lessen the need for visits to emergency department and hospitalization. The advantage of inhaled corticosteroids is application of the medication to sites where it is specifically needed, reducing the risk for systemic adverse effects.

The commonly used inhaled steroids include beclomethasone, budesonide and fluticasone. Budesonide and fluticasone are considered to be superior to beclomethasone. The main concern with the use of inhaled steroids is the effect on growth. An approximately 20% reduction in growth velocity during the first year of treatment with inhaled steroids is reported. Subsequently the growth velocity recovers and children ultimately attain predicted adult height.

Mast cell stabilizers. Cromolyn sodium reduces bronchial reactivity and symptoms induced by irritants, antigens and exercise. Indications for use of cromolyn includes mild to moderate persistent asthma and exercise induced asthma. It should be given at least for 6–8 weeks before declaring it ineffective. Nedocromil is another nonsteroidal drug used for control of mild to moderate asthma. Ketotifen is mast cell stabilizer. It is administered orally. Significant clinical improvement may be evident after 14 weeks of therapy.

Leukotriene modifiers. Leukotriene inhibitors are preferred agents for the treatment of mild to moderate persistent asthma and exercise-induced asthma. Leukotriene inhibitors act either by decreasing the synthesis of leukotrienes (zileuton) or by antagonizing the receptors (montelukast and zafirlukast). Montelukast and zafirlukast have received approval for use in pediatric asthma. Montelukast can be used in children above one year of age while zafirlukast above 12 yr of age.

Theophylline. Theophylline has concentration-dependent bronchodilator effects. The bronchodilator effect is exerted by inhibition of phosphodiesterase. In addition, theophylline has anti-inflammatory and immunomodulatory effects at therapeutic serum concentration that appears to be distinct from its bronchodilator properties. Most guidelines recommend theophylline as an alternative second-line therapy in combination with inhaled glucocorticoids in moderate persistent asthma in older children 5 yr and younger, as a second-line therapy for mild persistent asthma in older children and adult and as adjunctive therapy (largely for control of nocturnal symptoms) in moderate or severe persistent asthma.

Immunotherapy. This consists of administering gradually increasing quantities of an allergen extract to a clinically sensitive subject, so as to ameliorate the symptoms associated with subsequent exposure to causative allergen. This is considered only occasionally in highly selected children who are sensitive to a specific allergen such as grass pollen, mites, etc. It is done only under specialist supervision and involves longterm case.

Pharmacological Management

For optimal use of pharmacological agents one should go in a stepwise manner that includes: (i) assessment of severity of asthma; (ii) selection of medication; (iii) selection of appropriate inhalation device; and (iv) monitoring.

Table 14.5: Medications for longterm treatment of asthma

Medication, route	*Dose*	*Adverse effects*	*Comments*
Bronchodilators			
Salbutamol			
MDI, 100 µg per puff	1–2 puff q 4–6 hr	Tachycardia, tremors, headache, hypokalemia hyperglycemia (minimal with inhalation route)	Drug of choice for acute attack; use prior to exercise can prevent exercise-induced bronchospasm
Respirator solution, 5 mg per ml	0.15–0.2 mg/kg/dose nebulization		
Respules, 2.5 mg per 3 ml			
Dry powder capsules, 200 µg	1 cap q 4–6 hr		
Terbutaline MDI, 250 µg per puff	1–2 puff q 4–6 hr		
Salmeterol			
MDI, 25 µg per puff	1–2 puffs q 12–24 hr	Tachycardia, tremors, headache, hypokalemia, hyperglycemia (minimal with inhalation route)	Longterm prevention of symptoms; not for treatment of acute symptoms; useful for nocturnal symptoms and exercise induced bronchospasm
Dry powder capsules, 50 µg	1 cap q 12–24 hr		
Formoterol			
MDI, 12 µg per puff	1–2 puffs q 12–24 hr		Used with anti-inflammatory therapy; not as substitute
Dry powder capsules, 12 µg	1–2 cap q 12–24 hr		
Theophylline, oral tablets 100, 150, 200, 300 mg	2.5–7.5 mg/kg q 12 hr	Toxicity at >20 µg/ml: Nausea, headache, tachycardia, drowsiness, seizures	Drug interaction (anti-tubercular drugs, anticonvulsants, ciprofloxacin); may be used in step 2 when inhalation route not possible
Mast cell stabilizers			
Sodium cromoglycate, MDI 5 mg per puff	1–2 puffs q 6–8 hr	Medicinal taste, reflex coughing	Continuous prophylaxis for control of symptoms; may take 4–6 weeks for clinically evident effect
Nedocromil sodium inhalation		Bitter taste, cough	Safe medication
Ketotifen, tablet 1 mg, syrup 1 mg per 5 ml	1 mg q 12 hr	Sedation, weight gain	Use when oral route required
Inhaled corticosteroids			
Beclomethasone MDI 50, 100, 200, 250 µg per puff	50–800 µg/day in 2–3 divided doses	Cough, dysphonia, oral thrush (minimized by gargling, use of spacer)	Not recommended as relievers Budesonide and fluticasone are almost completely inactivated during first pass metabolism and have minimal side effects
Budesonide			
MDI, 50, 100, 200 µg per puff	25–400 µg q 12 hr	Negligible side effects at 400–800 µg/day	High dose for long duration may cause systemic side effects like growth and adrenal suppression
Respules, 0.5, 1 mg/ml			
Rotacaps,100, 200, 400 µg			
Fluticasone MDI 25, 50, 125 µg per puff	25–250 µg q 12 hr		Use minimum required dose preferably on alternate day
Dry powder capsules 50, 100, 250 µg			
Respules, 0.5, 1 mg per ml			
Ciclesonide, MDI 80, 160 µg	1 puff q 24 hr		Not advised for use <12 yr of age
Miscellaneous			
Montelukast 4, 5, 10 mg tabs	2–5 yr: 4 mg q 24 hr 5–12 yr: 5 mg q 24 hr >12 yr: 10 mg q 24 hr	Well tolerated; Churg-Strauss syndrome reported	Use in exercise induced asthma or as an alternative to long-acting β-agonist

Assessment of severity Successful management of asthma requires grading the severity of the disease according to the frequency and severity of symptoms and functional impairment. This is assessed by asking the frequency of symptoms including disturbance of sleep, effect on day-to-day activity of child and need for

medication, hospital visit and hospitalization. Result of pulmonary function tests by spirometer provides objective evidence of severity. PEFR measurement is an alternative to spirometry in day-to-day practice, in children older than 5–6 yr of age.

Children with asthma can be classified into 4 groups on the basis of information obtained from parents and PEFR measurement, i.e. *episodic, mild persistent, moderate persistent* and *severe persistent asthma* (Table 14.6).

Selection of medication After the assessment of severity, appropriate medications are selected. The stepwise treatment of asthma according to its severity is given in Table 14.7. Episodic asthma should be treated with salbutamol or terbutaline when required. If inhalation cannot be used due to any reason oral route can be used. Mild persistent asthma needs daily treatment with maintenance medication. They can be cromolyn sodium 5–10 mg by inhalation route, 6–8 hourly or inhalation steroids at a dose of 200 µg/day in two divided doses or slow release theophylline 5–15 mg/kg/day in two divided doses. The selection of either preparation is based on feasibility for inhalation, problems of compliance and cost of medications. The drug of choice in mild persistent asthma is a low dose inhaled steroid. If inhalation is not feasible due to any reason (cost of medication, not able to take inhalation) a trial of leukotriene modifiers or oral theophylline can be given. Moderate persistent asthma needs to be treated with inhalation steroid 200–400 µg/day in 2 divided doses and long-acting β-agonist (formoterol, salmeterol). Montelukast can be used at this step as add on treatment for better control of asthma symptoms.

Severe persistent asthma needs inhalation steroids at the dose of 400–800 µg/day in 2–3 divided doses. For relief of symptoms long-acting β-agonist and slow release theophylline needs to be given regularly. Montelukast can be used at this step as add on treatment for better control of asthma symptoms. If there is persistence of symptoms low dose prednisolone may have to be used, preferably alternate day.

Selection of appropriate inhalation device Drugs used as maintenance treatment of asthma can be administered by inhalation or oral route. Drugs used by the inhalation route are more effective, i.e. have a rapid onset of action and have fewer side effects. Most important in the delivery of effective therapy to asthmatic children is the optimal use of appropriate inhalation devices.

Table 14.7: Stepwise treatment of asthma

Classification	*Longterm prevention*
Step 1: Intermittent	Inhaled short-acting β-agonist as required for symptomatic relief. If needed >3 times/week, move to step 2
Step 2: Mild persistent	Inhaled short-acting β-agonist as required + inhaled budesonide, fluticasone or beclomethasone (100–200 µg) *or* cromolyn sodium *or* sustained release theophylline *or* leukotriene modifiers
Step 3: Moderate persistent	Inhaled short-acting β-agonist as required + inhaled budesonide, fluticasone *or* beclomethasone (100–200 µg q 12 hr). If needed, salmeterol (50 µg q 12–24 hr) *and/or* sustained release theophylline
Step 4: Severe persistent	Inhaled short-acting β-agonist as required + inhaled budesonide, fluticasone or beclomethasone (200–400 µg q 12–24 hr) + salmeterol or formoterol *and/or* sustained release theophylline + oral low dose prednisolone on alternate days (if symptoms not relieved with above treatment)

Metered dose inhaler. A metered dose inhaler (Fig. 14.4) is a device, which delivers a fixed amount of medication in

Use of metered dose inhaler

- Remove cap and shake inhaler in vertical direction
- Breathe out gently
- Put mouthpiece in mouth and at start of inspiration (which should be slow and deep), press canister down and continue to inhale deeply
- Hold breath for 10 seconds or as long as possible; then breathe out slowly
- Wait for a few seconds before repeating the inhalation once again

Fig. 14.4: Metered dose inhaler

Table 14.6: Classification of asthma according to severity

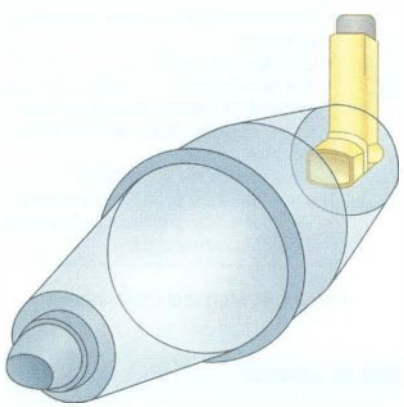
Step	*Symptoms*	*Night time symptoms*	*Peak expiratory flow rate*
Step 1: Intermittent	<1 time a week; asymptomatic and normal PEFR between attacks	≤2 times a mo	≥80% predicted; variability <20%
Step 2: Mild persistent	>1 time a week, but <1 time a day	>2 times a mo	≥80% predicted; variability 20–30%
Step 3: Moderate persistent	Daily use β_2-agonist; daily attacks affect activity	>1 times a week	>60% and <80% predicted; variability >30%
Step 4: Severe persistent	Continuous; limited physical activity	Frequent	≤60% predicted; variability >30%

aerosol form each time it is activated. It can be used for exacerbation and maintenance therapy. They are effective but require considerable coordination, i.e. press and breath coordination. This may not be possible in young children. After actuation the drug comes out at a pressure and a significant amount of the drug gets deposited in the oropharynx. To overcome this problem of coordination it is used with spacer. *MDIs continue to work past the labeled number of doses because of excess propellant.* Therefore, a track of number of actuations should be kept to ensure that children receive adequate therapy when needed.

Metered dose inhaler with spacer. Use of spacer inhalation device with a MDI (Fig. 14.5) should be encouraged as it results in a large proportion of the medication being deposited in the lung, with less impaction in the oropharynx. They also overcome the problems of poor technique and coordination of actuation and inspiration, which occur, with the use of MDIs alone. Furthermore, use of spacer allows MDI to be used for the young patient. MDI used with spacer has been found to be comparable to nebulizer in delivering salbutamol in acute exacerbation of asthma in children. Spacers have the limitation of being bulky, relatively costly and cannot be used in young infants and toddlers. A homemade spacer prepared from mineral water bottle has been shown to be equally effective in delivering salbutamol in acute exacerbation.

Metered dose inhaler with spacer with facemask. Attaching a facemask to the spacer facilitates their use in very young infants (Fig.14.6).

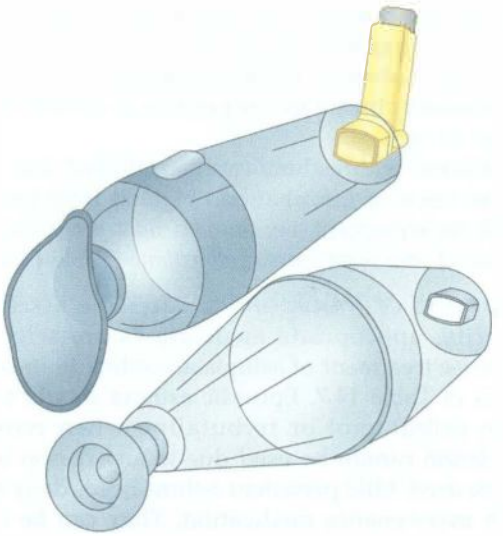
Dry powder inhaler (DPI). These are breathe-activated devices like rotahaler (Fig. 14.7), diskhaler, spinhaler, turbohaler and acuhaler. They can be used in children above 4–5 yr of age. They have the advantage of being portable and eliminate the need to co-ordinate actuation with breathing. In addition they are environmental friendly, as they do not contain CFC. Moreover, the effect of powder inhalers is dependent upon a certain inspiratory flow rate and therefore, there is a risk of reduced effect



Use of metered dose inhaler

- Remove cap, shake inhaler and insert into spacer device
- Place mouthpiece of spacer in mouth
- Start breathing in and out gently and observe movements of valve
- Once breathing pattern is established, press canister and continue to breathe 5–10 times (tidal breathing)
- Remove the device from mouth and wait for 30 seconds before repeating once again

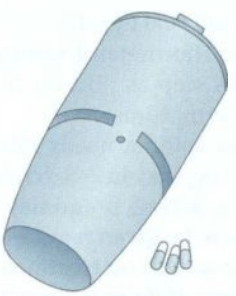
Fig. 14.5: Metered dose inhaler with spacer



Use of MDI with spacer and baby mask

- Attach baby mask to the mouth end of spacer
- Shake MDI and insert it in the MDI end of spacer device
- Cover baby's mouth and nose with baby mask
- Press canister and encourage the child to take tidal breathing with mouth open (if possible) 5–10 times
- Remove baby mask and wait for 30–60 seconds before repeating the above step

Fig. 14.6: Metered dose inhaler with spacer and baby mask



Use of rotahaler

- Hold rotahaler vertically and insert capsule (clear end first) into square hole, make sure that top of the capsule is level with top of hole
- Hold rotahaler horizontally, twist barrel in clockwise and anticlockwise direction, this will split the capsule into two
- Breathe out gently and put mouth end of rotahaler in mouth and take deep inspiration
- Remove rotahaler from mouth and hold breathe for 10 seconds

Fig. 14.7: Rotahaler

during episodes of acute wheeze or in children with low pulmonary function.

Nebulizers. Nebulizers with air compressors are bulky and inefficient aerosol delivery systems (Fig. 14.8). With the advent of efficient spacer systems, the need for nebulizers has greatly diminished. There is a place for the use of nebulized β-agonist in acute severe asthma in young irritable and hypoxic children who do not tolerate MDI used with spacer and facemask, because this allows the delivery of a large dose.

The following measures can improve the amount of drug delivered to the lung by nebulizer: the total fill volume should be about 3–5 ml. Tapping the side of nebulizer chamber during operation induces the droplets on the sides to fall back into the reservoirs, minimizing the loss. The optimal flow rate is 6–12 l/min; at this flow, 30–50% of aerosol in the respirable range of 1–5 mm. Creating a hole is the gas supply tube so that nebulization will occur only during inhalation, when the hole is closed, also decreases the aerosol loss. Slow, deep inhalations and breath holding can improve delivery.

It is important to select an appropriate device by which the maintenance medication has to be administered. Inhalation method should be chosen on individual basis. A rough guide is as follows:

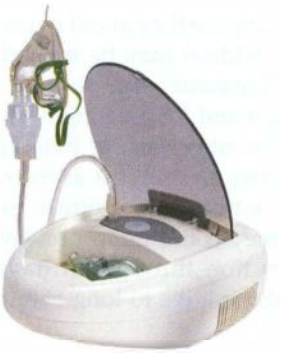
Children below 4-yr-old: MDI with spacer with facemask can be used successfully.

For children between 4- and 12-yr old: MDI with spacer is preferred.

For children above 12-yr-old: MDI may be used directly. However, use of spacer improves drug deposition in airways.

Monitoring and modification of treatment After starting appropriate treatment patients should be seen every 4–12 weeks. On each visit a detailed history regarding frequency of symptoms, sleep disturbance, physical activity, school absenteeism, visit to a doctor, need for bronchodilators (rescue drug) and PEFR is recorded. The patient or parents should be encouraged to maintain a symptom diary. Patient is assessed as controlled, partially controlled or uncontrolled (Table 14.8).

On each visit physician should examine the child, look for adverse effects of drugs and record height and weight.



Use of nebulizer

- Connect compressor to mains
- Connect output of compressor to nebulizer chamber by the tubings provided
- Put measured amount of drug in the nebulizer chamber and add normal saline to a total of 2.5–3 m
- Switch on the compressor and look for aerosol coming out from other end of the chamber
- Attach face mask to this end of nebulizer chamber and fit it to cover nose and mouth of the child
- Encourage child to take tidal breathing with open mouth

Fig. 14.8: Nebulizer

Pulmonary functions/PEFR should be measured in older children. Inhalation technique and compliance should be checked each time.

If disease is partially controlled or uncontrolled the causes could be poor compliance, wrong technique of inhalation, continued use of empty canister, inappropriate doses, infection (otitis media, sinusitis, pneumonitis) continued exposure to allergens or under assessment of illness. Many asthmatic children have allergic rhinitis and its treatment has a beneficial effect on asthma. Asthmatic children also have a higher incidence of sinusitis, which may trigger asthma. Bronchial hyper-responsiveness and asthma symptoms improve with therapy for these upper respiratory diseases.

If no cause is found a step up, i.e. increase in dose and frequency of medication, is required. Therapy can be stepped down if control is sustained for 3–6 months and follow a gradual stepwise reduction in treatment.

Exercise Induced Bronchoconstriction

Some children in addition to varying severity of asthma may develop bronchoconstriction after exercise. To avoid

Table 14.8: Assessment of control of asthma

Characteristics	*Controlled (all of the following)*	*Partially controlled (any measure present in any week)*	*Uncontrolled*
Daytime symptoms	None (≤2/week or less)	>2/week	≥3 features of partly controlled asthma in any week
Limitation of activity	None	Any	
Nocturnal symptoms or awakening	None	Any	
Need for reliever or rescue drugs	None (<2/week)	≥2/week	
Lung function (FEV1 or PEFR)	Normal	<80% predicted or personal best	
Exacerbations	None	≥1/yr	

FEV1 forced expiratory volume in first second; PEFR peak expiratory flow rate

unpleasant experience they avoid participation in outdoor games. These children may be treated with appropriate stepwise management, may require additional medications like short and long-acting beta-agonists or leukotriene modifiers. Short-acting beta-agonists should be taken before going for exercise, as their duration of action is short. Long-acting beta-agonists can be taken in the morning and they continue to prevent exercise-induced bronchoconstriction throughout daytime. Leukotriene modifiers are alternative to long-acting beta-agonists.

Seasonal Asthma

A small proportion of children get symptoms of asthma for a shorter period in a particular season. They remain asymptomatic for the rest of the year. These children can be started on maintenance treatment 2 weeks in advance. Medications are selected according to severity of asthma. These children should be examined again after discontinuing the medications after the season is over.

Education of Parents

Education of parents is an important aspect of asthma treatment. A description of the pathogenesis of asthma in plain language should be made. It needs to be emphasized that there is a wide spectrum of severity of asthma and that most children can lead active and normal lives. Parents also need to be involved in the steps required to minimize exposure to potential environmental triggers. Parents are also asked to maintain a record of daily symptoms such as cough, coryza, wheeze and breathlessness. A record of sleep disturbances, absence from school due to illness and medication required to keep the child symptom free is advised. These records help in stepping up or down the pharmacotherapy of the asthmatic child.

The parents should understand how the medicines work and how to take the medicines including the use of spacer and also the potential harmful effects of drugs. Those concerned about the use of steroids need to be reassured that in the conventional inhalation dosage, the risk of serious asthma out weights the side effects of medication. Peak flow monitoring done properly by informed parents can help by: (i) detecting early deterioration in lung function; (ii) managing asthma in patients who have difficulty in sensing the changes in severity of airway obstruction; and (iii) managing patients whose asthma severity changes very rapidly.

Home Treatment of Acute Exacerbation

An important part of health education is instructing the parent/patient on how to recognize and manage acute exacerbation of asthma at home. A written action plan should be given to them. Acute exacerbation can be identified by increase in cough, wheeze and breathlessness. PEFR, if measured, may be decreased by 15% from the baseline. For acute exacerbation parents should administer short-acting β_2-agonists by MDI $\pm$ spacer $\pm$ facemask, one puff at a time, repeated every 30–60 seconds up to a maximum of 10 puffs with monitoring of symptoms. If symptoms are relieved and PEFR is increased at the end of inhalation the child can be continued on salbutamol or terbutaline every 4–6 hr and a visit to treating physician is planned. If there is no improvement or partial improvement or there are symptoms of life threatening attack at any time, the child should be immediately transferred to a hospital.

Administration of a single dose of prednisolone (1–2 mg/kg) before going to hospital is advised in patient with symptoms of life threatening asthma or lack of satisfactory improvement after inhalation therapy at home.

Management of Acute Exacerbations

Increase in the symptoms in form of cough, wheeze and/or breathlessness is termed as exacerbation of asthma. The severity of exacerbation is variable and can be classified as mild, moderate, severe or life threatening on the basis of physical examination, measurement of PEFR/FEV1 and oxygen saturation (Table 14.9).

Management of Life-threatening Asthma

Such patients should immediately receive oxygen inhalation. An injection of terbutaline or adrenaline is given subcutaneously, inhalation of salbutamol or terutaline and ipratropium is started, and hydrocortisone 5 mg/kg is given IV and arrangement made to transfer the patient to ICU preferably with an accompanying physician.

If the patient shows improvement, the salbutamol or terbutaline inhalation is continued every 20–30 min, hydrocortisone (3–5 mg/kg) is continued every 6–8 hr till patient starts accepting orally. If patient does not improve or deteriorates, a slow IV infusion of magnesium sulphate (50 mg/kg) is given over 30 min. Alternatively, a loading dose of theophylline is infused. If there is no improvement with this management, patient is prepared for mechanical ventilation. Patient is also screened for causes of poor response such as acidosis, pneumothorax, electrolyte imbalance and infection.

Mild Acute Asthma

Such patients should be given β_2-agonists by nebulizer or MDI + spacer with or without face mask. One puff of the medication may be given every minute up to 10 puffs. If case of significant improvement the patient can be sent home on inhalation or oral beta-agonists every 6–8 hr along with general instructions and called back after 1–2 weeks for reassessment and longterm treatment. In case of no response or poor response the patient should be treated as moderate exacerbation.

Acute Moderate and Severe Asthma

Such patients should be treated with inhalation beta-agonist as described in treatment of mild asthma. It is repeated every 20 min, oxygen inhalation is begin and oral

Table 14.9: Grading of severity of acute asthma

Clinical parameter	*Mild*	*Moderate*	*Severe*
Color	Normal	Normal	Pale
Sensorium	Normal	Anxious	Agitated
Respiratory rate	Increased	Increased	Increased
Dyspnea	Absent	Moderate	Severe
Speech	Can speak sentences	Can speak in phrases	Difficulty in speech
Use of accessory muscles	Nil or minimal	Chest indrawing	Chest indrawing; flaring up of ala nasi
Pulsus paradoxus	<10 mm	10–20 mm	>20 mm
Rhonchi	Expiratory	Expiratory, inspiratory	Expiratory, inspiratory or absent
Peak expiratory flow rate, %	>80	60–80	<60
Saturation of O_2, %	>95	90–95	<90

dose of prednisolone 1–2 mg/kg is given. At end of one hour the patient is assessed for improvement. In case of improvement the child is continued on inhalation of β_2-agonists every 30 min and the interval is gradually increased to every 4–6 hr. Oxygen inhalation is stopped if able to maintain oxygen saturation of >95%. Prednisolone is continued once daily for 5–7 days and then stopped without tapering.

The patient can be discharged from hospital when the need for bronchodilators is every 4–6 hourly, able to feed and speak well, maintains oxygen saturation of >95% in room air and the PEFR is >75% of predicted. These patients should be educated about the disease, need for regular followup and avoidance of triggers. They should be assessed for longterm treatment.

In case of no improvement at end of one hour the inhalation of salbutamol is continued and ipratropium 250 µg is also added every 20 min. Hydrocortisone is administered at a dose of 10 mg/kg IV and reassessed at end of two hours. If good response the patient is treated like the early responders. If case of no response, injectable theophylline bolus followed by continuous infusion is started. Such patients may respond well to magnesium infusion at doses of 50 mg/kg dissolved in dextrose over 30 min. If no improvement these patients should be prepared for possible mechanical ventilation.

Monitoring during Acute Treatment

This includes vital signs (heart rate, respiratory rate) and for chest indrawing, oxygen saturation and sensorium.

Suggested Reading

Global Strategy for Asthma Management and Prevention (covering asthma care in adults and children older than 5 yr) http://www.ginasthma.org

Kabra SK, Lodha R, Menon PR. Long term treatment of asthma. In: Essential Pediatric Pulmonology, 2nd edn., Kabra SK, Lodha R eds. New Delhi, Nobel Vision 2010;186–98

Rodriguez C, Sossa M, Lozano JM. Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children. Cochrane Database Syst Rev 2008 Apr 16;(2):CD005536

Saharan S, Lodha R, Kabra SK. Management of status asthmaticus in children. Indian J Pediatr 2010;77:1417–23

Foreign Body Aspiration

Young children between 1 and 4 yr of age are especially prone to aspirate small objects in their air passages. The incidence of foreign body location is similar in the right and left sides. Unless recognized and treated, these children have significant morbidity, such as recurrent wheezing, cough and pneumonia. Immediate response to foreign body aspiration is a choke, gag, cough or localized wheeze. After the initial episode, symptoms may improve for some time and the whole episode may be forgotten. Subsequently, the course of illness depends on the nature of foreign body, its size, extent and the site of obstruction. Foreign bodies of organic or vegetable source swell up and cause more symptoms. A partial obstruction may cause 'ball valve' type effect leading to localized hyperinflation. The overlying chest wall may show hyperresonance, diminished vocal resonance and reduced air entry. In small children, it may be difficult to elicit hyperresonance. Thus a localized area of reduced air entry in a child with chronic respiratory illness should arouse suspicion of a foreign body. Complete obstruction and surrounding inflammation cause distal atelectasis and suppuration of the surrounding parenchyma of the lungs. The elastic recoil of the bronchi is lost and the bronchi show segmental dilatation with eventual development of bronchiectasis.

These children are treated by removal of foreign body through a rigid bronchoscope. Bronchoscopy should be undertaken if the clinical and radiological features suggests the diagnosis even if the history of foreign body aspiration is not forthcoming.

Suggested Reading

Foltran F, Ballali S, Passali FM, et al. Foreign bodies in the airways: a meta-analysis of published papers. Int J Pediatr Otorhinolaryngol 2012; 76:S12–9

Lung Abscess

Lung abscess in children is most frequently a complication of bacterial pneumonia especially those due to *S. aureus*, and *K. pneumoniae*. It may also develop in sequestration of lung tissue or in association with foreign bodies, bronchial cysts or stenosis. Staphylococcal lungs abscess

are often multiple, while those complicating aspiration are solitary. The abscess may rupture into the pleural space leading to pyopneumothorax. The main pathological changes are necrosis and liquefaction with inflammation in the surrounding lung tissue.

Clinical Features

The patient has fever, anorexia, lethargy, pallor, cough with foul smelling expectoration. Physical signs may be minimal. Amphoric breath sounds, coarse crepitations and whispering pectoriloquy are characteristic but often not elicitable. The diagnosis is confirmed by plain X-ray film, and ultrasound or CT scan of chest.

Treatment

Appropriate antibiotics to which the organisms isolated from the sputum or bronchoscopic aspirate are sensitive, are administered for 4 to 6 weeks. Physiotherapy is carried out for effective drainage of the pus. Surgical resection of the involved area of lung is indicated if medical therapy is not effective.

Bronchiectasis

Bronchiectasis is a chronic suppurative disease characterized by destruction of the bronchial and peribronchial tissues, dilatation of the bronchi and accumulation of infected material in the dependent bronchi.

Etiology

Most cases follow recurrent episodes of respiratory infections such as bronchitis, postmeasles or postpertussis pulmonary infections, cystic fibrosis and pneumonitis in infancy and early childhood. Infections damage the bronchial wall and cause segmental areas of collapse, which exert a negative pressure on the damaged bronchi, causing them to dilate. The bronchial dilation is widespread and patchy. The bronchi may show cylindrical, fusiform or saccular dilatation.

Aspiration of foreign body, food, or mucus plug in the bronchus may occlude the bronchial lumen and cause segmental areas of collapse. The bronchi are dilated due to negative pressure by the collapsed segment. If the occlusion is relieved before the stagnant secretions are infected and the bronchial wall is damaged, the bronchiectasis is reversible. The bronchial dilatations are generally segmental or lobar. Extrinsic compression by tuberculous lymph nodes often causes collapse of right middle lobe.

Congenital disorders of bronchi such as bronchomalacia, communicating type of bronchial cyst or sequestrated lung may be the cause of bronchiectasis in some cases. Kartagener syndrome is characterized by bronchiectasis, situs inversus and sinusitis and is attributed to primary ciliary dyskinesia.

Cystic fibrosis is characterised by recurrent lower respiratory infections associated with malabsorption. These patients have history of meconium ileus during neonatal period. This is a common cause of bronchiectasis in the Western countries.

Immunodeficiency syndromes may be responsible for recurrent pulmonary infections and bronchiectasis. Young syndrome patients have sinusitis, bronchiectasis and azoospermia.

Clinical Manifestations

The onset is insidious. The respiratory infections tend to persist longer and recur frequently with waxing and waning. Often the illness can be traced back to an episode of measles or whooping cough. A history of inhalation of foreign body is usually not forthcoming as it is often forgotten. The general health is poor, with recurrent infections. The patient complains of loss of appetite, irritability and poor weight gain; clubbing of fingers is seen in chronic cases.

The most prominent symptom is cough with copious mucopurulent expectoration. Cough is more marked in some postures because of irritation of the infected secretions draining into fresh areas of lung. Likewise the cough is more marked when the child wakes up in the morning due to a change of posture. Younger children may not expectorate and often swallow the sputum. In the course of illness, the sputum may become blood streaked or even frank hemoptysis may occur.

Investigations

X-ray film of the chest shows honeycombing of the involved area indicating multiple small abscess cavities. Bronchography which was considered as gold standard for diagnosis of bronchiectasis has been replaced with high resolution computerized scan (HRCT of chest). Bronchoscopy is undertaken where there is a possibility of surgical intervention. Sputum should be sent for culture and sensitivity. Tuberculin reaction is done to exclude tuberculosis. Pilocarpine iontophoresis is done for estimating sweat chloride in patients with suspected cystic fibrosis.

Prevention

Most cases follow acute respiratory infections, which are inadequately treated. All pulmonary infections should be treated promptly and adequately till the chest is clear of all signs, long after the fever has subsided. Even in ordinary pulmonary infections, airway should be kept patent by encouraging postural drainage. Measles and whooping cough should be prevented by specific immunization. Prompt medical help should be sought if there is any suspicion of inhalation of a foreign body.

Management

During acute exacerbations, bacterial infections should be controlled and airway kept clear of secretions. This is facilitated by effective cough at regular intervals and postural drainage. Assistance by a specially trained pulmonary physiotherapist may be useful. Surgical

resection of the involved area should be undertaken only in children who have marked symptoms and in whom in disease is localized. Extrinsic compression of bronchi requires surgical intervention.

Cystic Fibrosis

Cystic fibrosis (CF) is the most common life limiting recessive genetic disorder in caucasians with an incidence of approximately 1 in 2500 children born in the United Kingdom. It is less common in African Americans (1 in 15000) and in Asian Americans (1:31000). It also affects other ethnic groups such as black population with an incidence of 1 in 17,000 and the native American population with an approximate incidence of 1 in 80,000.

The incidence in migrant Indian populations in the UK has been estimated between 1 in 10000 and 12000. The precise incidence of CF among Indians is unknown.

Etiology

Mutation in the gene encoding the chloride conductance channel, CF transmembrane conductance regulator (CFTR) is the underlying cause. The failure of chloride conductance by epithelial cells leads to dehydration of secretions that are too viscid and difficult to clear. The defective gene is located at long arm of chromosome 7; the most common mutation is delta F508.

Clinical Features

The features depend on age of diagnosis and treatment received. The common clinical presentation includes meconium ileus in neonatal period, recurrent bronchiolitis in infancy and early childhood, recurrent lower respiratory tract infections, chronic lung disease, bronchiectasis, steatorrhoea and with increasing age pancreatitis, and azoospermia. Pancreatic insufficiency is present in >85% of CF patients (Table 14.10).

Table 14.10: Common clinical features of cystic fibrosis (%)

Age group, symptoms	*Proportion*
0–2 yr	
Meconium ileus	10–15%
Obstructive jaundice	
Hypoproteinemia or anemia	
Bleeding diathesis	
Heat prostration or hyponatremia	
Failure to thrive	
Steatorrhoea	85%
Rectal prolapse	20%
Bronchitis or bronchiolitis	
Staphylococcal pneumonia	
2 –12 yr	
Malabsorption	85%
Recurrent pneumonia	60%
Nasal polyposis	6–36%
Intussusception	1–5%
>13 yr	
Chronic pulmonary disease	70%
Clubbing	
Abnormal glucose tolerance	20–30%
Diabetes mellitus	7%
Chronic intestinal obstruction	10–20%
Focal biliary cirrhosis	
Portal hypertension	25%
Gallstones	4–14%
Azoospermia	98%

Diagnosis

The diagnosis should be suspected by the presence of a typical phenotype or family history and confirmed by the demonstration of a high sweat chloride (>60 mEq/l) on at least two occasions and/or by identifying CF causing mutations. Nasal potential difference measurements can be used as an adjunct to sweat test but is not widely available.

Management

The treatment of cystic fibrosis includes respiratory management, nutritional care, anticipation and early diagnosis of liver disease, diabetes and other organ dysfunction.

The principles of respiratory management include airway clearance techniques, antibiotics and anti-inflammatory agents. The aim of nutrition management is to achieve normal growth and development. Nutritional management of CF includes the following measures:

- Increasing caloric intake by encouraging parents to feed the child more frequently. If appetite is poor due to persistent infection; feeding may be given by nasogastric route or by gastrostomy.
- Supplement fat soluble vitamins at twice the recommended doses. These should be given along with food and enzymes.
- Enteric coated tablets or spherules of pancreatic enzymes are given with each feed. Enzymes are started at doses of 1–2000 IU of lipase/kg in divided doses and increased by observing improvement in malabsorption by noting weight gain, nature of stool and abdominal symptoms.

Suggested Reading

Cystic Fibrosis Foundation. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr 2009;155:S73–93

Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Cystic Fibrosis Foundation Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med 2010;182:398–406

Kabra S K, Kabra M, Lodha R, et al. Cystic fibrosis in India. Pediatric Pulmonol 2007;42:1087–94

Acute Respiratory Distress Syndrome (ARDS)

It is defined as pulmonary edema not originating from the heart. Most common cause is severe pneumonia followed by sepsis. Other predisposing factors include

shock, tissue injury, aspiration, toxins, microthrombi, intravascular coagulation, uremia and increased intracranial pressure.

Pathogenesis

There is increased permeability of alveolar capillary membrane leading to aggregation of leukocytes in pulmonary circulation. Mediators such as free oxygen radicals and platelet activating factors are released and injure vascular epitehlium. In the acute stage there is edema and hyaline membrane formation. Subsequently fibrosis occurs. Microthrombi formation in vessels contributes to increased pulmonary vascular resistance and right to left shunting.

Clinical Features

ARDS can occur at any age. Initially symptoms are less and lungs are clear. Later on within 6–8 hr, patient becomes breathless. After 12 hr of insult, refractory hypoxia occurs followed by hypercapnia. Radiologically most lung fields are affected with reticular opacities. Mortality is very high, being 50–60% even in good centers.

Treatment

Patient should be managed in an intensive care unit with cardiorespiratory monitoring and artificial ventilation. Ventilation is achieved by high PEEP or inverse ratio ventilation. The cause of ARDS should be treated simultaneously.

Suggested Reading

Saharan S, Lodha R, Kabra SK. Management of acute lung injury/ARDS. Indian J Pediatr 2010;77:1296–302

Diagnostic Approach to Chronic Cough

Chronic cough can be quite distressing. Parents are concerned and often seek consultation. The diagnosis can be made in most cases by a careful analysis of the following: Age of the child; nature of cough and sputum; relationship to the time of posture; presence of wheezing or stridor; effect of season; response to previous therapy; state of nutrition; physical signs in the chest and presence or absence of clubbing of fingers.

Type of cough. Staccato paroxysms of cough suggest whooping cough or chlamydia infection. Barking or brassy cough associated with changes in the voice indicate laryngotracheal disease. In case of postnasal drip, cough appears to be like an attempt to clear the throat and described as a hawking cough. Cough of psychogenic nature has a honking character (Table 14.11).

Sputum. Purulent sputum indicates the presence of suppurative lung disease. The sputum is mucoid in cases of asthma; yellow sputum may be present in some cases due to the presence of large number of eosinophils. Hemoptysis indicates the possibility of bronchiectasis, tuberculosis, mitral stenosis, cystic fibrosis or foreign body in the bronchus.

Table 14.11: Causes of chronic cough in relation to age at presentation

Onset of symptoms	*Etiology*
Birth	Laryngeal webs, vascular rings or H type tracheoesophageal fistula
First month	Congenital infections (rubella, CMV) leading to interstitial pneumonia
Early infancy	Gastroesophageal reflux leading to vomiting and aspiration of milk, saliva or gastric contents
Late infancy	Bronchitis, asthma, cystic fibrosis, whooping cough
Preschool age	Recurrent bronchitis, allergic bronchitis, asthma, foreign body, chronic suppurative lung disease, pulmonary eosinophilia
At all ages	Asthma, whooping cough, viral bronchitis, tuberculosis, foreign body aspiration

Wheezing. Wheezing is indicative of asthma.

Seasonal cough. Chronic cough, which is more common in certain seasons during the year should arouse the suspicion of asthma. Chronic cough occurring only in winter months is usually indicative of viral etiology.

Nutrition of the child. Severe nutritional disturbance in association with chronic cough is found is cases of tuberculosis, bronchiectasis, pertussis, cystic fibrosis, severe chronic asthma or immune deficiency syndromes.

Investigations

Chest X-ray film, examination of the sputum, blood counts and tuberculin test may be necessary for arriving at a definitive diagnosis. Bronchoscopy may be necessary in some cases. CT scan of chest is noninvasive important investigation.

Management

Bronchial asthma should be excluded before evaluating other causes of cough. Any predisposing factor(s) should be managed.

Nonspecific therapy. Cough suppressants are preferably avoided in children. These are indicated only, if the cough is dry and exhausting or, if it disturbs sleep and prevents adequate nutrition, e.g. in whooping cough. Dextromethorphan is an effective cough suppressant and is nonhabit forming. *Physiotherapy*, e.g. chest clapping, vibrations and postural drainage are useful in facilitating removal of bronchial secretions. *Bronchodilators* are useful in the treatment of children with cough due to occult asthma because of retained tracheobronchial secretions. Mucociliary transport of secretions is helped by beta-adrenergic agonists and the xanthine group of drugs both in asthmatic as well nonasthmatic children with chronic bronchitis.

Suggested Reading

Chang AB. Pediatric cough: children are not miniature adults. Lung 2010;188:S33–40

De Blasio F, Virchow JC, Polverino M, et al. Cough management: a practical approach. Cough 2011;7:7

Marchant JM, Masters IB, Taylor SM, et al. Evaluation and outcome of young children with chronic cough. Chest 2006;129:1132–41

Empyema Thoracis

Empyema thoracis is defined as collection of pus in the pleural cavity. This is commonly caused as a complication of staphylococcal (rarely *S. pneumoniae* or gram-negative bacilli) pneumonia or rupture of subdiaphragmatic or liver abscess in the pleura.

Clinical features include fever, breathing difficulty, toxic appearance of child. There is decreased movement of respiration with decreased air entry and vocal resonance. The percussion note is dull. Occasionally, it may manifest as a pulsatile swelling over chest, empyema necessitans.

An X-ray film of the chest shows shift in mediastinum with obliteration of costophrenic angle and varying degree of opacification. Pleural tap shows purulent fluid with pus cells, high protein and low sugar. Gram stain and culture may show causative agent. Empyema should be differentiated from other causes of pleural effusion including tuberculosis and neoplasia.

The treatment consist of administration of antibiotics active against *Staphylococcus*, e.g. cloxacillin, vancomycin. The pus collected in the pleural cavity is drained by intercostal drainage tube. Drainage of fluid under thoracoscopy is preferred if facility exists. If the lung fails to expand, despite intercostals drainage and antibiotics, a CT scan of chest is done.

Suggested Reading

Brims FJ, Lansley SM, Waterer GW, Lee YC. Empyema thoracis: new insights into an old disease. Eur Respir Rev 2010;19:220–8

Pulmonary Manifestations of HIV Infection

Pulmonary diseases are an important cause of morbidity and mortality in HIV infected children. Respiratory tract symptoms are the initial symptoms in more than 50% of these children. These illnesses range from recurrent upper respiratory tract infections to serious bacterial infections to opportunistic infections and exclusive conditions like lymphoid interstitial pneumonitis. In the west, the incidence of *Pneumocystis carinii* pneumonia has declined significantly due to early diagnosis of HIV infection and institution of cotrimoxazole prophylaxis. Also, the wide use of highly active antiretroviral therapy has improved the quality of life and survival in HIV infected children. Common pulmonary infections in HIV infected children are discussed in Chapter 10.

Suggested Reading

Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. Chest 2008;134:1287–98

Theron S, Andronikou S, George R, du Plessis J, Goussard P, Hayes M, Mapukata A, Gie R. Non-infective pulmonary disease in HIV positive children. Pediatr Radiol 2009;39:555–64

15 Disorders of Cardiovascular System

R Krishna Kumar, R Tandon, Manu Raj

Diseases of the cardiovascular system are an important cause of childhood morbidity and mortality. The majority of heart diseases presenting in early childhood are congenital, occurring due to structural defects during development. Despite substantial decline in the incidence of rheumatic fever, rheumatic heart disease continues to be prevalent in India. Systemic hypertension is increasingly recognized in childhood and may predispose to cardiovascular morbidity in adulthood. A variety of other cardiovascular conditions may present in childhood.

The management of children with cardiovascular diseases requires an integrated approach with inputs from various specialties. There have been substantial advances in the field of pediatric cardiology. Many congenital heart defects that were considered universally fatal can be corrected and affected children can expect to survive into adulthood. These developments include an improved understanding of the pathophysiology of disease, advances in diagnostic capability and successful surgical and medical management of various heart diseases. However, the access to pediatric cardiology services in developing nations is limited. The development of comprehensive pediatric heart programs across regions is essential to improve the management of children with cardiovascular diseases.

CONGESTIVE CARDIAC FAILURE

Congestive cardiac failure is the inability of the heart to maintain an output, at rest or during stress, necessary for the metabolic needs of the body (systolic failure) and inability to receive blood into the ventricular cavities at low pressure during diastole (diastolic failure). Thus, due to systolic failure it is unable to propel blood into the aorta and in diastolic failure it receives inadequate amount of blood. Diastolic heart failure is recognized by clinical features of heart failure with evidence of increased filling pressures with preserved systolic function and in many instances, cardiac output. An increase in left sided pressures results in dyspnea from pulmonary congestion. An increase in right sided pressures results in hepatomegaly and edema. Besides hypertrophied ventricles, diastolic failure occurs in restrictive heart disease and constrictive pericarditis. While mitral and tricuspid valve stenoses result in elevated atrial pressure, they are not, in the strictest sense diastolic heart failure.

Etiopathogenesis

The common causes of diastolic failure are indicated in Table 15.1. The causes of congestive failure can be classified according to age (Table 15.2). Rheumatic fever and rheumatic heart disease is typically encountered beyond 5 yr age; its prevalence appears to be declining in selected urban populations.

Heart failure from congenital heart disease typically happens within the first 1–2 yr of life. Patients with left to right shunts tend to develop CCF around six to eight weeks of life. Unlike left to right shunts, congenital leakage of the mitral or the tricuspid valve can result in heart failure at an early age. Congenital tricuspid regurgitation (TR) manifests early because the elevated pulmonary

Table 15.1: Heart failure due to diastolic dysfunction

Mitral or tricuspid valve stenosis*
Constrictive pericarditis
Restrictive cardiomyopathy
Acute ventricular volume overload (acute aortic or mitral valve regurgitation)
Myocardial ischemia#
Marked ventricular hypertrophy (hypertrophic cardiomyopathy, storage disorders, severe hypertension, severe aortic or pulmonary valve stenosis)
Dilated cardiomyopathy#

*Results in elevated atrial pressures with normal ventricular diastolic pressures (filling pressures)

#Often have combined systolic and diastolic dysfunction

Table 15.2: Causes of congestive cardiac failure

Infants
Congenital heart disease
Myocarditis and primary myocardial disease
Tachyarhythmias, bradyarhythmias
Kawasaki disease with coronary occlusion
Pulmonary hypertension (persistent pulmonary hypertension of the newborn; primary pulmonary hypertension; hypoxia, e.g. upper airway obstruction)
Miscellaneous causes
Anemia
Hypoglycemia
Infections
Hypocalcemia
Neonatal asphyxia (myocardial dysfunction, pulmonary hypertension)
Children
Rheumatic fever, rheumatic heart disease
Congenital heart disease complicated by anemia, infection or endocarditis
Systemic hypertension
Myocarditis, primary myocardial disease
Pulmonary hypertension (primary, secondary)

artery pressures increases its severity. If the TR is not severe, it may improve with time as pulmonary vascular resistance declines.

The age of occurrence of heart failure may point towards the underlying cause (Table 15.3). Heart failure at an unexpectedly early age for a patient thought to have a simple shunt lesion should prompt the search for an associated condition such as coarctation.

Arrhythmias are an important cause of congestive cardiac failure in infancy. Three-quarters of infants with paroxysmal supraventricular tachycardia are below 4 months old. Heart rates above 180/min tend to precipitate heart failure. There is usually no failure in the first 24 hr. If the tachycardia persists for 36 hr, about 20% will develop heart failure and almost 50% will do so in 48 hr. There is a tendency for recurrences of tachycardia if the onset is after 4 months of age. Any long-standing tachyarrhythmia can be associated with ventricular dysfunction that may mimic cardiomyopathy. Typical examples include ectopic atrial tachycardia and permanent junctional re-entrant tachycardia. Severe bradycardia, typically from complete heart block, can also result in heart failure.

With a normal heart, hemoglobin levels 5 g/dl can result in heart failure. In a heart compromised by disease, failure may be precipitated even with hemoglobin levels of 7–8 g/dl. Younger infants are more susceptible to develop failure with anemia.

Clinical Features

The recognition of cardiac failure in older children is based on the same features as in adults.

Symptoms. Slow weight gain is related to two factors. The infant takes small feeds because of easy fatigability and there is an excessive loss of calories from increased work of breathing. Uncommonly, there may be an unusual gain in weight due to collection of water, manifesting as facial puffiness or rarely as edema on the feet. The difficulty in feeding may manifest itself as 'poor feeder', a complaint that the baby does not take more than one to two ounces of milk at a time or that he is hungry within a few minutes after taking a small feed. Shortness of breath or fatigue from feeding results in the baby accepting only small amounts of milk at a time. A few minutes rest relieves the baby and since hunger persists, the result is an irritable infant crying all the time. Often a mother may state that the baby breathes too fast while feeding or that the baby is more comfortable and breathes better when held against the shoulder—which is the equivalent of orthopnea in older children. Not infrequently, the baby is brought with persistent hoarse crying, wheezing, excessive perspiration and less commonly, because of facial puffiness (Table 15.4).

Signs. Left sided failure is indicated by tachypnea and tachycardia. Persistent cough, especially on lying down, hoarse cry and wheezing are other evidences of left sided failure; basal rales in the chest are usually not audible.

Table 15.3: Time of onset of congestive failure

Age	*Lesion*
Birth-1 week	Duct dependent systemic circulation (hypoplastic left heart syndrome, critical aortic stenosis, severe coarctation, arch interruption); total anomalous pulmonary venous return (obstructed), congenital mitral and tricuspid valve regurgitation, neonatal Ebstein anomaly
1–4 weeks	Patent ductus arteriosus (PDA) in preterms, ventricular septal defect (VSD) with coarctation, persistent truncus arteriosus, transposition with large VSD or PDA, severe coarctation; critical aortic stenosis, congenital mitral or tricuspid regurgitation, single ventricle physiology with unrestrictive pulmonary blood flow
1–2 months	Transposition with VSD or PDA, endocardial cushion defects, VSD, PDA, severe coarctation; total anomalous pulmonary venous return, anomalous left coronary artery from pulmonary artery, single ventricle physiology with unrestrictive pulmonary flow
2–6 months	VSD, PDA, endocardial cushion defect; anomalous left coronary artery from the pulmonary artery, coarctation, single ventricle physiology with unrestrictive pulmonary blood flow

Table 15.4: Symptoms of cardiac failure

Poor weight gain
Difficulty in feeding
Breathes too fast; breathes better when held against the shoulder
Persistent cough and wheezing
Irritability, excessive perspiration and restlessness
Pedal edema

Right-sided failure is indicated by hepatomegaly and facial puffiness. Examination of the neck veins in small babies is not helpful. Firstly, it is difficult to evaluate the short neck with baby fat and secondly, hemodynamic studies show that right atrial mean pressures stays normal in more than one-half of infants with congestive failure. Edema on the feet occurs late. Common to both left and right sided failure is the presence of cardiac enlargement, third sound gallop and poor peripheral pulses with or without cyanosis (Table 15.5).

Table 15.5: Signs of congestive cardiac failure

Left-sided failure	*Failure of either side*	*Right-sided failure*
Tachypnea	Cardiac enlargement	Hepatomegaly
Tachycardia	Gallop rhythm (S3)	Facial edema
Cough	Peripheral cyanosis	Jugular venous engorgement
Wheezing	Small volume pulse	
Rales in chest	Lack of weight gain	Pedal edema

Treatment

Management of heart failure is a four-pronged approach for correction of inadequate cardiac output. The four-prongs are: (i) reducing cardiac work, (ii) augmenting myocardial contractility, (iii) improving cardiac performance, (iv) correcting the underlying cause. *Identification of the cause is important since it has direct bearing on survival.* If a newborn has heart failure due to duct dependent systemic circulation (critical coarctation, aortic stenosis, interrupted aortic arch), administration of prostaglandin to open the closing duct improves survival.

Reducing Cardiac Work (Fig. 15.1)

The work of the heart is reduced by *restricting patient activities, sedatives, treatment of fever, anemia, obesity, and by vasodilators. Mechanical ventilation helps when heart failure is severe by eliminating the work of breathing.*

Neonates with heart failure are nursed in an incubator. They are handled minimally. The baby is kept propped up at an incline of about 30°. The pooling of edema fluid in the dependent areas reduces the collection of fluid in lungs, thus reducing the work of breathing. At a temperature of 36–37°C, the overall circulatory and metabolic needs are minimal, thus reducing work of heart. Humidified oxygen to maintain a concentration of 40 to

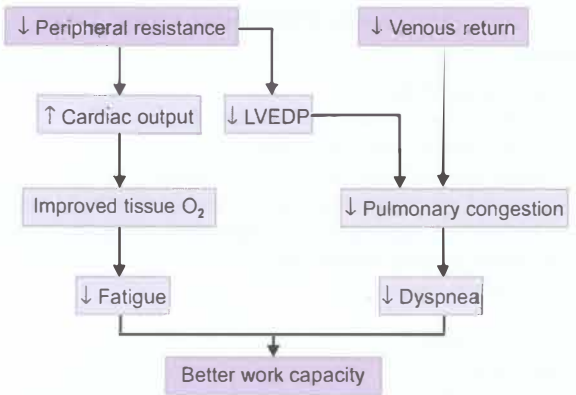


Fig. 15.1: By reducing the systemic vascular resistance and decreasing the venous tone vasodilators provide better work capacity. LVEDP left ventricular end-diastolic pressure

50%, improves impaired oxygenation secondary to pulmonary congestion.

If the infant or the child is restless or dyspneic, sedatives are used. Morphine sulfate in doses of 0.05 mg/kg SC provides effective sedation. A benzodiazepine such as midazolam is useful for sedation in selected circumstances. Sedatives reduce anxiety and lower the catecholamine secretion, thus reducing physical activity, respiratory and heart rate. Requirement of oxygen for body tissues goes down, and this reduces the cardiac workload.

Fever, anemia or infection also increase the work of the heart. In infants and smaller children the presence of superadded pulmonary infection is difficult to recognize. Antibiotics are therefore, sometimes administered empirically. In older children antibiotics are used, only if evidence of infection is present.

Anemia imposes stress on the heart because of the decreased oxygen carrying capacity of blood. Anemia results in tachycardia and in a hyperkinetic circulatory state. Correction of anemia will result in decreased cardiac work. If transfusion is indicated packed red cells can be administered. Typically packed cell volumes of 10–20 ml/kg are required to correct severe anemia; a single dose of frusemide IV is often given prior to the transfusion. Less common conditions causing stress to the heart are repeated *pulmonary emboli, thyrotoxicosis* and *obesity.*

Vasodilators counteract the compensatory mechanisms in heart failure and improve cardiac output (Fig. 15.1). Arteriolar and venous vasoconstriction is mediated through catecholamines. Arteriolar constriction maintains blood pressure by increasing the systemic vascular resistance, which increases the work of heart (Fig. 15.2). Veno-constriction results in decreased venous capacitance and increased venous return, increasing the filling pressures of the ventricles to increase the cardiac output. Since compensatory mechanisms are inappropriately excessive, vasodilators, by reducing the arteriolar and venous vasoconstriction, reduce the work of heart. Nitrates are used

as preferential venodilators and hydralazine as an arteriolar dilator.

ACE inhibitors (captopril, enalapril) are effective for treating heart failure in infants and children. These agents are effective vasodilators, suppress renin-angiotensin-aldosterone system, reducing vasoconstriction and salt and water retention. By suppressing catecholamines, they prevent arrhythmias and other adverse effects on the myocardium. The major side effect of ACE inhibitors is cough, which can be troublesome. Persistent cough may necessitate the use of angiotensin receptor blockers, such as losartan. Initially it is necessary to monitor the renal function: urinalysis, blood levels of creatinine and electrolytes once a week for six to eight weeks. These medications may cause first-dose hypotension; the first dose should be one-quarter of the calculated dose. The patient should ideally remain recumbent for the first 6 hr to prevent an unusual fall in blood pressure.

Although beta-blockers might precipitate CCF, they improve symptoms and survival especially in patients with dilated cardiomyopathy, who continue to have tachycardia. Useful agents include metoprolol and carvedilol. The latter is preferred since it has properties of beta-blockers with peripheral vasodilation; treatment is started at low dose and increased depending on tolerability (0.08 to 0.4 mg/kg/day, maximum 1.0 mg/kg/day). Calcium channel blockers have adverse effects in heart failure and should be avoided unless indicated for systemic hypertension.

In the acute care setting, sodium nitroprusside is used as a vasodilator, since it acts on the venous and arterial systems. Phosphodiesterase inhibitors such as milrinone have become popular especially in postoperative period. These agents have powerful vasodilatory and inotropic effects. Specific indications for use of vasodilators include acute mitral or aortic regurgitation, ventricular dysfunction resulting from myocarditis, anomalous coronary artery from pulmonary artery and in the early post operative setting.

Augmenting Myocardial Contractility

Augmenting myocardial contractility by inotropic agents like digitalis improves cardiac output. In infants and children, only digoxin is used. It has a rapid onset of action and is eliminated quickly. It is available for oral and parenteral administration. Oral digoxin is available as 0.25 mg tablets and as digoxin elixir (1 ml = 0.05 mg) (Table 15.6). Parenteral digoxin (0.5 mg/2 ml) is available; its dose is 70% of the oral dose.

Infants tolerate digitalis well. In a hospitalized patient full digitalization should be sought to maximize benefit. Children are digitalized within a 24 hr period; ½ of the calculated digitalizing dose is given initially, followed by ¼ in 6–8 hr and the final ¼ after another 6–8 hr. The maintenance dose is usually one-quarter of the digitalizing dose (Table 15.6). Before the third daily dose, an electrocardiogram is done to rule out digitalis toxicity.

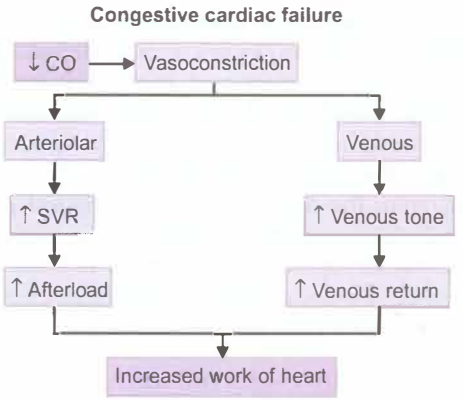


Fig. 15.2: Low cardiac output (CO) results in vasoconstriction, increasing systemic vascular resistance (SVR) and venous tone leading to increase in the work of heart

Table 15.6: Dosage of digoxin and diuretics

	Digitalizing dose, mg/kg	*Maintenance (fraction of digitalizing dose)*
Digoxin		
Premature, neonates	0.04	1/4
1 month to one year	0.08	1/3 to 1/4
1 to 3 yr	0.06	1/3 to 1/4
Above 3 yr	0.04	1/3
Diuretics		
Frusemide	1–3 mg/kg per day orally or 1 mg/kg per dose IV	
Spironolactone	1 mg/kg orally every 12 hr	

Toxicity can be controlled by omitting the next one or two doses. The PR interval is a useful indicator; if it exceeds the initial interval by 50%, digitalis toxicity is present. The upper limit of normal PR interval in infants is 0.14 second.

Digitalis is used with caution in the following situations: (i) premature neonates; (ii) heart failure due to myocarditis; and (iii) very cyanotic patients. In other situations, it is better to use half the calculated digitalizing and the maintenance dose initially. Myocardial damage, gross cardiomegaly, hypoxia, acidosis, hepatic, renal and pulmonary insufficiency increase the sensitivity of the myocardium to digitalis. Digoxin is beneficial for symptom relief and is advised in patients with mild, moderately severe or severe congestive failure, with or without sinus rhythm. Digoxin can be combined with ACE inhibitors for synergistic effect. By increasing cardiac output, digoxin lowers systemic impedance indirectly, unloading the ventricles.

Inotropic Agents

These agents belong to two groups: (i) catecholamine inotropes, like dopamine, dobutamine and adrenaline and (ii) phosphodiesterase inhibitors like amrinone and milrinone. These agents combine inotropic effects with peripheral vasodilation. If blood pressure is low, dopa-

mine should be used, as an intravenous infusion. At a dose of less than 5 microgram/kg per minute, dopamine causes peripheral vasodilation and increases myocardial contractility. Renal blood flow improves, resulting in natriuresis; higher doses result in peripheral vasoconstriction. The dose of dobutamine is 2.5 to 15 microgram/kg/min; the dose should be increased gradually until the desired response is achieved. In patients with dilated cardiomyopathy, dobutamine is used as 24 hr infusion once or twice a week and retains its effectiveness for varying lengths of time.

Improving Cardiac Performance by Reducing Venous Return (Preload)

Diuretics reduce the blood volume, decrease venous return and ventricular filling. This tends to reduce the heart size. The larger the heart, the more the wall tension and the poorer is its performance. With reduction in heart size and volume, the myocardial function and the cardiac output improve. Diuretics reduce the total body sodium thereby, reducing blood pressure and peripheral vascular resistance. This helps in increasing the cardiac output and reducing the work of the heart.

Diuretics are the first line of management in congestive failure. The action of oral frusemide starts within 20 min. Frusemide should be used in combination with a potassium sparing diuretic (triamterene, spironolactone, amiloride) instead of using potassium supplements. The combination prevent potassium and magnesium loss and reduces the risk of arrhythmias. Frusemide activates the renin angiotensin aldosterone axis, which is responsible for vasoconstriction and sodium and water retention. When frusemide is combined with ACE inhibitors, the combination suppresses the axis and is therefore synergistic.

The other method of altering the body fluid volume is by restricting the sodium intake. Sodium restriction is difficult to implement in infants and young children. Low sodium diets should be used only if the heart failure cannot be controlled with digitalis, diuretics and ACE inhibitors. However, it is prudent to advise such patients to avoid salt rich foods such as chips and pickles. Since heart failure increases calorie requirements, adequate intakes is advised.

Correcting the Underlying Cause

Non-invasive tests (especially echocardiography) allow identification of the cause in most children with suspected heart disease. Many of these are managed by curative or palliative operations. A diagnosis of idiopathic dilated cardiomyopathy requires exclusion of conditions that are known to cause ventricular dysfunction. The conditions that might be missed are sustained tachyarrhythmias, coarctation of aorta and obstructive aortitis, anomalous origin of the left coronary artery from pulmonary artery and hypocalcemia. It is important to look for subtle evidence of sustained tachyarrhthmias. Anomalous origin of the left coronary artery is treated surgically.

The presence of CCF in a child with rheumatic heart disease does not necessarily mean presence of active carditis. In any patient of rheumatic heart disease, if active carditis has been excluded and an adequate trial has been given to medical management, operative treatment should be considered. Uncommon causes of CCF in infants and children include upper respiratory obstruction, hypoglycemia, neonatal asphyxia and hypocalcemia.

Prognosis

The mortality of CCF in children is high and prognosis depends on the underlying cause.

CONGENITAL HEART DISEASE

Congenital heart disease (CHD) encompasses a broad and diverse range of conditions that manifest from prenatal period to late adulthood. In common usage, CHD refers to structural heart defects that are present at birth. History, physical examination, chest X-ray, ECG and echocardiography help in identifying the presence of CHD, except perhaps in the early newborn period where the diagnosis can be challenging. Palliative or corrective surgery is feasible for most patients with CHD, provided if undertaken in a timely fashion. It is also possible to identify and determine the severity of specific lesions through echocardiography.

A substantial proportion of patients with CHD have significant problems involving other organ systems, or specific chromosomal and single gene disorders. Pediatricians need to identify associated conditions, since they might have significant bearing on outcomes. It is important to recognize that, in spite of significant recent advances, longterm concerns after palliation and corrective surgery are significant and many children need lifelong followup.

Epidemiology and Etiology

CHD accounts for nearly one-third of all major congenital anomalies. The prevalence of CHD in infancy is estimated at 6--8 per 1000 live births; 25% are life threatening and require early intervention. A proportion of patients with CHD have an identifiable genetic basis (Table 15.7). Table 15.8 shows the association of CHD with acquired disorders and teratogens.

Physiology of Congenital Heart Disease

Pressure, Flow and Resistances

The pressures and resistances in the pulmonary and systemic circulations are indicated in Table 15.9. The pulmonary and systemic flows are equal if there are no abnormal communications between the two sides.

According to Poiseuille's equation, modified for application to blood flow through vessels.

$$Pressure = Flow \times Resistance$$

Table 15.7: Common genetic conditions linked to occurrence of congenital heart disease

Syndrome	*Genetic mutation; inheritance*	*Cardiac lesions*	*Other features*
CATCH 22	Microdeletion in 22q; autosomal dominant (AD)	Interrupted aortic arch, TOF, VSD, persistent truncus arteriosus, double outlet right ventricle	Cleft palate, hypocalcemia, thymic hypoplasia, nasal regurgitation, gastroesophageal reflux, learning disability
Williams Beuren	Microdeletion in *elastin* (7q11.23) ; AD	Supravalvar aortic stenosis, pulmonary stenosis, hypertension	Elfin facies, mental retardation, hypersocial personality, short stature, hypercalcemia
Down	Trisomy 21; Robertsonian translocation or mosaicism	AV canal defect, perimembranous VSD, TOF	Characteristic facies, clinodactyly, mental retardation; hypotonia
Turner	45XO or 46/45XO; mosaic	Bicuspid aortic valve, coarctation	Short stature, gonadal dysgenesis lymphedema,
Noonan	*PTPN11;* AD	Pulmonic stenosis, hypertrophic cardiomyopathy, ASD	Short stature, dysmorphic facies, webbed neck, developmental delay, cryptorchidism
VATER association	Sporadic	VSD, TOF	Vertebral, renal and limb defects, anal atresia, tracheoesophageal fistula
Holt Oram	*TBX5;* AD	Ostium secundum ASD; VSD	Radial ray anomalies
CHARGE association	*CHD7;* often *de novo*	Branch pulmonary artery stenosis, TOF, VSD	Coloboma, growth failure, choanal atresia, genital hypoplasia, ear anomalies
Alagille	*JAG1;* most cases are *de novo*	Pulmonary stenosis, TOF	Dysmorphic facies, cholestatic jaundice, butterfly vertebrae, renal anomalies

AD autosomal dominant; AV atrioventricular; ASD atrial septal defect; TOF tetralogy of Fallot; VSD ventricular septal defect

Table 15.8: Prenatal exposure that increase risk of congenital heart disease

Gestational diabetes (transposition, atrioventricular septal defects, hypoplastic left heart, cardiomyopathy, PDA)
Febrile illness in first trimester (increased risk)
Rubella (PDA, peripheral pulmonary stenosis, VSD)
Lupus (complete heart block)
Phenylketonuria (VSD, TOF, PDA, single ventricle)
Vitamin deficiency (increased risk of heart disease)
Teratogens, (first trimester) e.g. anticonvulsants, NSAIDs, cotrimoxazole, thalidomide, retinoic acid
Exposure to organic solvents, herbicides, pesticides, ionizing radiation

NSAIDs nonsteroidal anti-inflammatory drugs; PDA patent ductus arteriosus; TOF tetralogy of Fallot; VSD ventricular septal defect

The pressure is measured in mm of mercury, flow in liters/ min and resistance in dynes/sec/cm^5 or units (80 dynes/ sec/cm^5 = 1 unit). Although this equation is not strictly accurate when applied to flow of blood in pulmonary and systemic circuits, it does serve a useful purpose in understanding the hemodynamics. Thus:

Systemic pressure =
systemic flow × peripheral vascular resistance

Pulmonary arterial pressure =
pulmonary flow × pulmonary vascular resistance

It is thus obvious that the pressure in a vessel is dependent on the *flow* through the vessel and the *resistance*, offered by the vessel to the flow of blood. It is possible to increase the pressure in a vessel either by increasing the flow or by increasing the resistance. Increase in flow through the pulmonary artery means a left to right shunt, as occurs in atrial or ventricular septal defect or patent ductus arteriosus. Generally, this increase in flow is not associated with significant increase in pressure as the *resistance falls* or *remains the same.* At the same time the distensibility characteristics of the pulmonary artery are such that it can accommodate almost three times the normal flow without an increase in pressure. *Hence, large left to right shunts can take place without an increase in pressure.*

Increase in pulmonary vascular resistance means obstructive disease in the pulmonary circuit. The pulmonary vessels develop medial hypertrophy and later intimal changes are added, to further obstruct the flow of blood through the pulmonary circulation. After a certain stage it is an irreversible process. The increase in resistance to flow in the pulmonary circuit is associated with *reduction in flow.* The increase in pressure in the pulmonary artery associated with normal resistance is called *hyperkinetic pulmonary arterial hypertension* whereas when the pressure is increased due to increase in pulmonary vascular resistance, it is called *obstructive pulmonary arterial hypertension.* Clinically both situations are seen and can be separated from each other on the bedside.

Table 15.9: Systolic and diastolic pressures and resistance in the pulmonary and systemic circuits

Chamber/Vessel	*Pressure (mm Hg)*	*Chamber/Vessel*	*Pressure (mm Hg)*
Superior vena cava	0–6	Pulmonary vein	6–10
Right atrium	0–6	Left atrium	6–10
Right ventricle	25/0–6	Left ventricle	80–120/5–10
Pulmonary artery	25/10	Aorta	80–120/60–85
Resistance, dynes/sec/cm^5			
Pulmonary vascular	80–240	Systemic vascular	800–1600

Fetal Circulation (Fig. 15.3)

The heart assumes its normal four-chambered shape by the end of six weeks of intrauterine life. From then on only minor changes occur and consist mainly in the growth of the heart as a whole with increasing age of the fetus. For the exchange of gases the fetus is dependent on placental circulation, whereas the neonate is dependent on the lungs. Immediately following birth, with the first inspiration, the lungs expand with air and the gas exchange function is transferred from the placenta to the lungs. This necessitates circulatory adjustments following birth to transform the fetal circulation to the postnatal circulation.

Blood oxygenated in the placenta is returned by way of umbilical veins, which enter the fetus at the umbilicus and join the portal vein (Fig. 15.3). The ductus venosus provides a low resistance bypass between the portal vein and the inferior vena cava. Most of the umbilical venous blood shunts through the ductus venosus to the inferior vena cava. Only a small proportion mixes with the portal venous blood and passes through the liver. Blood from inferior vena cava comprising that from hepatic veins, umbilical veins and that from lower extremities and kidneys enters the right atrium. On reaching the right atrium the blood stream is divided into two by the inferior margin of septum secundum—the crista dividens. About one-third of the inferior vena cava blood enters the left atrium, through the foramen ovale, the rest two-thirds mixes with the venous return from the superior vena cava to enter the right ventricle.

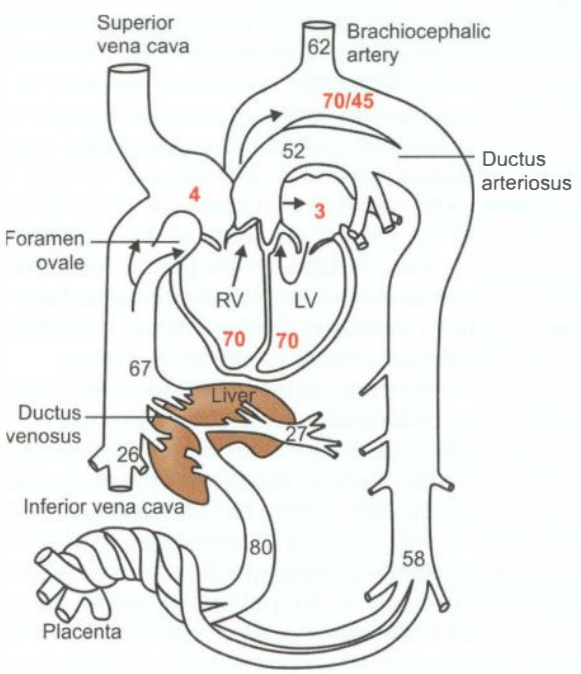


Fig. 15.3: Fetal Circulation: Details of the circulation are provided in the text. Saturations of blood (%) in various chambers and vessels are indicated in black font and pressures (mm Hg) are indicated in red font

The blood reaching the left atrium from the right atrium mixes with small amount of blood reaching the left atrium through the pulmonary veins and passes to the left ventricle. The left ventricle pumps out the blood into the ascending aorta for distribution to the coronaries, head and upper extremities. The superior vena cava stream, comprising blood returning from the head and arms, passes almost directly to the right ventricle. Only minor quantities (1 to 3%) reaches the left atrium. The right ventricle pumps out blood into the pulmonary trunk. A small amount of this blood enters the pulmonary circulation, the rest passes through the ductus arteriosus into the descending aorta to mix with the small amount of blood reaching the descending aorta from the aortic arch (derived from the left ventricle).

The main differences between the fetal and postnatal circulation are: (i) presence of placental circulation, which provides gas exchange for the fetus; (ii) absence of gas exchange in the collapsed lungs; this results in very little flow of blood to the lungs and thus little pulmonary venous return to left atrium; (iii) presence of ductus venosus, joining the portal vein with the inferior vena cava, providing a low resistance bypass for umbilical venous blood to reach the inferior vena cava; (iv) widely open foramen ovale to enable oxygenated blood (through umbilical veins) to reach the left atrium and ventricle for distribution to the coronaries and the brain; and lastly (v) wide open ductus arteriosus to allow right ventricular blood to reach the descending aorta, since lungs are non-functioning.

Circulatory Adjustments at Birth—Transitional Circulation

Circulatory adjustments continue to occur for a variable period following birth. This change is brought about because of a shift from placental dependence for gas

exchange in the fetus to pulmonary gas exchange in the neonate. Loss of placental circulation and clamping of the umbilical cord, after birth, results in a sudden increase in systemic vascular resistance with the exclusion of the low resistance placental circulation. This tends to increase the aortic blood pressure and the left ventricular systolic pressure. The left ventricular diastolic pressure also tends to rise and increases the left atrial pressure. The loss of placental circulation results in a sudden reduction of flow through the ductus venosus that closes off. Flow through the ductus venosus disappears by the 7th day of postnatal life. The loss of placental flow results in a decrease in the volume of blood returning to the right atrium. The right atrial pressure decreases. The left atrial pressure becomes higher than the right atrial pressure and the septum primum, which acts as a valve of the fossa ovalis, approximates with the septum secundum to close off the foramen ovale. Functional closure of the foramen ovale occurs relatively quickly. Over a period of months to years, the septum primum and septum secundum become firmly adherent resulting in anatomical closure of the foramen ovale.

Sudden expansion of lungs with the first few breaths causes a fall in pulmonary vascular resistance and an increased flow into the pulmonary trunk and arteries. The pulmonary artery pressure falls due to lowering of pulmonary vascular resistance. The pressure relations between the aorta and pulmonary trunk are reversed so that the flow through the ductus is reversed. Instead of blood flowing from the pulmonary artery to aorta, the direction of flow through the ductus, is from the aorta to pulmonary trunk. The increased saturation following birth causes the ductus arteriosus to constrict and close. Some functional patency and flow can be demonstrated through the ductus arteriosus for a few days after birth. The ductus arteriosus closes anatomically within 10 to 21 days.

This results in the establishment of the postnatal circulation. Over the next several weeks, the pulmonary vascular resistance continues to decline. There is fall in the pulmonary artery and right ventricular pressures. The adult relationship of pressures and resistances in the pulmonary and systemic circulations is established by the end of approximately two to three weeks (Fig. 15.4).

Hemodynamic Classification of Congenital Heart Disease

CHD has been broadly classified as cyanotic and acyanotic heart disease (Table 15.10). While broad classifications work for most situations, there are patients who cannot be classified into common physiologic categories. Additionally there are often specific issues such as valve regurgitation that determine the clinical manifestations. The following physiological concepts are important to understand common congenital malformations:

i. Pre-tricuspid versus post-tricuspid shunts
ii. The VSD-PS physiology
iii. Single ventricle physiology
iv. Duct dependent lesions
vi. Unfavorable streaming and parallel circulation

Pre-tricuspid versus post-tricuspid shunts Acyanotic heart disease with left to right shunts is traditionally classified as pre-tricuspid and post-tricuspid shunts. There are important differences in physiology that impact clinical manifestations and natural history. Left to right shunts at

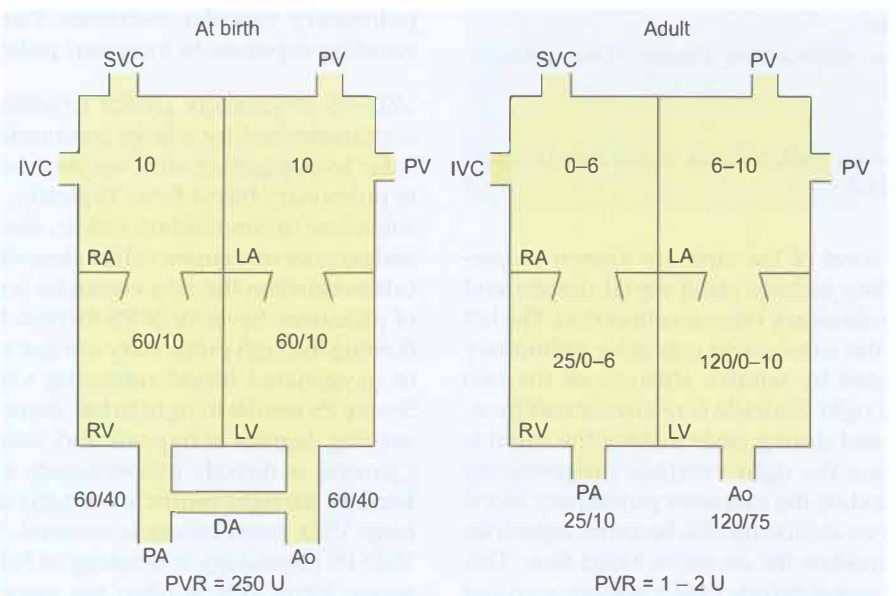


Fig. 15.4: Pressure and resistance in the right and left-sided chambers and vessels at birth compared to adults. Ao aorta; DA ductus arteriosus; IVC inferior vena cava; LA left atrium; LV left ventricle; PA pulmonary artery; PV pulmonary vein; PVR peripheral vascular resistance; RA right atrium; RV right ventricle; SVC superior vena cava

Table 15.10: Broad physiologic categories of congenital heart disease

Acyanotic heart disease: Left to right shunts
Pre-tricuspid: Partial anomalous pulmonary venous drainage, atrial septal defect
Ventricular: Ventricular septal defects (VSD)
Great artery: Aorto-pulmonary window, patent ductus; ruptured sinus of Valsalva
Both pre- and post-tricuspid: Atrioventricular septal defect, left ventricle to right atrial communications
Acyanotic heart disease: Obstructive lesions
Inflow: Cor-triatriatum, obstructive lesions of the mitral valve
Right ventricle: Infundibular stenosis, pulmonary valve stenosis, branch pulmonary artery stenosis
Left ventricle: Subaortic membrane, valvar aortic stenosis, supravalvar aortic stenosis, coarctation of aorta
Miscellaneous: Coronary artery abnormalities, congenital mitral and tricuspid valve regurgitation
Cyanotic heart disease
Reduced pulmonary blood flow
Intact interventricular septum: Pulmonary atresia with intact ventricular septum, critical pulmonic stenosis with right to left shunt at atrial level, Ebstein anomaly; isolated right ventricular hypoplasia
Unrestrictive ventricular communication: All conditions listed under VSD with pulmonic stenosis
Increased pulmonary blood flow
Pre-tricuspid: Total anomalous pulmonary venous communication, common atrium
Post-tricuspid: All single ventricle physiology lesions without pulmonic stenosis, persistent truncus arteriosus, transposition of great vessels
Pulmonary hypertension
Pulmonary vascular obstructive disease (Eisenmenger physiology)
Miscellaneous
Pulmonary arteriovenous malformation, anomalous drainage of systemic veins to LA

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or proximal to the level of the atria are known as pre-tricuspid shunts. They include atrial septal defects and partial anomalous pulmonary venous connection. The left to right shunt and the consequent excessive pulmonary blood flow is dictated by relative stiffness of the two ventricles. Since the right ventricle is relatively stiff (non-compliant) at birth and during early infancy the shunt is small. Over the years the right ventricle progressively enlarges to accommodate the excessive pulmonary blood flow. The pulmonary vasculature also becomes capacious to gradually accommodate the excessive blood flow. This explains why atrial septal defects (ASD) seldom manifest with symptoms of pulmonary over-circulation during infancy and childhood. The clinical signs are also easily explained by the physiology of pre-tricuspid shunts. The diastolic flow murmur of ASD is across the much larger tricuspid valve and is therefore relatively subtle or even inaudible. The excessive blood in the right ventricle is ejected into the pulmonary artery resulting in an ejection systolic murmur. The second heart sound splits widely and is fixed because of the prolonged right ventricular ejection time and prolonged "hang-out" interval resulting from increased capacitance of the pulmonary circulation. Pulmonary arterial hypertension (PAH) is typically absent or, at most, mild. The presence of moderate or severe PAH in ASD is uncommon but worrisome and may suggest the onset of irreversible changes in the pulmonary vasculature.

Post-tricuspid shunts are different in that there is direct transmission of pressure from the systemic to the pulmonary circuit at the ventricular level (VSD) or great arteries (PDA and aorto-pulmonary window). The shunted blood passes through the lungs and finally leads to a diastolic volume overload of the left ventricle. The hemodynamic consequences are dictated by the size of the defect. For patients with large post-tricuspid shunts, symptoms begin in early infancy, typically after some regression of elevated pulmonary vascular resistance in the newborn period together with progressive development of the pulmonary vascular tree.

The excessive pulmonary blood flow returns to left atrium and flows through the mitral valve resulting in apical diastolic flow murmur that is a consistent marker of large post-tricuspid shunts. The left atrium and ventricle are dilated as a result of this extra volume. Elevated pulmonary artery pressure is an inevitable consequence of large post-tricuspid shunts, and is labeled hyperkinetic PAH. This needs to be distinguished from elevated pulmonary vascular resistance that results from long-standing exposure to increased pulmonary blood flow.

VSD-PS physiology (Fallot physiology) This situation is characterized by a large communication at the ventricular level together with varying degrees of obstruction to pulmonary blood flow. Typically, this is in the form of subvalvar (infundibular), valvar, annular (small annulus) and occasionally supra-valvar stenosis. The free communication between the two ventricles results in equalization of pressures. Severity of PS dictates the volume of blood flowing through pulmonary arteries and therefore amount of oxygenated blood returning via pulmonary veins. Severe PS results in right to left shunt across the VSD with varying degrees of hypoxia and, consequently, cyanosis. Cyanosis is directly proportionate to the severity of PS. Because the right ventricle is readily decompressed by the large VSD, heart failure is unusual. The best example of VSD-PS physiology is tetralogy of Fallot (TOF). In its least severe form, TOF is often not associated with cyanosis (pink TOF). Here PS is significant enough to result in a large pressure gradient across the right ventricular outflow tract (RVOT), but not severe enough to result in a

reduction in pulmonary blood flow. Pink TOF is typically associated with a loud ejection systolic murmur because of a reasonable volume of blood flowing across the RVOT. As the severity of PS increases, pulmonary blood flow declines and the intensity of murmur declines progressively. Identical symptoms and physical findings are present in (i) complete transposition of great arteries with VSD and pulmonic stenosis, (ii) double outlet right ventricle with pulmonic stenosis and a large subaortic VSD, (iii) tricuspid atresia with diminished pulmonary blood flow, (iv) single ventricle with pulmonic stenosis, and (v) corrected transposition of great arteries with VSD and pulmonic stenosis.

Single ventricle physiology This refers to a group of conditions where there is complete mixing of pulmonary and systemic venous returns. In addition to single ventricle (double inlet ventricle), a variety of conditions come under the category of single ventricular physiology. Atresia of one of the AV valves, severe hypoplasia of one of the ventricles, severe straddling of one of the AV valves over a large VSD are all examples of situations where there is mixing of pulmonary and systemic venous returns. The clinical manifestations are dictated by the whether or not there is PS. In absence of PS, there is excessive pulmonary flow especially in infants because of the relatively lower pulmonary vascular resistance. The proportion of oxygenated blood from pulmonary veins that mixes with the systemic venous return is high. Cyanosis is minimal and measured oxygen saturation may be in the 90s. However, the price for preserved oxygenation is heart failure and permanent elevation of pulmonary vascular resistance (pulmonary vascular obstructive disease or PVOD). If the child survives infancy, pulmonary vascular resistance progressively increases with increasing cyanosis.

Single ventricle and its physiologic variants can be associated with varying degrees of PS. The features are similar to VSD-PS physiology except for relatively severe hypoxia because of free mixing of systemic and pulmonary venous return.

Palliative operations are the only option for the large number of conditions that come under the category of single ventricle physiology. Single ventricle palliation is done in stages. The final procedure is the Fontan operation that allows separation of systemic venous return from pulmonary venous return thereby, eliminating cyanosis.

Duct dependent lesions An infant or a newborn with CHD that is dependent on the patency of the ductus-arteriosus for survival can be termed as having a duct dependent lesion. These are newborns where the systemic blood supply is critically dependent on an open PDA (duct dependent systemic circulation, DDSC) or pulmonary blood flow is duct dependent (duct dependent pulmonary circulation, DDPC). Closure of the PDA in DDSC results in systemic hypoperfusion (often mistaken as neonatal sepsis), as in hypoplastic left heart syndrome where the entire systemic circulation is supported by the right ventricle through the PDA and interrupted aortic arch where the descending aortic flow is entirely through the PDA. Severe coarctation and critical aortic stenosis are also examples of DDSC. Closure of PDA in DDPC results in severe hypoxia and cyanosis in neonates; examples include all forms of pulmonary atresia (irrespective of underlying heart defect) where the PDA is the predominant source of pulmonary blood flow. Patients with pulmonary atresia, where pulmonary blood supply is from major aorto-pulmonary collaterals, may survive even after the PDA closes. Critical PS can present as duct dependent pulmonary blood flow. Newborns with severe Ebstein anomaly can also present as DDPC (physiologic pulmonary atresia) even though the pulmonary valve is anatomically normal because of inability of the right ventricle to function effectively.

Neonates with duct dependent physiology require prostaglandin E1 (PGE1) for survival. Early recognition of a duct dependent situation allows early initiation of PGE1 and stabilization until definitive procedure is accomplished.

Unfavorable streaming and parallel circulation Unfavorable streaming refers to a situation where oxygen rich pulmonary blood flow is directed towards the pulmonary valve and poorly oxygenated blood towards the aortic valve. The best example of unfavorable streaming is the parallel circulation in transposition of great arteries (TGA) with intact ventricular septum. Here survival is dependent of the presence of a communication (ideally at atrial level) that allows mixing of pulmonary and systemic venous return. The presence of a VSD may improve the situation in TGA but significant cyanosis is usually present unless the pulmonary blood flow is torrential.

Recognition and Diagnostic Approach

While it is often easy to recognize the presence of CHD in older children, manifestations of heart disease can often be subtle in newborns and young infants. Conditions that do not primarily involve the cardiovascular system can result in clinical manifestations that overlap with those resulting from CHD in the newborn. Nonetheless, careful clinical evaluation is often rewarding and allows identification of CHD in most infants and many newborns. The following clinical features should alert the paediatrician regarding the presence of CHD.

Cyanosis. Parents seldom report cyanosis unless it is relatively severe (saturation <80%). It is often easier for them to notice episodic cyanosis (when the child cries or exerts).

Difficult feeding and poor growth. The parent of an infant with CHD may complain that the child has difficulty with feeds. This is usually a feature of an infant with congestive heart failure resulting from CHD. The history may be of slow feeding, small volumes consumed during each feed,

tiring easily following feeds and requirement of periods of rest during feeds. Excessive sweating involving forehead or occiput is commonly associated. Not infrequently, no history of feeding difficulty may be obtained, but examination of the growth charts will reveal that the child's growth rate is not appropriate for age. A recent decline in growth rate (falling off the growth curve) or weight that is inappropriate for age (<5th centile) may result from a large left to right shunt. Characteristically, growth retardation affects weight more that height.

Difficult breathing. Tachypnea (respiratory rates more than 60/min in infants <2 months; >50/min in older infants; >40/min after 1 yr) is a characteristic manifestation of heart failure in newborns. For infants, subcostal or intercostal retractions together with flaring of nostrils are frequently associated with tachypnea.

Frequent respiratory infections. The association of respiratory infections that are frequent, severe and difficult to treat with large left to right shunts is not a specific feature.

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Specific syndromes. The presence of chromosomal anomalies or other syndromes that are associated with CHD should alert the clinician to the presence of specific cardiac defects. Trisomy 21 is the commonest anomaly associated with heart disease; others include trisomy 13 and 18, Turner and Noonan syndromes, and velocardiofacial and Di George syndromes (Table 15.7).

Nadas' Criteria

The assessment for presence of heart disease can be done using the *Nadas' criteria.* Presence of one major or two minor criteria are essential for indicating the presence of heart disease (Table 15.11). It is important to recognize that these criteria are of limited use in newborns, where clinical signs are subtle.

Major criteria

(i) *Systolic murmur grade III or more in intensity. A pansystolic murmur* is always abnormal no matter what is its intensity. There are only three lesions that produce a pansystolic murmur, and these are (*a*) VSD, (*b*) mitral regurgitation and (*c*) tricuspid regurgitation. An *ejection systolic murmur* may be due to an organic cause or it may be *functional.* An ejection systolic murmur associated with a thrill is an organic murmur. Grade III ejection systolic murmur of a functional type may be heard in anemia or high fever especially in small children.

A number of children around the age of 5 yr may have a soft ejection systolic murmur. If it is accompanied with a normal second sound then it is unlikely to be significant. Before discarding a murmur as of no significance, it is necessary to obtain an electrocardiogram, and a thoracic roentgenogram. If they are also normal, one can exclude heart disease, but at least one more evaluation after six months is essential.

(ii) *Diastolic murmur.* The presence of a diastolic murmur almost always indicates the presence of organic heart disease.

(iii) *Central cyanosis.* Central cyanosis suggests that either unoxygenated blood is entering the systemic circulation through a *right to left shunt* or the *blood passing through the lungs is not getting fully oxygenated.* The oxygen saturation of the arterial blood is less than normal, the normal being around 98%. If the blood is not getting fully oxygenated in the lungs, it is called *pulmonary venous desaturation* and indicates severe lung disease. Cyanosis due to a right to left cardiac shunt indicates presence of heart disease. Central cyanosis is present in fingers and toes as well as in the mucous membranes of mouth and tongue. It results in *polycythemia and clubbing.*

Peripheral cyanosis does not imply the presence of heart disease. *Peripheral cyanosis is the result of increased oxygen extraction from the blood by the tissues.* It is seen in fingers and toes but not in mucous membrane of mouth and tongue. The arterial oxygen saturation is normal. Presence of central cyanosis always indicates presence of CHD if lung disease has been excluded. However, cyanosis that is obvious clinically usually results from significant desaturation (typically <85%). Poor lighting, anemia, dark skin complexion may further mask hypoxia. Routine use of the pulse oximeter allows detection of milder forms of hypoxia. Saturations of 95% or lower while breathing room air are abnormal.

(iv) *Congestive cardiac failure.* Presence of congestive cardiac failure indicates heart disease except in neonates and infants, who might show cardiac failure due to extra-cardiac causes, including anemia and hypoglycemia.

Minor criteria

(i) *Systolic murmur less than grade III.* It is emphasized that soft, less than grade three murmurs by themselves do not exclude heart disease.

(ii) *Abnormal second sound.* Abnormalities of the second sound always indicate presence of heart disease. It has been included as a minor criterion only because auscultation is an individual and subjective finding.

(iii) *Abnormal electrocardiogram.* Electrocardiogram is used to determine the mean QRS axis, right or left atrial hypertrophy and right or left ventricular hypertrophy.

Table 15.11: Nadas' criteria for clinical diagnosis of congenital heart disease

Major	*Minor*
Systolic murmur grade III or more	Systolic murmur grade I or II
	Abnormal second sound
Diastolic murmur	Abnormal electrocardiogram
Cyanosis	Abnormal X-ray
Congestive cardiac failure	Abnormal blood pressure

Criteria for ventricular hypertrophy, based only on voltage criteria are not diagnostic for the presence of heart disease. The voltage of the QRS complexes can be affected by changes in blood viscosity, electrolyte imbalance, position of the electrode on the chest wall and thickness of the chest wall.

(iv) *Abnormal X-ray.* The reason for considering abnormal X-ray as a minor criterion is twofold. In infants and smaller children, the heart size varies considerably in expiration and inspiration. If there is cardiomegaly on a good inspiratory film, it suggests presence of heart disease. The second reason is the presence of thymus in children up to the age of two years, which might mimic cardiomegaly. Fluoroscopy is helpful in separating the shadow of the thymus from the heart.

(v) Abnormal blood pressure. It is difficult to obtain accurate blood pressure in smaller children. It is important to use appropriate sized cuffs while measuring blood pressure.

Diagnostic Implications of the Second Heart Sound

Auscultation of the heart provides important diagnostic information. Of the various heart sounds and murmurs the most important is the assessment of the second heart sound (Fig. 15.5). The normal second heart sound can be described in three parts:

i. Has two components: aortic closure sound (A2) and pulmonary closure sound (P2).
ii. During quiet breathing both the components are superimposed on each other during expiration, thus only a single second sound is heard. During inspiration, the aortic component comes early whereas the pulmonary component is delayed, resulting in a splitting of the second sound in which the A2 precedes the P2.
iii. The aortic component is louder than the pulmonary component, except in infants below 3–6 months old.

When we say that the second sound is normal, it is in context of the above three aspects. Abnormalities of the second sound might occur in each of these aspects.

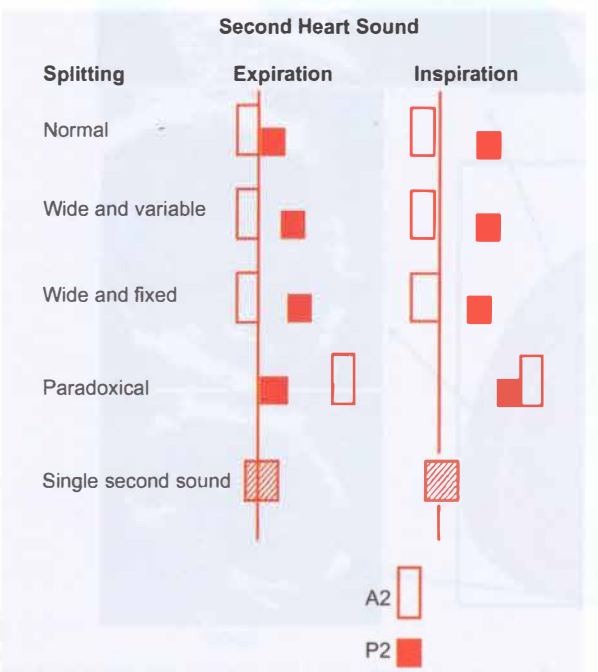

Fig. 15.5: Second sound (S2): The relationship of aortic (A2) and pulmonic component (P2) in inspiration and expiration. Single S2 means that it may be either A2 or P2 or a combination of both

Abnormalities of Aortic Component of the Second Sound

The A2 may be *accentuated or diminished* in intensity. It can also occur early or late in timing. The A2 is accentuated in systemic hypertension from any cause and in AR, and diminished or may be absent when the aortic valve is immobile because of fibrosis or calcification or if absent, as in aortic valve atresia.

The A2 is *delayed* when the left ventricular ejection is prolonged as in aortic valvar or subvalvar stenosis, patent ductus arteriosus with a large left to right shunt, AR, left bundle branch block and left ventricular failure. The A2 occurs *early* in VSD, mitral regurgitation and constrictive pericarditis.

Abnormalities of Pulmonic Component of the Second Sound

The P2 may be *accentuated* or *diminished* in intensity or *delayed* in timing. Although it may be occurring early in tricuspid regurgitation, it is not recognized as such on the bedside since tricuspid regurgitation as an isolated lesion (without pulmonary arterial hypertension) is rare. *Accentuated* P2 is present in pulmonary arterial hypertension from any cause. The P2 is *diminished* in intensity in pulmonic stenosis. It is absent when the pulmonary valve is absent as in pulmonary valvar atresia. The P2 is *delayed* in pulmonic stenosis, atrial septal defect, right bundle branch block, total anomalous pulmonary venous connection and type A WPW syndrome.

Abnormalities in Splitting of the Second Sound (S2)

As indicated above the normal S2 is single (or closely split, <0.03 sec) in expiration and split in inspiration with the louder A2 preceding P2. *Wide splitting of the second sound* is defined as splitting during expiration due to an early A2 or late P2 or the A2–P2 interval 0.03 sec or more during expiration. If the interval increases during inspiration, it is called wide variable splitting, but if it is the same in expiration and inspiration it is defined as widely split and fixed second sound. *Wide and variable splitting of S2* is seen in pulmonic stenosis, mitral regurgitation and VSD. In pulmonic stenosis it is due to a delay in P2 whereas in mitral regurgitation and VSD it is due to an early A2. *Wide and fixed splitting* of the S2 occurs in atrial septal defect,

right bundle branch block and total anomalous pulmonary venous connection and is due to a delay in P2.

The delay in A2 results in closely split, single or paradoxically split S2. In paradoxically split S2, the split is wide in expiration but narrows during inspiration (Fig. 15.5). A *single second sound* means that it is either A2 or P2 or a combination. The decision whether it is aortic or pulmonic or a combination, depends not on the location or intensity of the single second sound, but on the clinical profile. In tetralogy of Fallot only a single S2 is heard and it is the A2 since the pulmonic component is delayed and so soft that it is inaudible. In VSD with pulmonary arterial hypertension and right to left shunt (Eisenmenger complex) again a single S2 is heard and represents a combination of A2 and P2. While based on auscultation alone, it might be difficult to differentiate between tetralogy of Fallot and Eisenmenger complex, the history and thoracic roentgenogram can easily distinguish between these conditions. Thus, the interpretation of single second sound is not dependent on auscultation alone.

Imaging Studies

Echocardiography (Fig. 15.6) Echocardiography has revolutionised the diagnosis of CHD and its high diagnostic yield makes this investigation cost effective. This is particularly true for infants and newborns in whom excellent images are readily obtained. Transesophageal echocardiography can supplement transthoracic studies.

Cardiac magnetic resonance imaging Cardiac magnetic resonance imaging is an important modality for evaluation of CHD, especially in older patients and for postoperative evaluation. Magnetic resonance imaging can also define extracardiac structures such as branch pulmonary arteries, pulmonary veins and aortopulmonary collaterals. Very useful physiologic data (especially blood

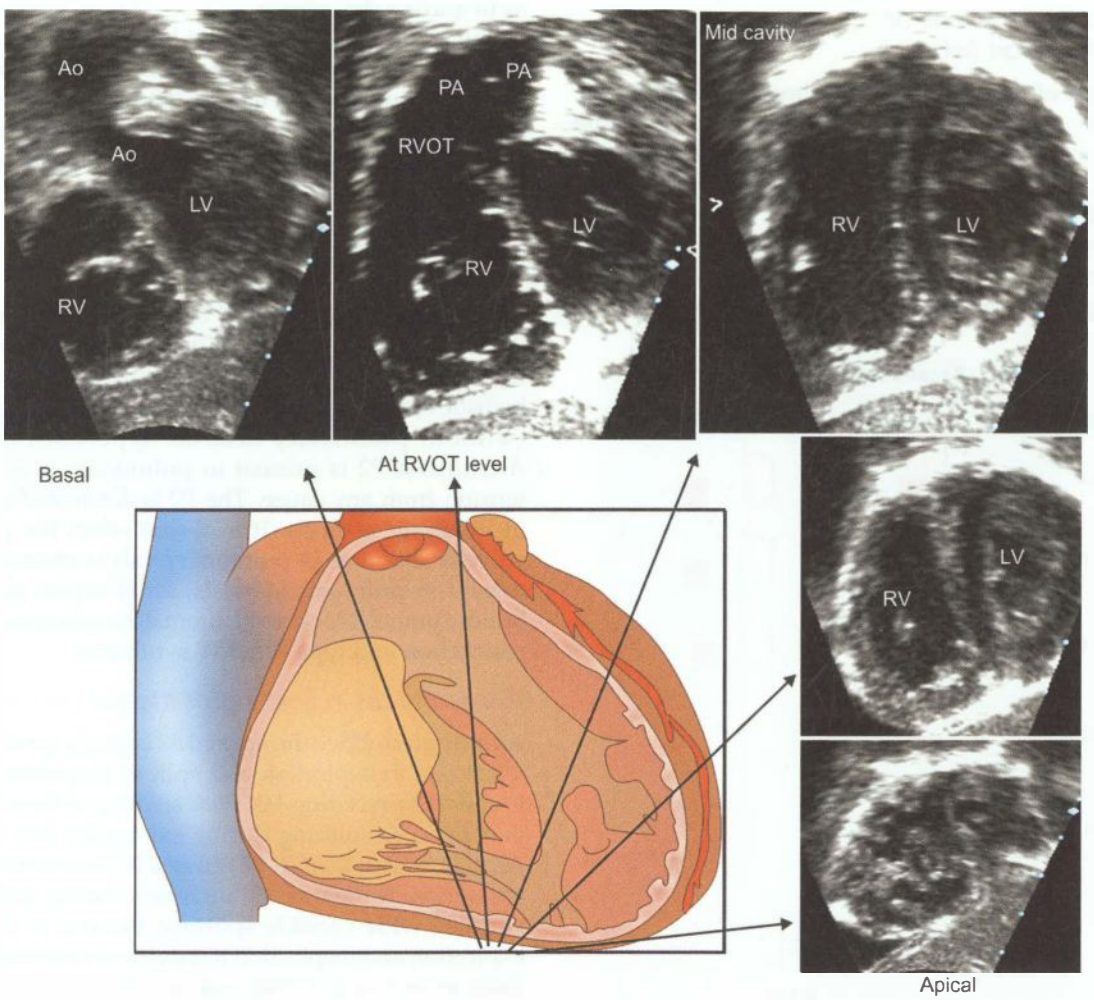

Fig. 15.6: Two dimensional echocardiography. An illustrative example of how the ventricular septum can be sectioned at different levels to screen for ventricular septal defects. The lines with arrows represent levels at which cross-sctional images are obtained. The still frames of the respective echocardiograms are shown in relation to each of the level at which a section is obtained. Ao aorta; LV left ventricle; PA pulmonary artery; RV right ventricle; RVOT right ventricular outflow tract

flow calculations at a number of locations) is also obtained. Limitations include lack of expertise for interpretation and requirement of general anaesthesia to enable breath-holding.

Computed tomography (CT) CT overcomes some of the limitations of magnetic resonance imaging because it has a much lower image acquisition time. However, exposure to ionizing radiation is a major concern.

Diagnostic cardiac catheterization The role of diagnostic cardiac catheterization for patients with CHD has declined with the availability of high quality echocardiography, MRI and CT. Since cardiac catheterization is an invasive procedure its performance requires careful planning so that the information desired may be obtained with minimum risk to the patient. Diagnostic cardiac catheterization should be advised if non-invasive investigations do not provide information that is required for surgery. Accurate estimation of filling pressures and pulmonary artery pressures, determination of blood flow and vascular resistance and definition of coronary arteries are best performed through cardiac catheterization.

Definitive and Palliative Treatment

To ensure the best possible results of management of CHD it is necessary to assemble a team of qualified individuals who are a part of a comprehensive pediatric heart program. The details are shown in Fig. 15.7. Definitive treatment for CHD requires the collaborative use of surgery and catheter-based interventions.

Surgery

Surgery is still the best option for definitive treatment or palliation of most CHD. A simple scheme of classification of surgery for congenital heart disease is shown in Fig. 15.8. Surgeries for CHD are broadly classified as open heart (requiring use of cardiopulmonary bypass - CPB)

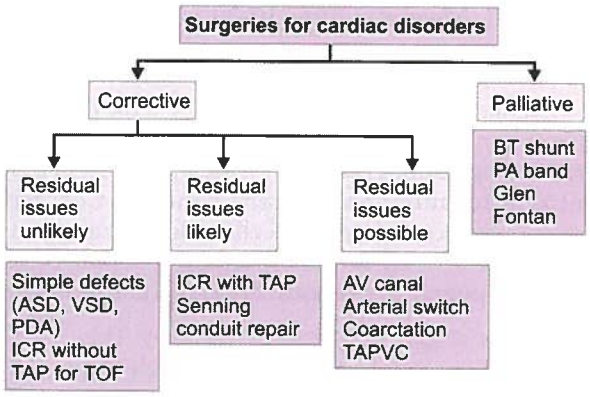

Fig. 15.8: Classification of common congenital heart operations. ASD atrial septal defect; BT shunt Blalock–Taussig shunt; Fontan total cavopulmonary anastomosis; Glen bidirectional cavopulmonary anastomosis; ICR intracardiac repair; PA band pulmonary arterial band; PDA patent ductus arteriosus; TAP transannular patch; TAPVC total anomalous pulmonary venous connection

and closed heart (not requiring CPB). Most corrective operations and many palliative operations fall under the former category. These procedures are generally a more significant and expensive undertaking because of the use of the CPB circuit and a substantially larger number of disposable items. The morbidity of open heart operations is proportionate to the duration of exposure to CPB and the cross-clamp time (the period of time when heart beating is deliberately brought to a standstill through the use of cardioplegia).

Corrective operations Corrective surgery is possible for most atrial and ventricular septal defects, with no significant longterm concerns (Fig. 15.8). If the repair of TOF does not result in pulmonary valve incompetence, longterm concerns are minimal. Certain operations require careful longterm followup because longterm concerns are

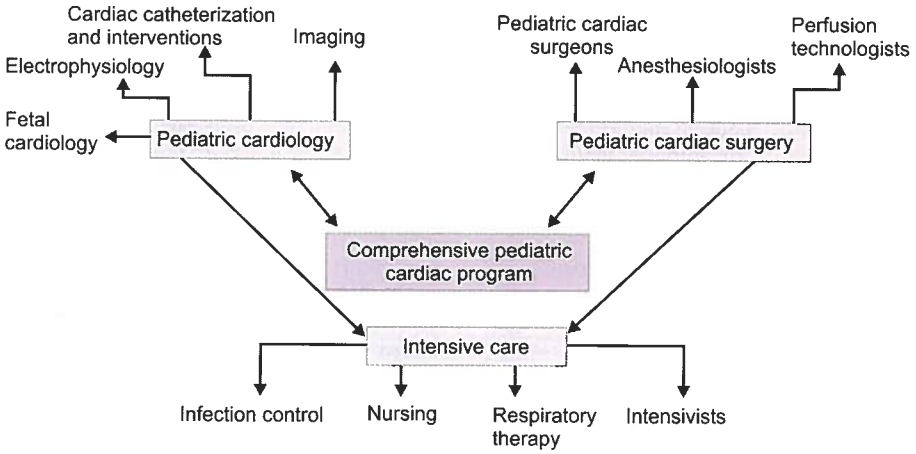

Fig. 15.7: The constituents of a comprehensive pediatric heart program for optimal care of children with congenital heart disease. For the best and consistently reproducible results in newborn and infant heart surgery the presence of such a team is vital

substantial, especially after 10–20 yr followup. These include the Senning operations (atrial switch) for transposition where the right ventricle continues to support the systemic circulation, TOF repair where the pulmonary valve is rendered incompetent through a transannular patch and operations that require the placement of a right ventricle to pulmonary artery conduit. Corrective surgeries associated with excellent longterm survival include the arterial switch operations, repair of total anomalous pulmonary venous connection and coarctation.

Surgery for single ventricle physiology This category includes all anatomic examples of single ventricle. In addition, this includes situations when one atrioventricular valve is atretic or one of the ventricles is hypoplastic. The surgical management of single ventricle physiology is performed in stages. The first stage involves early pulmonary arterial band (usually under the age of 3 months) for patients who have increased pulmonary blood flow and the modified Blalock-Taussig shunt for those who have reduced pulmonary blood flow with cyanosis. The second operation is the bidirectional Glen shunt. The superior vena cava is anastomosed to the right pulmonary artery. This operation allows effective palliation until the age of 4–6 yr. The Fontan operation is finally required for elimination of cyanosis. All the systemic venous return is routed to the pulmonary artery. Several requirements should be fulfilled before this operation can be successfully undertaken. This is a palliative procedure and there are important longterm issues in a substantial proportion of the survivors.

Catheter Interventions

Catheter interventions are possible in many patients with CHD. Many simple defects such as secundum ASD, PDA and selected muscular VSD can now be closed in the catherization laboratory. Additionally, balloon valvotomy is now the first line of treatment for congenital stenosis of the pulmonary and aortic valves. Additional details of catheter intervention procedures are shown in Table 15.12. Catheter-based interventions are far less traumatic than surgery, accomplished with ease and allow rapid recovery.

Complications of Congenital Heart Disease

A number of complications occur in patients with CHD.

Pulmonary arterial hypertension (PAH) Lesions that have the greatest likelihood of developing PAH include cyanotic heart disease with increased pulmonary blood flow. Here irreversible changes in pulmonary vasculature develops rapidly often during infancy. It is particularly important to correct or appropriately palliate these lesions early (ideally within the first few months of life). Large

Table 15.12: Congenital heart defects amenable to catheter-based interventions

Lesion	*Procedure*	*Comments*
Atrial septal defect	Device closure	Amenable to device closure if the defect is in the fossa ovalis and has sufficient margins
Patent ductus arteriosus (PDA)	Coil or device closure	Majority can be closed by catheter interventions, except large PDA in infants
Muscular ventricular septal defect (VSD)	Device closure	Device closure is an option for older infants (>8 kg)
Membranous VSD	Device closure	Controversial; carries a small risk of heart block
Pulmonary valve stenosis	Balloon pulmonary valvotomy	Treatment of choice for most forms except dysplastic valves in Noonan syndrome
Aortic valve stenosis	Balloon aortic valvotomy	Initial treatment of choice at all ages; however, dilated aortic valves eventually need surgery
Branch pulmonary artery stenosis	Balloon dilation with stenting	Stenting preferred to surgery
Coarctation of aorta	Balloon dilation with or without stenting	Neonates: Surgery preferred due to high risk of recurrence Older infants: balloon dilatation satisfactory Children >10 yr: Dilatation with stenting provides complete relief
Coronary artery fistula	Coil or device closure	Treatment of choice
Pulmonary arteriovenous malformations	Coil or device closure	Treatment of choice when discrete; surgery preferred for diffuse malformations
Duct dependent pulmonary circulation	Stenting of the PDA	Offered, in selected cases, as an alternative to Blalock-Taussig shunt
Pulmonary atresia with intact ventricular septum	Valve perforation followed by balloon dilation	Preferred procedure in some centers
Ruptured sinus of Valsalva aneurysm	Device closure	Preferred option in selected cases
Transposition of great arteries	Balloon atrial septosomy	For palliation before definitive surgery

acyanotic post-tricuspid shunts are also prone to early development of PAH and should be ideally corrected early, preferably within the first year. In pre-tricuspid shunts, PAH develops slowly and unpredictably. While most patients with ASD will have mild or no PAH throughout their lives, a small proportion develop accelerated changes in the pulmonary vasculature. Some of the key features associated with the development of PAH include: large size of the defect; presence of pulmonary venous hypertension; airway obstruction or syndromic association, (e.g. trisomy 21); prolonged duration of exposure to increased pulmonary blood flow; and residence at high altitude.

Infective endocarditis or endarteritis (IE) Endocarditis can complicate CHD, especially in patients with significant turbulence created by high-pressure gradients, e.g. restrictive VSD and PDA, tetralogy of Fallot, and left ventricular outflow tract obstruction. Some surgical operations (such as the Blalock-Taussig shunt) are also associated with increased risk of IE or endarteritis. Lesions with little or no turbulent flows, such as ASD are not associated with increased risk. The risk of endocarditis increases after dentition, hence the importance of good dental hygiene in patients with CHD cannot be over emphasized.

Growth and nutrition This is affected in all forms of CHD and is particularly striking in large left to right shunts. Children with CHD show high prevalence of malnutrition, which improves after correction of the underlying condition. Catch up growth is slow if CHD is corrected late.

Myocardial dysfunction Chronic volume overload results in ventricular enlargement and ventricular dysfunction that is typically reversed after correction. A small proportion of patients with severe hypoxia also develop severe dysfunction involving both ventricles. Heart failure is mostly the result of hemodynamic consequences of increased pulmonary blood flow, mitral or tricuspid valve regurgitation and severe myocardial hypertrophy. Systolic dysfunction is a relatively less common cause.

Neurologic and neurodevelopmental consequences Chronic hypoxia, *in utero* hypoxia and hypoperfusion and open-heart surgery contribute substantially to morbidity. Brain abscess is uniquely associated with cyanotic heart disease (typically beyond the age of 2 yr) where the right to left shunt bypasses the pulmonary filter.

Polycythemia Older children with cyanotic CHD are prone to complications from a chronically elevated red cell turnover. These include symptoms of hyperviscosity, gout, renal failure and gall stones.

Rhythm disorders and sudden death Chronic enlargement of heart chambers predispose to tachyarrhythmia. Chronic right atrial enlargement (such as atrial septal defect, Ebstein syndrome, severe tricuspid regurgitation) predisposes to atrial flutter, which might be persistent and refractory. Chronic right ventricular enlargement predisposes to ventricular tachycardia and may precipitate sudden cardiac arrest. This is a significant longterm concern after TOF repair where the pulmonary valve is rendered incompetent. Similarly left ventricular hypertrophy and dysfunction are associated with high risk of ventricular tachycardia.

Cyanotic spells Patients with the VSD-PS physiology are prone to cyanotic spells. Cyanotic spells are due to an acute decrease in pulmonary blood flow, increased right to left shunt and systemic desaturation due to (i) Infundibular spasm due to increase in circulating catecholamines, during feeding or crying; (ii) Activation of mechanoreceptors in right ventricle (due to decrease in systemic venous return) or in left ventricle (due to decrease in pulmonary blood flow), leads to peripheral vasodilatation and fall in systemic vascular resistance producing increased right to left shunt and systemic desaturation.

A cyanotic spell is an emergency, which requires prompt recognition and intervention to prevent disabling cerebrovascular insults or death. The spell needs to be taken seriously not just because of the immediate threat but also because it indicates the need for early operation. It is commonly seen below 2 yr (peaks between 2 and 6 months). The onset is spontaneous and unpredictable and occurs more often in early morning, although it can occur at anytime in the day. The infant cries incessantly, is irritable and inconsolable. Tachypnea is prominent feature; there is deep and rapid breathing without significant subcostal recession. Cyanosis deepens as the spell progresses. Later gasping respiration and apnea ensues, which leads to limpness and ultimately anoxic seizures. Spells can last from minutes to hours. Auscultation reveals softening or disappearance of pulmonary ejection murmur. The management is summarized in Table 15.13.

Natural History

Some defects have a tendency towards spontaneous closure and this can influence the timing of intervention. The defects known to close spontaneously are atrial and ventricular septal defects, and patent ductus arteriosus. The variables influencing the likelihood of spontaneous closure include: age at evaluation (lower likelihood of closure with increasing age), size of the defect (smaller defects more likely to close) and location of the defects (fossa ovalis ASD and perimembranous and muscular VSDs can close on their own) (Table 15.14).

A review of natural history of common forms of CHD shows that without correction, many children with CHD (especially those with cyanotic CHD) will not survive beyond early childhood. The outcomes are improved by correction through surgery and, in some situations, through catheter interventions. Despite curative surgery, some patients have important longterm sequelae. For example, patients with tetralogy of Fallot who have

Table 15.13: Management of hypercyanotic spells

Immediate steps

Check airway; deliver oxygen by face mask or nasal cannula
Knee chest position
Sedate with morphine (0.2 mg/kg subcutaneously *or* ketamine 3–5 mg/kg/dose intramuscular)
Administer sodium bicarbonate at 1–2 ml/kg (diluted 1:1 or in 10 ml/kg N/5 in 5% dextrose)
Correct hypovolemia (10 ml/kg of dextrose normal saline)
Keep child warm
Transfuse packed red cell if anemic (hemoglobin <12 g/dl)
Use beta blockers unless contraindicated by bronchial asthma or ventricular dysfunction; metoprolol is given at 0.1 mg/kg IV slowly over 5 min and repeated every 5 min for maximum 3 doses; may be followed by infusion at 1–2 µg/kg/min
Monitor saturation, heart rates and blood pressure; keep heart rate below 100/minute

Persistent desaturation and no significant improvement

Consider vasopressor infusion: methoxamine 0.1–0.2 mg/kg/dose IV or 0.1– 0.4 mg/kg/dose IM, or phenylephrine 5 µg/kg as IV bolus and 1–4 µg/kg/min as infusion
If spells persist: Paralyze the patient, electively intubate and ventilate; plan for palliative or corrective surgery
Seizures are managed with diazepam at 0.2 mg/kg IV or midazolam at 0.1–0.2 mg/kg/dose IV

Following a spell

Conduct a careful neurological examination; perform CNS imaging if focal deficits are present
Initiate therapy with beta-blocker at the maximally tolerated dose (propranolol 0.5–1.5 mg/kg q 6–8 hr); helps improve resting saturation and decreases frequency of spells
Ensure detailed echocardiography for disease morphology
Plan early corrective or palliative surgery
Administer iron in therapeutic (if anemic) or prophylactic dose

Prevention

Counsel parents regarding the possibility of recurrence of spells and precipitating factors (dehydration, fever, pain) and measures to avoid them (e.g. use of local anesthetic patches and/or sedation with IM ketamine to avoid pain during venesection)
Encourage early surgical repair

undergone curative repair might show progressive right ventricular dilation with increased risk of late heart failure and sudden cardiac death. There are longterm concerns after the arterial switch operation (aortic root dilation, silent coronary occlusion), AV canal repair (AV valve regurgitation) and coarctation (residual hypertension, aortic aneurysm). Operations that involve placement of conduits (pulmonary atresia, Rastelli operations) require replacement upon growth of the child. Conditions associated with satisfactory longterm survival include small left to right shunts and bicuspid aortic valves. survival is also satisfactory for many patients with atrial septal defect, coarctation of aorta, pink TOF, mild Ebstein anomaly and some forms of corrected transposition of great arteries.

Prevention of CHD

Education of lay public on the risks associated with consanguinity, drugs and teratogens in the first trimester of pregnancy and widespread immunization against rubella has limited role in preventing CHD. However, most CHD do not have an identifiable etiology and there is no effective strategy for their prevention in the periconceptional period.

Fetal echocardiography is emerging as a modality for early diagnosis of CHD. Conditions that involve major chamber discrepancy (such as hypoplastic left heart syndrome), single ventricles and common AV canal can be identified by routine screening as early as 14–16 weeks gestation. With some refinement, additional conditions such as tetralogy of Fallot, large VSD, transposition of great vessels and persistent truncus arteriosus can be detected. Once a serious CHD is identified, it is vital to counsel the families about postnatal manifestations, natural history, surgical options and their longterm outlook. Before 20 weeks of gestation, medical termination of pregnancy is an option. Results of fetal echocardiography enable delivery at a center with comprehensive pediatric heart program. While echocardiography is recommended for future pregnancies after diagnosis of serious CHD in a child, this practice has low yield because only 2–8% CHD recur. The

Table 15.14: Spontaneous closure of heart defects

Variable	*Likelihood of spontaneous closure*
Age at evaluation	More likely in younger patients; most ASD and VSD that finally close or become very small do so by the age of 3 yr; PDA either close in the first 2–4 weeks or not at all, particularly in preterm infants
Size of the defect	Larger defects are unlikely to close spontaneously, such as ASD >8 mm and large unrestrictive VSD
Location of the defect	Fossa ovalis ASD tend to close spontaneously while ostium primum and sinus venosus defects do not close; muscular VSD have high likelihood of spontaneous closure; perimembranous VSD can also close spontaneously; outlet (sub-pulmonic) VSD may close by prolapse of the aortic valve, resulting in aortic regurgitation; inlet VSD and malaligned VSD (as in tetralogy of Fallot) do not close spontaneously

ASD atrial septal defect; PDA patent ductus arteriosus; VSD ventricular septal defect

highest chance of recurrence is with obstructive lesions of the left heart.

ACYANOTIC CONGENITAL HEART DEFECTS

Atrial Septal Defect

Atrial septal defect (ASD) account for as an isolated anomaly 5–10% of all CHD. Based on anatomy, ASD is classified as follows:

Fossa ovalis ASD. They are located in the central portion of atrial septum, in the position of foramen ovale. These defects are amenable to closure in the catheterization laboratory.

Sinus venosus ASD. These are located at junction of superior vena cava and right atrium. These defects do not have a superior margin because the superior vena cava straddles the defect. These defects are associated with anomalous drainage of one or more right pulmonary veins.

Ostium primum ASD. These defects are created by failure of septum primum, and are in lower part of the atrial septum; inferior margin of ASD is formed by the atrioventricular valve.

Coronary sinus ASD. An unroofed coronary sinus is a rare communication between the coronary sinus and the left atrium, which produces features similar to other types of ASD.

Physiology and Findings

The physiology of ASD is that of a pre-tricuspid shunt. The enlarged right ventricle results in a parasternal impulse. The ejection systolic murmur originates from the pulmonary valve because of the increased blood flow. An increased flow through the tricuspid valve may result in a soft delayed diastolic rumble at the lower left sternal border. The overload of the right ventricle due to an increase in venous return prolongs the time required for its emptying resulting in delayed P2. This delay also results from the prolonged 'hang-out' interval because of the very low resistance in the pulmonary circulation. Additionally, since the two atria being linked *via* the large ASD, inspiration does not produce any net pressure change between them and respiration related fluctuations in systemic venous return to the right side of the heart are abolished; thereby the fixed S2 (Fig. 15.9).

The *electrocardiogram* of ostium secundum ASD is characterized by right axis deviation and right ventricular hypertrophy. The characteristic configuration of the lead V1 is rsR' seen in almost 90% patients (Fig. 15.10). Presence of left axis deviation beyond –30° suggests ostium primum ASD (Fig. 15.11). The chest X-ray shows mild to moderate cardiomegaly, right atrial and right ventricular enlargement, prominent main pulmonary artery segment, a relatively small aortic shadow and plethoric lung fields. The left atrium does not enlarge in size in atrial septal defect, unless associated with other anomalies like mitral

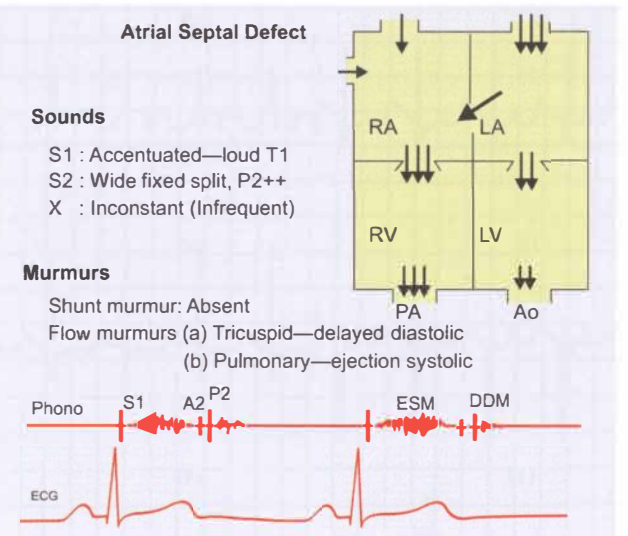

Fig. 15.9: Summary of auscultatory findings in the atrial septal defect, Ao aorta; A2 aortic component of the second sound; ESM ejection systolic murmur; LA left atrium; LV left ventricle; PA pulmonary artery; P2 pulmonic component of the second sound; RA right atrium; RV right ventricle; S1 first sound; S2 second sound; X click

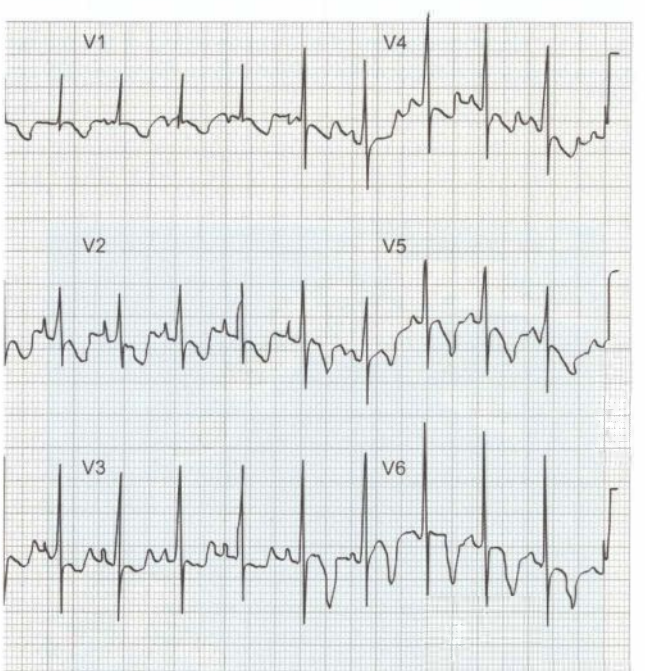

Fig. 15.10: Electrocardiogram of atrial septal defect of the secundum type showing rSR' pattern in lead V1

regurgitation. Echocardiogram shows increased size of the right ventricle with paradoxical ventricular septal motion. 2D echo in subcostal view often best identifies the defect. The echocardiogram allows decision regarding suitability of catheter closure, based on measurements of the defect and the adequacy of margins (Fig. 15.12).

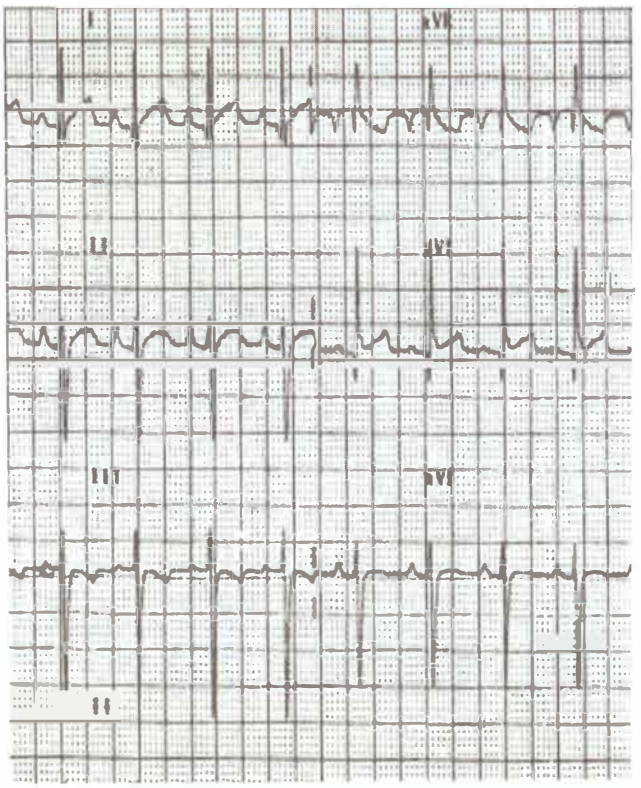

Fig. 15.11: Electrocardiogram of atrial septal defect of the primum type associated with endocardial cushion defect. The mean QRS axis is–60°

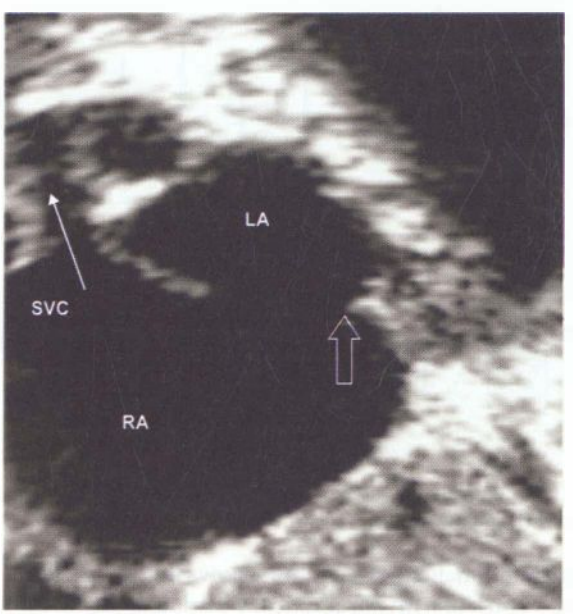

Fig. 15.12: Echocardiogram of atrial septal defect Subxiphoid short axis view of the atrial septum shows deficient posterior-inferior rim (arrow). IVC inferior vena cava; LA left atrium; RA right atrium; SVC superior vena cava

Assessment of the Severity

The size of the left to right shunt is directly proportional to the intensity of the murmurs and heart size. The larger the shunt, the more the cardiomegaly and the louder the pulmonary and tricuspid murmurs.

Natural History and Complications

Heart failure is exceptional in infancy. A small proportion of patients might develop pulmonary hypertension, by the second or third decade. ASD closure is recommended to prevent complications of atrial arrhythmias and heart failure in late adulthood.

Treatment

Most fossa ovalis defects with good margins can be closed percutaneously in the catheterization laboratory with occlusive devices. Others require surgical closure. Closure is recommended before school entry to prevent late complications. Small defects (<8 mm) can be observed. Spontaneous closure is well recognized in small defects that are diagnosed in infancy or early childhood.

Ventricular Septal Defect (VSD)

This is the most common congenital cardiac lesion identified at birth accounting for one-quarter of all CHD. VSD is a communication between the two ventricles; 90% are located in the membranous part of the ventricular septum with variable extension into the muscular septum. Others are located in the muscular septum and can be multiple (Fig. 15.13).

Hemodynamics

VSD results in shunting of oxygenated blood from the left to the right ventricle. The left ventricle starts contracting

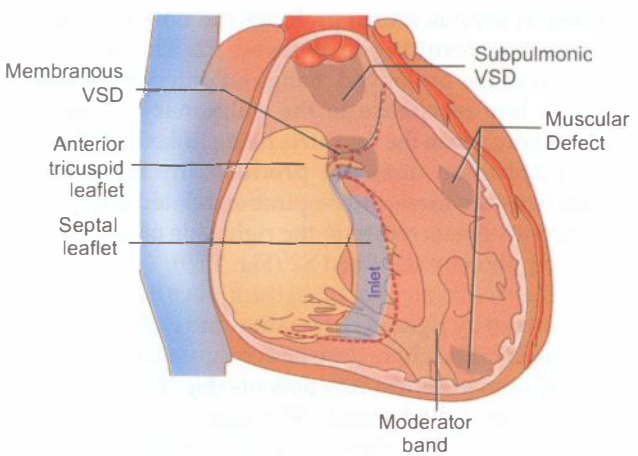

Fig. 15.13: Diagrammatic representation of the common locations of ventricular septal defects (VSD). Membranous septum is the commonest location. Subpulmonic VSD, located in the outlet septum, have a high risk of aortic valve prolapse. Muscular VSDs can occur anywhere in the muscular part of septum

before the right ventricle. The flow of blood from the left ventricle to the right ventricle starts early in systole. When the defect is restrictive, a high pressure gradient is maintained between the two ventricles throughout the systole. The murmur, starts early, masking the first sound and continues throughout the systole with almost the same intensity appearing as a pansystolic murmur on auscultation and palpable as a thrill. Toward the end of systole, the declining left ventricular pressure becomes lower than the aortic pressure. This results in closure of the aortic valve and occurrence of A2. At this time, however, the left ventricular pressure is still higher than the right ventricular pressure and the left to right shunt continues. The pansystolic murmur, therefore, ends beyond A2 completely masking it (Fig. 15.14).

The left to right ventricular shunt occurs during systole at a time when the right ventricle is also contracting and its volume is decreasing. The left to right shunt, therefore, streams to the pulmonary artery more or less directly. This flow of blood across the normal pulmonary valve results in an *ejection systolic murmur at the pulmonary valve.* On the bedside, however, the ejection systolic murmur cannot be separated from the pansystolic murmur. The effect of the ejection systolic murmur is a *selective transmission of the pansystolic murmur to the upper left sternal border,* where its ejection character can be recognized since it does not mask the aortic component of the second sound.

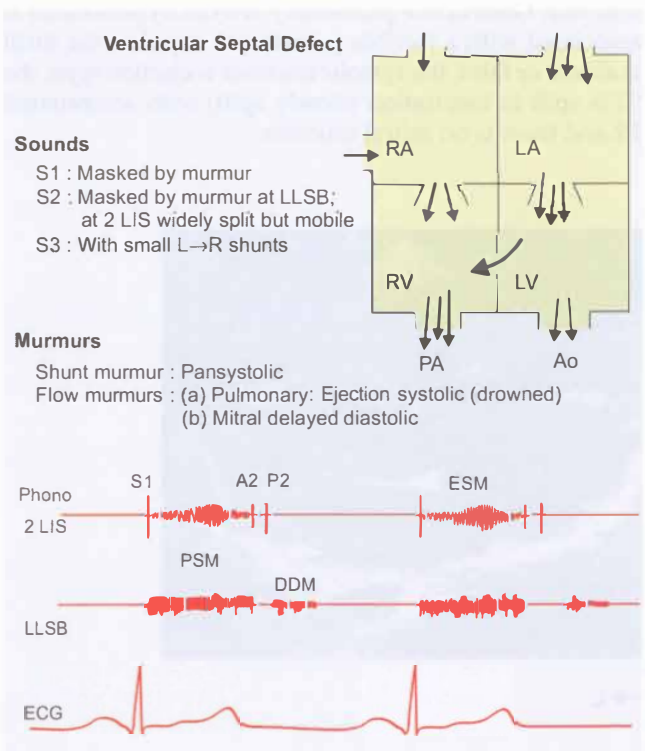

Fig. 15.14: Summary of auscultatory findings in ventricular septal defect. 2 LIS second left interspace; LLSB lower left sternal border; PSM pansystolic murmur

The large volume of blood passing through the lungs is recognized in the chest X-ray as *pulmonary plethora.* The increased volume of blood finally reaches the left atrium and may result in *left atrial enlargement.* Passing through a normal mitral valve the large volume of blood results in a *delayed diastolic murmur at the apex.* The intensity and duration of the delayed diastolic murmur at the apex is directly related to the size of the shunt. The large flow across the normal mitral valve also results in *accentuated first sound,* not appreciable on the bedside as it is drowned by the pansystolic murmur. Since the left ventricle has two outlets, the aortic valve allowing forward flow and the VSD resulting in a backward leak, it empties relatively early. This results in an early A2. *Since the ejection into the right ventricle and pulmonary artery is increased because of the left to right shunt the P2 is delayed.* Therefore, the second sound is *widely split but varies with respiration* in patients with VSD and a large left to right shunt. There is also an increase in the intensity of the P2.

Clinical Features

Patients with VSD can become symptomatic around 6 to 10 weeks of age with congestive cardiac failure. Premature babies with a VSD can become symptomatic even earlier. Palpitation, dyspnea on exertion and frequent chest infection are the main symptoms in older children. The precordium is *hyperkinetic with a systolic thrill* at the left sternal border. The heart size is moderately enlarged with a left ventricular type of apex. *The first and the second sounds are masked by a pansystolic murmur* at the left sternal border. The second sound can, however, be made out at the second left interspace or higher. It is *widely split and variable with accentuated P2. A third sound may be audible at the apex. A loud pansystolic murmur is present at the left sternal border. The maximum intensity of the murmur may be in the third, fourth or the fifth left interspace. It is well heard at the second left interspace but not conducted beyond the apex.* A delayed diastolic murmur, starting with the third sound is audible at the apex (Fig. 15.14).

The electrocardiogram in VSD is variable. Initially all patients with VSD have right ventricular hypertrophy. Because of the delay in the fall of pulmonary vascular resistance due to the presence of VSD, the regression of pulmonary arterial hypertension is delayed and right ventricular hypertrophy regresses more slowly. In small or medium sized VSD, the electrocardiogram becomes normal. In patients with VSD and a large left to right shunt, without pulmonary arterial hypertension, the electrocardiogram shows left ventricular hypertrophy by the time they are six months to a year old. There are, however, no ST and T changes suggestive of left ventricular strain pattern. Patients of VSD who have either pulmonic stenosis or pulmonary arterial hypertension may show right as well as left ventricular hypertrophy or pure right ventricular hypertrophy. The mean QRS axis in the frontal plane generally lies between +30 and +90°.

The cardiac silhouette on chest X-ray is left ventricular type with the heart size determined by the size of the left to right shunt (Fig. 15.15). The pulmonary vasculature is increased; aorta appears normal or smaller than normal in size. There may be left atrial enlargement in patients with large left to right shunts. Patients of VSD with a small shunt either because the ventricular defect is small or because of the associated pulmonic stenosis or pulmonary arterial hypertension have a normal sized heart. Echocardiogram shows increased left atrial and ventricular size as well as exaggerated mitral valve motion. 2D echo can identify the site and size of defect almost all cases (Fig. 15.16), presence or absence of pulmonic stenosis or pulmonary hypertension and associated defects.

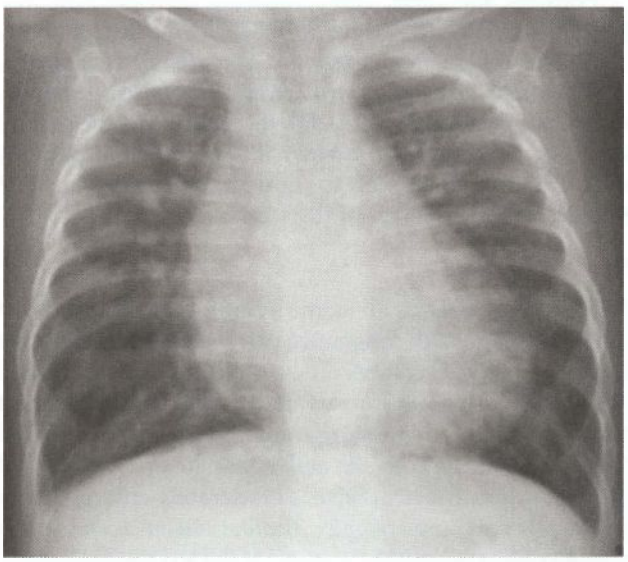

Fig. 15.15: Chest X-ray in ventricular septal defect. Note the cardiac enlargement mainly involving the left ventricle together with increased lung vasculature as suggested by the size and increased number of end-on vessels in the lung fields

Assessment of Severity

If the *VSD is small, the left to right shunt murmur continues to be pansystolic* but since the shunt is small, the second sound is normally split and the intensity of P2 is normal. There is also *absence of the delayed diastolic mitral murmur.* If the VSD is very small it acts as a stenotic area resulting in an ejection systolic murmur. This is a relatively common cause of systolic murmurs in young infants that disappear because of the spontaneous closure.

If the *VSD is large it results in transmission of left ventricular systolic pressure to the right ventricle.* The right ventricular pressure increases and the difference in the systolic pressure between the two ventricles decreases. The *left to right shunt murmur becomes shorter and softer* and on the bedside appears as an ejection systolic murmur.

Patients of VSD may have either *hyperkinetic* or *obstructive pulmonary arterial hypertension.* The P2 is accentuated in both. In the former, there is large left to right shunt whereas the latter is associated with a small left to right shunt. In hyperkinetic pulmonary arterial hypertension the cardiac impulse is hyperkinetic with a pansystolic murmur and thrill, widely split and variable S2 with accentuated P2 and a mitral delayed diastolic murmur. Obstructive pulmonary arterial hypertension is associated with a forcible parasternal impulse, the thrill is absent or faint, the systolic murmur is ejection type, the S2 is spilt in inspiration (closely split) with accentuated P2 and there is no mitral murmur.

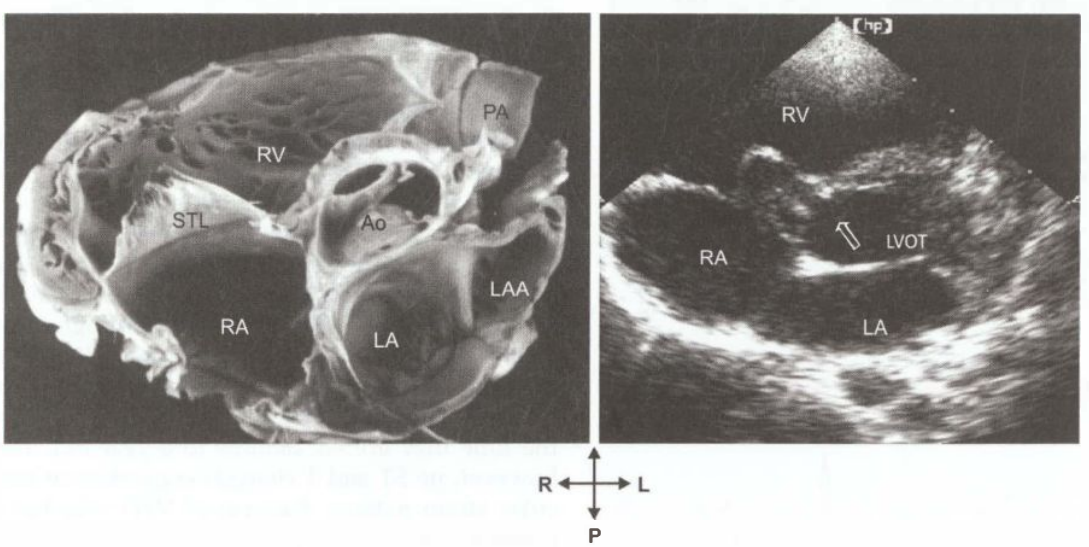

Fig. 15.16: Echocardiogram (right frame) with anatomic correlates (left) in membranous ventricular septal defects. This view is a parasternal short axis view. Ao aortic root; LA left atrium; LVOT left ventricular outflow tract; RA right atrium, RV right ventricle; arrow points to the VSD that is partly closed by aneurysm of the septal leaflet of the tricuspid valve

Thus on the basis of the assessment of physical findings it is possible to separate very small, small, medium sized and large VSD. It is also possible to decide whether there is associated pulmonic stenosis or pulmonary arterial hypertension of the hyperkinetic or obstructive variety. Doppler echo estimates the gradient between the left and right ventricles, thus helping in the assessment of right ventricular and pulmonary artery pressure.

Course and Complications

Patients with VSD have a very variable course. They may develop congestive cardiac failure in infancy which is potentially life threatening. It has been estimated that almost 70% of all ventricular defects become smaller in size. A smaller proportion will disappear entirely. In almost 90% of patients who have spontaneous closure of the defect, it occurs by the age of three years, though it may occur as late as 25 yr or more. Muscular VSD have the highest likelihood of spontaneous closure. Perimembranous VSD close with the help of the septal leaflet of the tricuspid valve and sub-pulmonic VSDs often become smaller as the aortic valve prolapses through it. However, this is not a desirable consequence and is often and indication for surgical closure.

Patients born with an uncomplicated VSD may develop *pulmonic stenosis* due to hypertrophy of the right ventricular infundibulum, develop *pulmonary arterial hypertension* or rarely develop *aortic regurgitation* due to prolapse of the right coronary or the non-coronary cusp of the aortic valve. Development of pulmonary arterial hypertension is a dreaded complication since if it is of the obstructive type the patient becomes inoperable.

A patient with a relatively small VSD often lives a lifetime without any symptoms or difficulty. Lastly, the VSD is the *commonest congenital lesion complicated by infective endocarditis*. The incidence of infective endocarditis has been estimated as 2/100 patients in a followup of ten years, that is 1/500 patient years. The incidence of infective endocarditis is small enough that it is not an indication for operation in small defects. However, it is important to emphasize good oral-dental hygiene in all patients with VSD.

Treatment

Medical management consists in control of congestive cardiac failure, treatment of repeated chest infections and prevention and treatment of anemia and infective endocarditis. The patients should be followed carefully to assess the development of pulmonic stenosis, pulmonary arterial hypertension or aortic regurgitation.

Surgical treatment is indicated if: (i) congestive cardiac failure occurs in infancy; (ii) the left to right shunt is large (pulmonary flow more than twice the systemic flow); and (iii) if there is associated pulmonic stenosis, pulmonary arterial hypertension or aortic regurgitation. Surgical treatment is not indicated in patients with a small VSD and in those patients who have developed severe pulmonary arterial hypertension and significant right to left shunt.

Operative treatment consists in closure of VSD with the use of a patch. The operation is performed through the right atrium. The operation can be done as early as a few months after birth if congestive failure cannot be controlled with medical management. With evidence of pulmonary hypertension, the operation should be performed as early as possible. Modern centers prefer to close VSD surgically in young infants. It is unwise to make the sick infants to wait for a certain weight threshold because most infants with large VSD do not gain weight satisfactorily. Episodes of respiratory infections require hospitalization and are particularly difficult to manage. For sick infants with pneumonia who require mechanical ventilation, surgery is considered after initial control of the infection. Major complications of surgery are: (i) complete heart block, (ii) bifascicular block, and (iii) residual VSD. These complications are rare and risk of surgery in uncomplicated defects is less than 1% in most centers.

Catheter closure of VSD is best suited for muscular defects in relatively older children (> 8–10 kg). There is a device designed for perimembranous defects as well. However, the risk of complete heart block with the membranous VSD occluder is significant and can occur late after implantation. Device closures of VSD require considerable technical expertise and should be attempted in dedicated centers.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is a communication between the pulmonary artery and the aorta. The aortic attachment of the ductus arteriosus is just distal to the left subclavian artery. The ductus arteriosus closes functionally and anatomically soon after birth; its persistence is called PDA.

Hemodynamics and Clinical Features

PDA results in a left to right shunt from the aorta to the pulmonary artery. *The flow occurs both during systole and diastole as a pressure gradient is present throughout the cardiac cycle between the two great arteries*, if the pulmonary artery pressure is normal. The flow of blood results in a murmur that starts in systole, after the first sound, and reaches a peak at the second sound. The murmur then diminishes in intensity and is audible during only a part of the diastole. Thus, it is a continuous murmur.

The PDA results in a systolic as well as diastolic overloading of the pulmonary artery. The increased flow after passing through the lungs reaches the left atrium. To accommodate the flow the left atrium enlarges in size. The increased volume of blood reaching the left atrium enters the left ventricle in diastole, across a normal mitral valve. The passage of this increased flow across the mitral valve results in *an accentuated first sound as well as a mitral*

delayed diastolic murmur. The large volume of blood in the left ventricle causes a prolongation of the left ventricular systole and an increase in the size of the left ventricle to accommodate the extra volume. The prolonged left ventricular systole results in *delayed closure of the aortic* valve and a late A2. With large left to right shunts, the S2 *may be paradoxically split*.

The large left ventricular volume ejected into the aorta results in *dilatation of the ascending aorta*. A dilated ascending aorta results in an *aortic ejection click*, which is audible all over the precordium and precedes the start of the continuous murmur. The large volume of blood from the left ventricle passing through a normal aortic valve results in an aortic ejection systolic murmur, however, on the bedside it is drowned by the loud continuous murmur and is usually not made out as a separate murmur.

Patients with PDA may become symptomatic in early life and develop congestive cardiac failure around 6–10 weeks of age. Older children give history of effort intolerance, palpitation and frequent chest infections. The flow from the aorta to the pulmonary artery is a leak from the systemic flow. This results in a *wide pulse pressure* and many of the signs of *wide pulse pressure* enumerated earlier in association with aortic regurgitation are present in patients who have a PDA. On the bedside, presence of prominent carotid pulsations in a patient with features of a left to right shunt suggests the presence of PDA. The cardiac impulse is hyperkinetic with a left ventricular type of apex. A systolic or a continuous thrill may be palpable at the second left interspace. *The first sound is accentuated and the second narrowly or paradoxically split with large left to right shunts*. With small shunts the second sound is normally split. The P2 is louder than normal. It is difficult to evaluate the S2 in patients with PDA, since the maximum intensity of the continuous murmur occurs at S2 and tends to mask the S2. The continuous murmur indicates presence of both a systolic as well as a diastolic difference in pressure between the aorta and pulmonary artery, thus excluding significant pulmonary arterial hypertension. *The murmur starts after the first sound and reaches the peak at the second sound. The murmur then diminishes in intensity and is audible only during a part of the diastole*. The peak at the second sound differentiates the PDA murmur from other causes of a continuous murmur. Additionally, the systolic portion of the murmur is very grating and rough. It appears to be broken into multiple systolic sounds—the multiple clicks. The murmur is best heard at the second left interspace and is *also well heard below the left clavicle* where it maintains its continuous character. There is a third sound at the apex, followed by a delayed diastolic murmur in large shunts (Fig. 15.17).

The electrocardiogram shows normal axis with left ventricular dominance or hypertrophy. Deep Q waves in left chest leads with tall T waves are characteristic of volume overloading of left ventricle. The roentgenogram (Fig. 15.18) exhibits cardiac enlargement with a left ventricular silhouette; cardiac size depends on the size of the left to right shunt. There may be left atrial enlargement. The ascending aorta and the aortic knuckle are prominent; pulmonary vasculature is plethoric. 2D echocardiogram

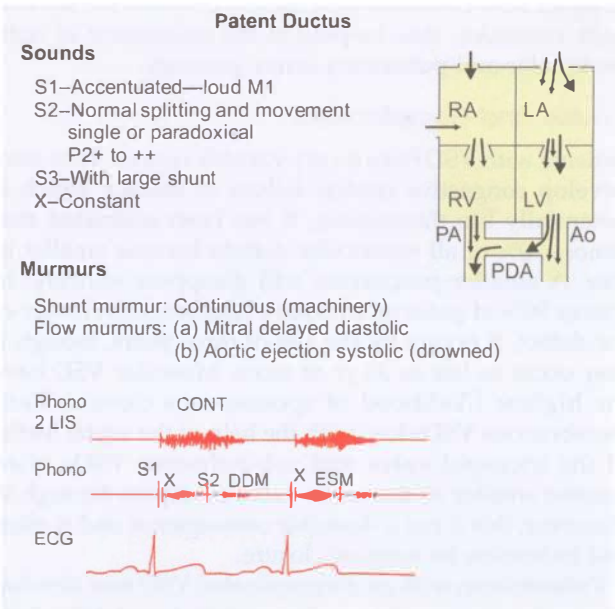

Fig. 15.17: Summary of auscultatory findings in patent ductus arteriosus (PDA) CONT continuous; DDM delayed diastolic murmur; ESM ejection systolic murmur; M1 mitral component of first sound

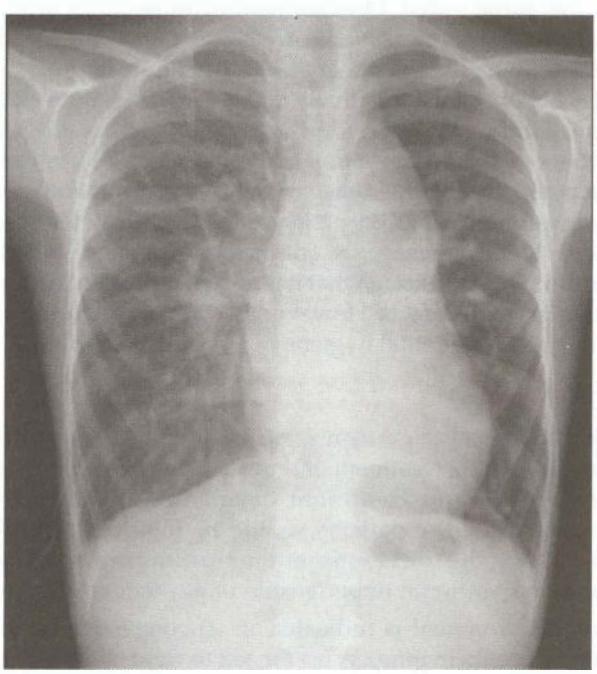

Fig. 15.18: Chest X-ray in an adolescent with a large patent ductus arteriosus. Note the enlargement of the aorta with a prominent aortic knuckle, large main pulmonary artery-left pulmonary artery and increased vasculature. There is no X-ray evidence of cardiac enlargement

confirms the diagnosis and measures size of PDA and identify its hemodynamic consequences. It is possible to obtain a semiquantitative assessment of shunt size and assess pulmonary artery pressure (Fig. 15.19).

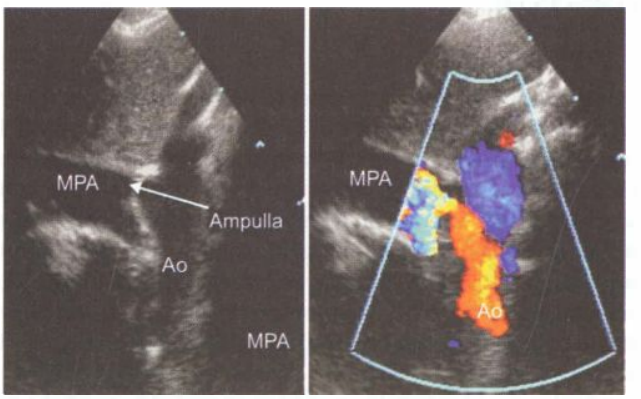

Fig. 15.19: Echocardiography in patent ductus arteriosus (PDA). The frame on the left is a cross sectional two dimensional view of the PDA and the frame on the right is a color flow image. The red flow represents flow reversal in the descending thoracic aorta as a result of a left to right shunt across the PDA. Ao aorta; MPA main pulmonary artery

Assessment of Severity

The evaluation of the size of the left to right shunt depends on a number of features: (i) the larger the heart size the larger the left to right shunt; (ii) absence of the third sound and delayed diastolic murmur indicates a small left to right shunt. Presence of the third sound indicates a moderate left to right shunt whereas an audible delayed diastolic murmur suggests a large left to right shunt; (iii) the wider the pulse pressure the larger the shunt.

Course and Complications

Neonates and infants have pulmonary hypertension at birth. The regression of pulmonary hypertension occurs slowly in the presence of PDA. The PDA murmur, therefore, is an ejection systolic murmur to start with (like in VSD) and assumes the continuous character only some weeks or months later. Congestive cardiac failure may occur within the first six weeks of life; cardiac failure can be controlled medically in uncomplicated patients. Patients with PDA develop pulmonary arterial hypertension earlier than VSD.

PDA may be associated with hyperkinetic or obstructive pulmonary arterial hypertension as in VSD. In both situations the murmur tends to lose the diastolic component and the P2 is accentuated. The hyperkinetic pulmonary hypertension is associated with a large heart and mitral delayed diastolic murmur whereas the obstructive variety is accompanied with a normal heart size and absence of the mitral diastolic murmur. With severe pulmonary arterial hypertension and a right to left shunt through a PDA, the normal splitting of S2 is maintained but the murmur disappears and the patients develop differential cyanosis.

Differential Diagnosis

The differential diagnosis of PDA includes conditions capable of giving a continuous murmur over the precordium. In addition, combination of a pansystolic murmur with an early diastolic murmur, which are partly superimposed on each other, may simulate a continuous murmur over the precordium. Differential diagnosis of a continuous murmur includes: (i) coronary arteriovenous fistula; (ii) ruptured sinus of Valsalva fistulae into the right side, (iii) aortopulmonary window; (iv) systemic arteriovenous fistula over the chest; (v) bronchial collateral murmurs; (vi) pulmonary arteriovenous fistula; (vii) peripheral pulmonic stenosis; (viii) venous hum including that associated with total anomalous pulmonary venous connection; and (ix) small atrial septal defect associated with mitral stenosis (Lutembacher syndrome). The impression of continuous murmur due to a combination of a pansystolic murmur and regurgitant diastolic murmur occurs most commonly in VSD associated with aortic regurgitation.

Treatment

A large PDA is better tolerated by term newborns when compared to premature newborns. Premature newborns with hemodynamically significant PDA that results in heart failure, respiratory distress or necrotizing enterocolitis require prompt management. Indomethacin or ibuprofen is likely to be effective before the age of 2-weeks in preterm newborns and is unlikely to be useful in term babies. The dose of indomethacin is 0.2 mg/kg/dose, orally, every 12–24 hr for three doses (second and third doses are at 0.1 mg/kg/dose for <48 hr-old and 0.25 mg/kg/dose for >7-days-old). Hepatic or renal insufficiency and bleeding tendency are contraindications. Newborns not responding to these agents require surgical ligation. The PDA in term infants may close spontaneously as late as one month after birth and it is worth waiting if the duct is large unless the heart failure is refractory.

Large PDA may result in congestive cardiac failure in infancy. Echocardiography allows ready confirmation of the diagnosis and estimation of hemodynamic severity of the PDA. Catheter based treatment (occlusive devices or coils) is now realistic in most patients with PDA (Fig. 15.20). They are technically challenging in small infants especially those <5 kg and should be performed in centers with experience. Indications for surgery for PDA include small infants with large ducts, preterm infants, and ducts that are very large (larger than the size of available devices) or in situations where surgery is the only affordable option (occlusive devices cost 2–3 time more than surgery).

Patients who have a PDA with pulmonary arterial hypertension are considered inoperable if a right to left shunt has appeared because of pulmonary arterial

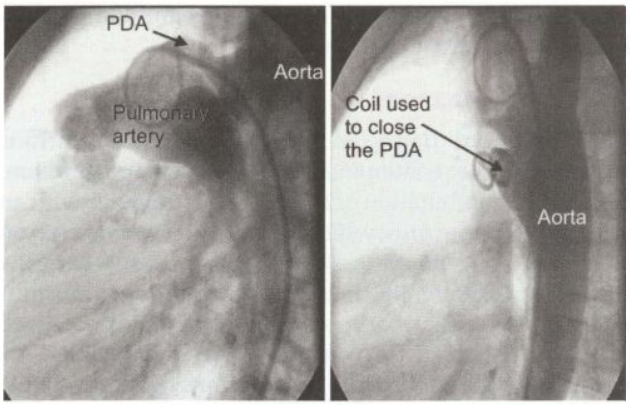

Fig. 15.20: Angiograms (aortogram) obtained before and after coil occlusion of a moderately large patent ductus arteriosus (PDA) showing complete occlusion

hypertension. Since the right to left shunt through the PDA flows down the descending aorta, cyanosis is present in toes but not in fingers. This is called differential cyanosis and is characteristic of PDA with pulmonary arterial hypertension and right to left shunt.

15

CYANOTIC HEART DISEASE

Tetralogy of Fallot

Among cyanotic CHD, tetralogy of Fallot (TOF) has a relatively favorable natural history that allows survival beyond infancy in about 75% of cases. As a result it is the most common cyanotic CHD encountered beyond the age of 1-yr constituting almost 75% of all blue patients. The physiology is that of VSD with pulmonic stenosis, as described above. Anatomically it is characterized by the classic tetrad: severe right ventricle outflow obstruction, large VSD, aorta that overrides the VSD and right ventricular hypertrophy. Multiple anatomical variations of TOF exist, which have a bearing on treatment (Table 15.15).

Hemodynamics

Physiologically the pulmonic stenosis causes *concentric right ventricular hypertrophy without cardiac enlargement* and an increase in right ventricular pressure (Fig. 15.21). When the right ventricular pressure is as high as the left ventricular or the aortic pressure, a right to left shunt appears to decompress the right ventricle. Once the right and left ventricular pressures have become identical, increasing severity of pulmonic stenosis reduces the flow of blood into the pulmonary artery and increases the right to left shunt. As the systolic pressures between the two ventricles are identical there is little or no left to right shunt and the VSD is silent. The right to left shunt is also silent since it occurs at insignificant difference in pressure between the right ventricle and the aorta. The flow from the right ventricle into the pulmonary artery occurs across the pulmonic stenosis producing an ejection systolic murmur. The more severe the pulmonic stenosis, the less the flow into the pulmonary artery and the bigger the right to left shunt. Thus the more severe the pulmonic stenosis, the shorter the ejection systolic murmur and the more the cyanosis. *Thus the severity of cyanosis is directly proportional to the severity of pulmonic stenosis, but the intensity of the systolic murmur is inversely related to the severity of pulmonic stenosis.* The VSD of TOF is always large enough to allow

Table 15.15: Anatomic variations in tetralogy of Fallot

Structure	*Common variation*	*Implications*
Right ventricular outflow tract	Degree of stenosis at various levels: infundibulum, valve, pulmonary annulus, main pulmonary artery stenosis	Severe stenosis manifests early; annular narrowing requires correction with transannular patch with significant late sequelae; predominant valvar stenosis may allow palliation with balloon valvotomy in selected cases
Branch pulmonary arteries (PA)	Stenosis of left pulmonary artery (LPA), absence of either branch PA, hypoplastic	Small branch PA may not allow surgical correction at early age; absent branch PA require placement of PA conduit
Pulmonary valve	Absent pulmonary valve with aneurysmal branch PA	Severe airway compression; manifestations chiefly respiratory
Ventricular septal defect (VSD)	VSD extended to inlet or outlet septum; restrictive VSD with severe right ventricular hypertrophy; additional muscular VSD	Surgical approach needs to be tailored
Coronary arteries	Origin of left anterior descending artery from right coronary artery	Abnormal vessel comes in way of corrective surgery
Atrial communication	Atrial septal defects, patent foramen ovale	Patent foramen ovale often helpful in early post-operative period; enables recovery
Aortopulmonary collaterals	Large major aortopulmonary collaterals	Collaterals need to be defined and closed if their supply overlaps with the native pulmonary artery supply

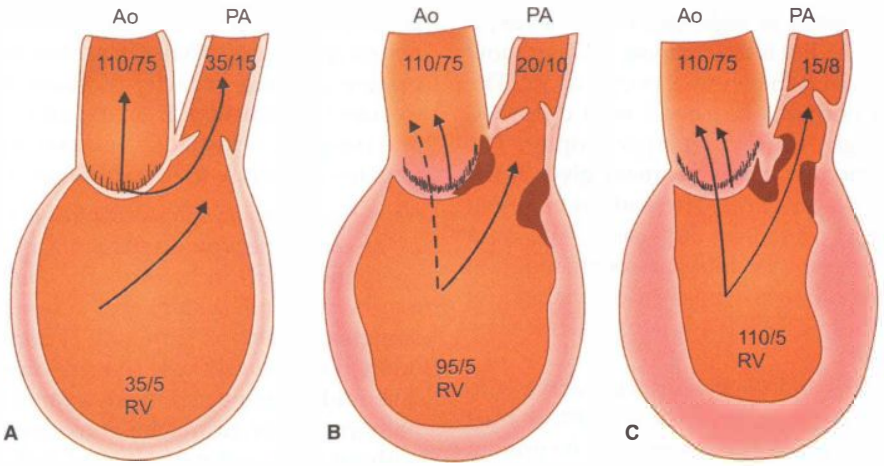

Fig. 15.21: Diagrammatic portrayal: (A) ventricular septal defect, (B) ventricular septal defect with moderate pulmonic stenosis, and (C) Fallot's tetralogy. (A) In the absence of pulmonic stenosis the right ventricular (RV) and the pulmonary artery (PA) pressures are normal or slightly elevated. Since the left ventricular (LV) pressure is higher, there is a systolic flow of blood from the LV into the PA through the RV. (B) If a VSD is associated with moderate pulmonic stenosis, the RV systolic pressure increases and there is RV hypertrophy. The left to right shunt decreases and the VSD murmur becomes softer. The pulmonic stenosis murmur, however, is loud. (C). In Fallot's tetralogy the RV and LV pressures are identical. There is no left to right shunt and as such the VSD is silent. The flow from RV to PA decreases, decreasing the intensity of pulmonic stenosis murmur. A right to left shunt occurs from RV to Aorta (Ao) at identical pressures. As such the right to left shunt is silent

free exit to the right to left shunt. Since the right ventricle is effectively decompressed by the VSD, congestive failure never occurs in TOF. The exceptions to this rule are (i) anemia; (ii) infective endocarditis; (iii) systemic hypertension; (iv) unrelated myocarditis complicating TOF; and (v) aortic or pulmonary valve regurgitation.

The right ventricular outflow obstruction results in a delay in the P2. Since the pulmonary artery pressure is reduced, the P2 is also reduced in intensity. The late and soft P2 is generally inaudible in TOF. The S2 is, therefore, single and the audible sound is A2. Since the aorta is somewhat anteriorly displaced, the audible single A2 is quite loud. The ascending aorta in TOF is large and may result in an aortic ejection click. On auscultation, the diastolic interval is completely clear in TOF as there is no third or fourth sound or a diastolic murmur.

Concentric right ventricular hypertrophy reduces the distensibility of the right ventricle during diastole. The right atrial contraction at the end of diastole causes a relatively large 'a' waves. Although the 'a' waves are prominent in the jugular venous pulse, they are not too tall unless right ventricular dysfunction is present.

Clinical Features

Patients with TOF may become symptomatic any time after birth. Neonates as well as infants may develop anoxic spells (paroxysmal attacks of dyspnea). Cyanosis may be present from birth or make its appearance some years after birth. The commonest symptoms are dyspnea on exertion and exercise intolerance. The patients assume a sitting posture—squatting—as soon as they get dyspneic. Although squatting is not specific for TOF, it is the commonest congenital lesion in which squatting is noted. Anoxic spells occur predominantly after waking up or following exertion. The child starts crying, becomes dyspneic, bluer than before and may lose consciousness. Convulsions may occur. The frequency varies from once in a few days to numerous attacks every day.

Physical examination discloses cyanosis, clubbing, slightly prominent 'a' waves in the jugular venous pulse, normal sized heart with a mild parasternal impulse, a systolic thrill in less than 30% patients, normal first sound, single second sound and an ejection systolic murmur which ends before the audible single second sound (Fig. 15.22). The electrocardiogram in TOF shows right axis deviation with right ventricular hypertrophy. The 'T'

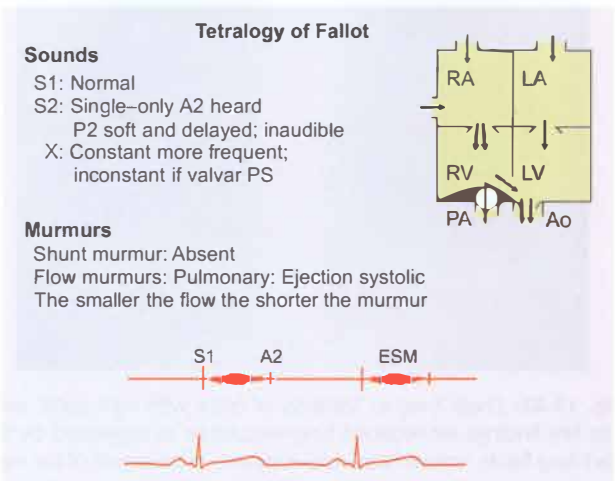

Fig. 15.22: Summary of auscultatory findings in tetralogy of Fallot. X systolic click. PS pulmonic stenosis

waves are usually inverted in right precordial leads; *P pulmonale* may be present, but is uncommon. V1 may show pure 'R' but transition to R/S complex occurs at V2. The chest X-ray shows a normal sized heart with upturned apex suggestive of right ventricular hypertrophy. The absence of main pulmonary artery segment gives it the shape described as *Coeur en Sabot*. The aorta is enlarged and right aortic arch is present in 30% cases. The right aortic arch in a posteroanterior thoracic roentgenogram is easily recognized by its concave impression on the right side of trachea. The pulmonary fields are oligemic (Fig. 15.23).

The murmur shortens and the cyanosis increases with increasing severity of the right ventricular outflow tract obstruction. Paroxysmal attacks of dyspnea can be present with mild as well as severe TOF. However, effort intolerance is directly related to the severity.

Diagnosis

The diagnosis of TOF is confirmed by echocardiography; cardiac catheterization is seldom necessary. Additional specific information required for surgical decision is also obtained through echocardiography. Cardiac catheterization or CT/MRI may be required in older children with limited echo windows.

Course and Complications

Patients with TOF are subject to many difficulties. The pulmonic stenosis becomes progressively severe with age. The dyspnea and increasing exercise intolerance limit patient activities. Each attack of paroxysmal dyspnea or anoxic spell is potentially fatal. Anemia, by decreasing the oxygen carrying capacity of blood, reduces the exercise tolerance still further. It can result in cardiac enlargement and congestive cardiac failure making diagnosis difficult. Patients are prone to *infective endocarditis.*

Neurological complications occur frequently. Anoxic infarction in the central nervous system may occur during an anoxic spell and result in hemiplegia. *Paradoxical embolism* to central nervous system and venous thrombosis due to sluggish circulation from polycythemia can also result in *hemiplegia. Brain abscess* is not an infrequent complication. It should be suspected in any cyanotic patient presenting with irritability, headache, convulsions, vomiting with or without fever and neurological deficit. The fundus need expert evaluation since polycythemia results in congested retina and recognition of papilledema is difficult.

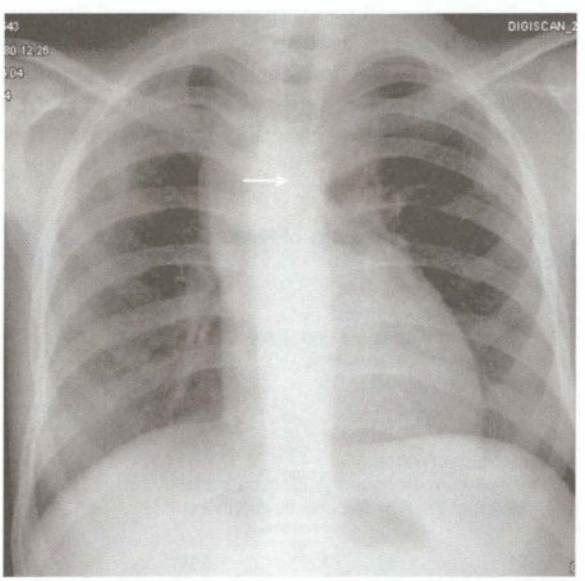

Fig. 15.23: Chest X-ray in Tetralogy of Fallot with right aortic arch. The key findings are reduced lung vasculature as suggested by the dark lung fields, normal heart size, concavity in the region of the main pulmonary artery (pulmonary bay). This X-ray also shows a right aortic arch. The arrow indicates the indentation of the right arch on the right side of the trachea

Treatment

The medical management of TOF is limited to prevention and management of complications and correction of anemia. Oral beta-blockers help prevent cyanotic spells. Maximally tolerated doses of propranolol ranging from 0.5–1.5 mg/kg/dose should be administered. Iron supplementation is recommended for all infants and young children with TOF. The management of anoxic spells is indicated in Table 15.16.

Definitive surgery for TOF involves closure of the VSD and relief of the RVOT obstruction. Often the relief of the RVOT obstruction involves the placement of a transannular patch across the pulmonary valve and valvectomy resulting in severe pulmonary regurgitation. There is growing emphasis on retaining the pulmonary valve during initial repair to prevent pulmonary regurgitation and its major late consequences (RV dilation, arrhythmia, heart failure and sudden death). However, this is not often possible if the pulmonary annulus is small.

Although definitive operation is feasible in young infants, some centers opt for palliative options initially. This is typically done through the Blalock-Taussig shunt, which consists of subclavian artery-pulmonary artery anastomosis using a Goretex graft. Alternatives include balloon dilation of the pulmonary valve or stenting of the patent arterial duct (if present). A number of longterm concerns have emerged in survivors of TOF repair 2–3 decades after the operation. These include heart failure and risk of ventricular tachyarrhythmias as a result of right ventricular dilation that results from chronic pulmonary regurgitation, as well as the scar on the right ventricle if ventriculotomy has been done during operation.

Tricuspid Atresia

Congenital absence of the tricuspid valve is called tricuspid atresia (Fig. 15.24). The right ventricle is hypoplastic. The inflow portion is absent. The hemodynamics is described above; see single ventricle physiology.

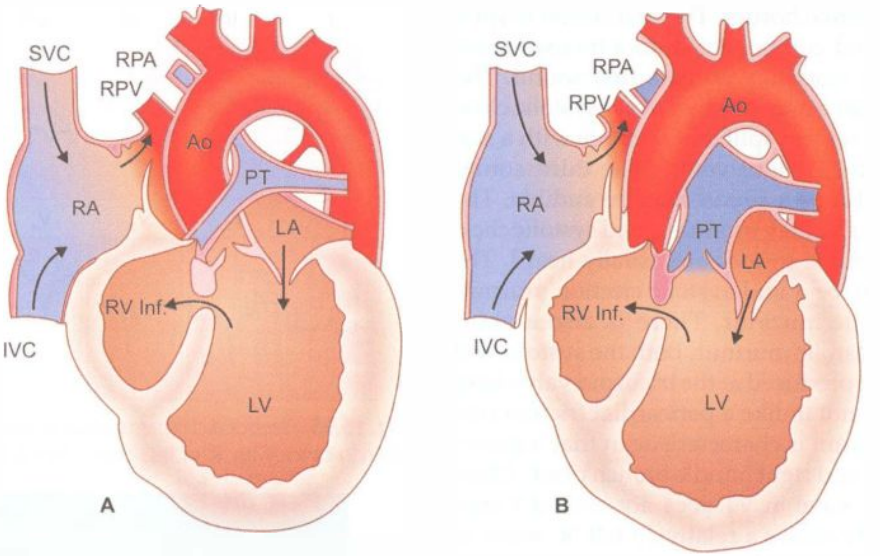

Fig. 15.24: Tricuspid atresia (A) Normally related great arteries. Systemic venous blood reaching the RA through the superior (SVC) and inferior vena cava (IVC) reaches the LA through an atrial defect (or patent foramen ovale). There is complete mixing of the systemic and pulmonary venous blood in the LA. The LV is large. Aorta (Ao) arises from the LV. A muscular ventricular septal defects is the only route through which blood can reach the hypoplastic right ventricle (RV Inf.). The pulmonary trunk (PT) arises from the right ventricle. RPV and LPV right and left pulmonary veins. (B) Transposed great arteries with tricuspid atresia. The PT is arising from the LV whereas the Ao is arising from RV (LA left artium; RA right artium; RPA and LPA right and left; RV Inf. right ventricular infundibulum; RV and LV right and left ventricle; SVC and IVC superior and inferior vena cava

Clinical Features

Clinical presentation depends on the state of pulmonary flow that may be diminished or increased. Clinically, patients who have diminished pulmonary blood flow constitute 90% and symptoms and physical signs are more or less identical to TOF. Features suggesting tricuspid atresia are (i) left ventricular type of apical impulse; (ii) prominent large a waves in jugular venous pulse; (iii) enlarged liver with presystolic pulsations (a waves); and (iv) the electrocardiogram which is characterized by left axis deviation and left ventricular hypertrophy. The mean QRS axis is around –45°. Patients with tricuspid atresia and increased pulmonary blood flow cannot be diagnosed accurately clinically.

Course

Patients with tricuspid atresia follow a course similar to TOF. They are cyanosed at birth. Anoxic spells and squatting may be present; patients are relatively sicker than TOF.

Treatment

Tricuspid atresia is categorized as 'single ventricle physiology' and management is on similar lines.

Ebstein Anomaly

An unusual and rare cyanotic congenital heart disease with diminished pulmonary blood flow results from an abnormality of the tricuspid valve. The posterior as well as the septal leaflet of the tricuspid valve is displaced downwards to a variable extent. The result is an attachment to the posterior wall of the right ventricle. In addition, the leaflets are malformed and fused resulting in obstruction to flow of blood into the right ventricle. The portion of the right ventricle above the leaflet attachment thins out and is called *atrialized right ventricle*. The right ventricular contraction is also abnormal.

Hemodynamics

The tricuspid valve anomaly results in obstruction to forward flow of blood as well as regurgitation of blood from the right ventricle into the right atrium. In addition, there is a large part of the right ventricle that is atrialized as a result of downward displacement of the tricuspid valve attachment. This atrialized right ventricle contracts with the rest of the ventricle and does not allow effective forward flow into the pulmonary circulation. The right atrium progressively dilates, to accommodate the extra volume. The foramen ovale may be patent or there is an atrial septal defect allowing a right to left shunt to occur. This results in cyanosis. The greater the tricuspid valve displacement, the more the cyanosis.

Clinical Features

Patients present with history of cyanosis, effort intolerance and fatigue. They may also give history suggestive of paroxysmal attacks of tachycardia. Cyanosis varies from slight to severe; clubbing is present. The jugular venous pulse may show a dominant 'V' wave but there is usually no venous engorgement. The precordium is quiet with a left ventricular apical impulse. A systolic thrill may be

palpable at the left stemal border. The first sound is split, however, the tricuspid component cannot be made out, resulting in a single, normally audible first sound. The abnormal tricuspid valve may produce a mid systolic click. The second sound is widely split, but variable with a soft pulmonic component. A right ventricular third sound and/or a right atrial fourth sound may be audible. The abnormal tricuspid valve may produce a mid systolic click. Thus, triple or quadruple sounds are usually heard. The systolic murmur may be a mid-systolic ejection murmur or a loud pansystolic murmur. There is also a short tricuspid delayed diastolic murmur. Both the systolic and the diastolic murmur produced at the tricuspid valve have a scratchy character, not unlike a pericardial friction rub.

The electrocardiogram is characteristic in that it shows prominent 'P' waves and right bundle branch block. Characteristically the 'R' wave in V1 does not exceed 7 mm. The lead V6 generally shows a relatively tall 'R' wave as well as a broad 'S' wave. Wolff Parkinson White type of conduction abnormality may be seen in the electrocardiogram (Fig. 15.25). The X-ray shows cardiac enlargement due to right atrial and right ventricular enlargement. The main pulmonary artery segment may be prominent and the aortic knuckle small (Fig. 15.26). The pulmonary vasculature is diminished. Two dimension echocardiogram is diagnostic as it outlines the displaced tricuspid valve (Fig. 15.27).

Diagnosis and Treatment

The diagnosis can be easily confirmed by echocardiography, which can not only identify the anomaly but also indicate the severity. Surgical treatment consists in obliterating the atrialized portion of the right ventricle and repairing the tricuspid valve.

Transposition of Great Vessels

Transposition of great vessels (TGA) is defined as *aorta arising from the right ventricle and pulmonary artery from the left ventricle*. By definition, therefore, the great vessels (aorta and the pulmonary artery) arise from inappropriate ventricles, both of which must be present and identifiable. In TGA the aorta generally lies anterior and to the right of the pulmonary artery. For this reason, this is also referred to as D-TGA. Since the systemic and pulmonary circulations are separate, survival depends on the presence of atrial, ventricular or aortopulmonary communications. TGA is classified into (*a*) with intact ventricular septum, and (*b*) with VSD. The latter group is further subdivided into cases with and without pulmonic stenosis. Patients with complete TGA, VSD and pulmonic stenosis are included in tetralogy physiology.

In patients with TGA the oxygenated pulmonary venous blood recirculates in the lungs whereas the systemic venous blood recirculates in the systemic circulation. The pulmonary artery saturation is thus always higher than the aortic saturation. Survival depends on the mixing available

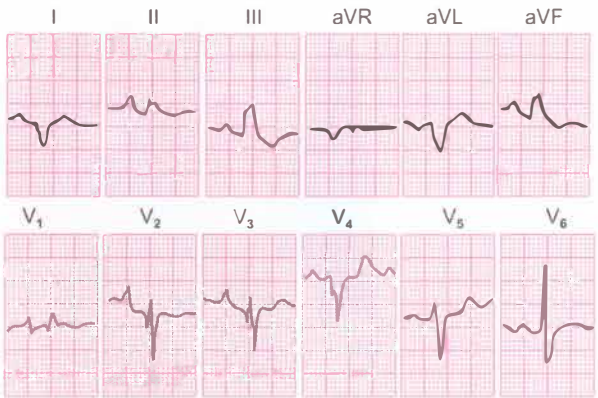

Fig. 15.25: Electrocardiogram typical of Ebstein anomaly. Right bundle branch block with 'R' of less than 7 mm is present

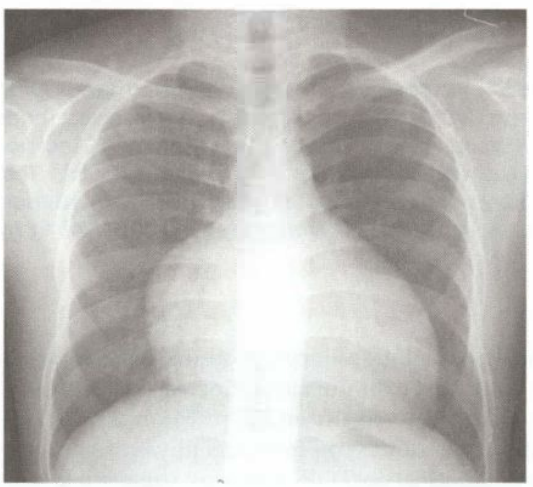

Fig. 15.26: Chest X-ray in Ebstein anomaly. There is considerable enlargement of the right atrium. The lung vascularity is reduced

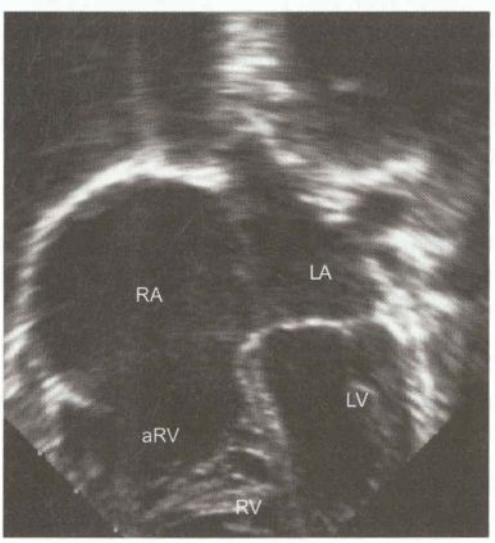

Fig. 15.27: Apical four chamber view from a patient with Ebstein anomaly. Note the downward displacement of the septal leaflet of the tricuspid valve (arrow). aRV: atriaized right ventricle, LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle

between the two circulations. In patients with intact ventricular septum, the mixing site is the atrial communication. Generally, the atrial communication is the patent foramen ovale and this being small, the mixing is very poor (Fig. 15.28). The neonates become symptomatic due to severe hypoxemia and systemic acidosis soon after birth.

Presence of a VSD of adequate size results in good mixing. As the fetal pulmonary vasculature regresses, the pulmonary blood flow increases and results in congestive failure around 4–10 weeks of age. The failing left ventricle as well as the large pulmonary blood flow increase the left atrial pressure. The patients, therefore, have pulmonary venous hypertension as well. The mixing with a large VSD can be so good that at times cyanosis can be missed. The presence of a large VSD equalizes pressures in the two ventricles as well as the great arteries. The pulmonary artery also carries a large flow. Patients with TGA and a large VSD develop pulmonary vascular obstructive disease (Eisenmenger physiology) early in life.

Clinical Features

Patients of complete TGA with intact ventricular septum are cyanotic at birth. Since the interatrial communication results in poor mixing, the neonates present with rapid breathing and congestive failure secondary to hypoxemia within the first week of life. The heart size can be normal in the first two weeks of life but enlarges rapidly. Physical examination shows severe cyanosis, congestive failure, normal first sound, single second sound and an insignificant grade one to two ejection systolic murmur. The electrocardiogram shows right axis deviation and right ventricular hypertrophy. The thoracic roentgenogram shows cardiomegaly with a narrow base and plethoric lung fields. The cardiac silhouette can have an "egg on side" appearance: The right upper lung fields appear more plethoric than other areas. The thymic shadow is often absent (Fig. 15.29).

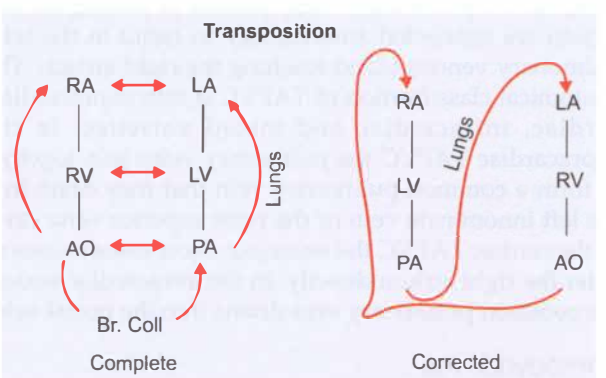

Fig. 15.28: The route of blood flow in complete TGA results in two separate circulations and survival depends on mixing. The mixing can occur at the atrial, ventricular or great vessel level. Bronchial collaterals (Br. Coll.) also increase pulmonary blood flow: In corrected TGA the route of blood flow is normal. Hemodynamics depend on associated anomalies

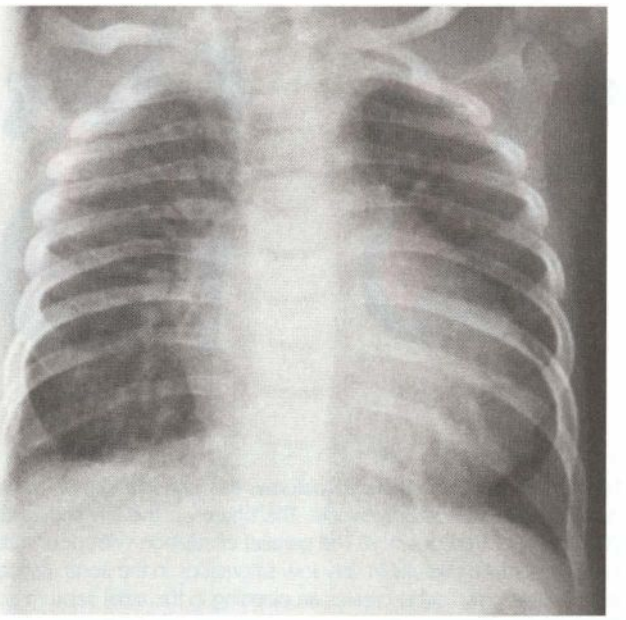

Fig. 15.29: Egg on side appearance in transposition. This characteristic appearance is seen only in about one-third cases and results from a narrow pedicle of the heart because of malpostion of great vessels

Patients of TGA with VSD have increased pulmonary blood flow; mixing at the ventricular level determines the severity of cyanosis. They develop congestive failure around 4-10 weeks of age. Physical findings consist of cyanosis, cardiomegaly, congestive failure, normal first sound, single or normally split second sound and grade II–IV ejection systolic murmur. Apical third sound gallop or a mid-diastolic rumble may be present. Electrocardiogram shows right axis deviation with biventricular, right ventricular or left ventricular hypertrophy. Chest X-ray shows cardiomegaly, plethoric lung fields and features of pulmonary venous hypertension.

Treatment

Prostagladin E1 can help reduce cyanosis in selected cases by keeping the PDA open. Interim palliation can be accomplished through a balloon atrial septostomy (Fig. 15.30). This procedure can be accomplished in catheterization laboratory or in the ICU under echocardiographic guidance. Septostomy is successful only up to the age of 6–12 weeks and gives temporary relief by providing better mixing and reducing left atrial pressure.

The *arterial switch operation* is now established as the treatment of choice for TGA and most centers endeavor to offer this procedure for all infants with TGA. In this operation, the pulmonary artery and aorta are transected. The distal aorta is anastomosed to the proximal pulmonary stump (neo-aortic root) and the pulmonary artery to the proximal aortic stump (neopulmonary artery). The coronary arteries are moved along to the neo-aortic root along with a cuff of aortic tissue to allow suturing without

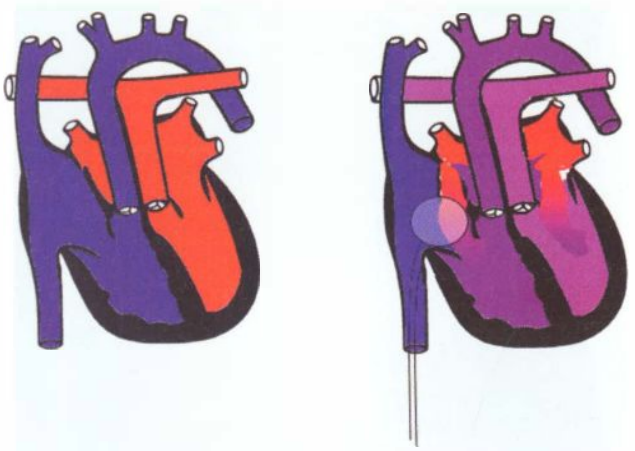

Fig. 15.30: Balloon atrial septostomy; this cartoon shows how a balloon atrial septostomy works. The figure on the left shows the physiology of transposition. The parallel circulation with poor inter-circulatory mixing results in very low saturations in the aorta. Balloon atrial septostomy (right) creates an opening in the atrial septum and allows better inter-circulatory mixing with improved saturation that is often life saving

compromise of coronary blood flow. Most modern pediatric cardiac centers strive to achieve excellence with the neonatal arterial switch operation because the longterm results are very satisfying. There is a limited window of time for performing the arterial switch for TGA. Infants with TGA and intact septum should ideally undergo this procedure within the first 2–4 weeks of life. As pulmonary vascular resistance falls after birth the left ventricle regresses rapidly. In 1–2 months the left ventricle has the ability to adjust to the elevated systemic vascular resistance after the arterial switch through hyperplasia of the available muscle. After this it is difficult for the left ventricle to adapt to an arterial switch. Later in infancy, the *atrial switch operation* (Senning operation) is the only option for TGA with intact ventricular septum. This is not an ideal longterm option because the right ventricle remains as the systemic ventricle for life. Over time, right ventricle dysfunction and severe tricuspid regurgitation sets in. Additionally, extensive restructuring of atria predisposes to atrial rhythm disturbances.

In the presence of a sizable PDA or VSD there is no fear of early regression of LV because the PA pressures are elevated. Nevertheless, the window of time for operation of TGA-VSD and TGA-PDA is also limited. This is because there is accelerated development of pulmonary vascular obstructive disease in these patients. Surgical correction involves the arterial switch operation with closure of the VSD or PDA. This should ideally be accomplished within 3 months of age. Beyond this age, an increasing proportion of infants show irreversible changes in the pulmonary vasculature. Consequently postoperative recovery may be complicated by pulmonary hypertensive crisis and longterm results are unsatisfactory.

Many centers are able to perform arterial switch operations with operative mortality of <5%. Twenty year survival is >90%. Longterm concerns after surgery include development of aortic root dilation and aortic regurgitation, right ventricular outflow tract obstruction and coronary artery occlusion.

Corrected TGA

In corrected TGA the right atium is connected to the left ventricle and vice-versa. The left ventricle gives rise to the pulmonary artery and right ventricle to the aorta. The aorta lies anterior and to the left of the pulmonary artery (hence the term L-TGA). The ascending aorta forms the left upper border of the cardiac silhouette. Since the route of blood flow is normal, it is the associated anomalies that determine the clinical features. The associated anomalies are present in more than 98% cases. The commonest anomalies include (i) a VSD with or without pulmonic stenosis; (ii) left sided Ebstein anomaly of the tricuspid valve (clinically simulates mitral regurgitation); and (iii) atrioventricular conduction abnormalities including complete atrioventricular block, each in approximately 65% cases. The most useful clue for the diagnosis of corrected TGA is related to inversion of the ventricles. The precordial leads V4R, V1, and V2 may show a 'Q' wave that is absent in the left precordial leads. Chest X-ray shows a smooth left upper border corresponding to the ascending aorta. The diagnosis depends on echocardiographic identification of ventricular inversion as well as the additional anomalies. Management depends on the type of associated anomalies. The need to retain the morphologic left ventricle as the systemic ventricle makes the surgical management of corrected transposition rather complex.

Total Anomalous Pulmonary Venous Connection (TAPVC)

Here, all the pulmonary veins instead of joining the left atrium are connected anomalously to result in the total pulmonary venous blood reaching the right atrium. The anatomical classification of TAPVC is into supracardiac, cardiac, infracardiac and mixed varieties. In the supracardiac TAPVC the pulmonary veins join together to form a common pulmonary vein that may drain into the left innominate vein or the right superior vena cava. In the cardiac TAPVC the veins join the coronary sinus or enter the right atrium directly. In the infracardiac variety the common pulmonary vein drains into the portal vein.

Hemodynamics

TAPVC results in the pulmonary venous blood reaching the right atrium, which also receives the systemic venous blood. This results in almost complete mixing of the two venous returns. The blood flow to the left atrium is the right to left shunt through a patient foramen ovale or atrial septal defect. The oxygen saturation of the blood in the

pulmonary artery is often identical to that in the aorta because of mixing of the blood in the right atrium. Physiologically TAPVC can be divided into (a) patients with pulmonary venous obstruction, and (b) patients without pulmonary venous obstruction. Pulmonary venous obstruction results in pulmonary arterial hypertension as well as restriction to pulmonary blood flow. In the absence of pulmonary venous obstruction, pulmonary blood flow is large and results in cardiac failure between 4–10 weeks of age. TAPVC of the infracardiac type is always obstructive whereas cardiac and supracardiac types may or may not have pulmonary venous obstruction. Generally the left atrium and ventricle are of normal size but can be small.

Clinical Picture

TAPVC of the *non-obstructive type* is commoner than the obstructive type. Patients present with cyanosis and congestive failure as the fetal pulmonary vasculature regresses. The onset of congestive failure is around four to ten weeks of age. Occasionally, with large pulmonary blood flow, the cyanosis may be minimal or clinically not recognizable. The patients are irritable and have failure to thrive. Besides features of congestive failure the patients have cardiomegaly, hyperkinetic precordium normal or accentuated first sound, widely split and fixed second sound with accentuated pulmonic component, a grade two to four pulmonary ejection systolic murmur and a tricuspid flow murmur. The physical findings are identical to that of an atrial septal defect. Presence of congestive failure at this age suggests TAPVC since congestive failure in atrial septal defect at this age is very rare. A continuous venous hum may be audible at the upper left or right sternal border or in the suprasternal notch.

Patients with *obstructive type* of TAPVC present with marked cyanosis and congestive failure typically within the first one to two weeks of life. In India, however, we do frequently come across infants presenting later with obstructed TAPVC. The physical findings consist of a normal sized heart with parasternal heave, normal first sound, accentuated pulmonic component of S2 and insignificant murmurs. Tricuspid regurgitation can occur and results in cardiomegaly. These infants are severely compromised and need admission in an intensive care unit and emergency corrective surgery.

The electrocardiogram in TAPVC with or without pulmonary venous obstruction shows right axis deviation and right ventricular hypertrophy. Chest roentgenogram shows cardiomegaly with plethoric lung fields in non-obstructive TAPVC. The characteristic pattern of the "snowman" or figure of '8' configuration in the supracardiac TAPVC draining to left innominate vein is seen only after the age of 2 yr (Fig. 15.31). The characteristic X-ray of the obstructive TAPVC consists of a normal sized heart with severe pulmonary venous hypertension resulting in "ground glass" appearance of the lungs very

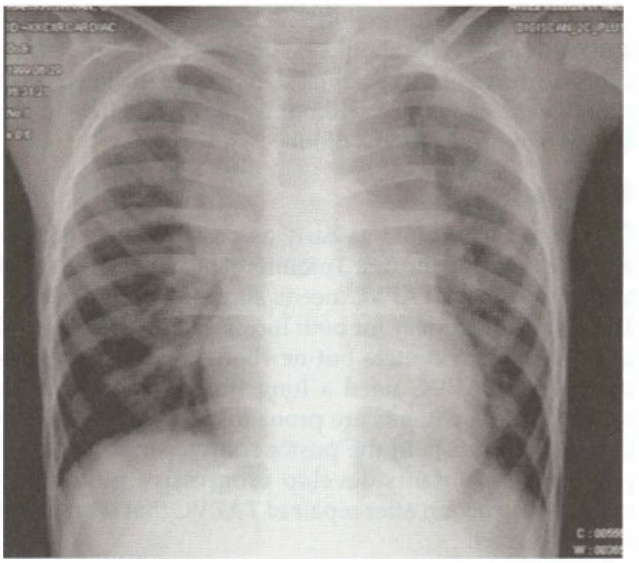

Fig. 15.31: Chest X-ray in unobstructed supracardiac total anomalous pulmonary venous connection to the innominate vein via the left vertical vein in an 8-year-old child. This is the characteristic figure of '8' sign or the snowman's sign

much like that of hyaline membrane disease (Fig. 15.32). Echocardiogram allows confirmation of the diagnosis, definition of the individual pulmonary veins and assessment of the site of obstruction. In addition the pulmonary artery pressure can be quantified. In most situations echo alone is adequate for surgical planning.

The diagnosis of the obstructive TAPVC is made in a neonate with cyanosis and normal sized heart with

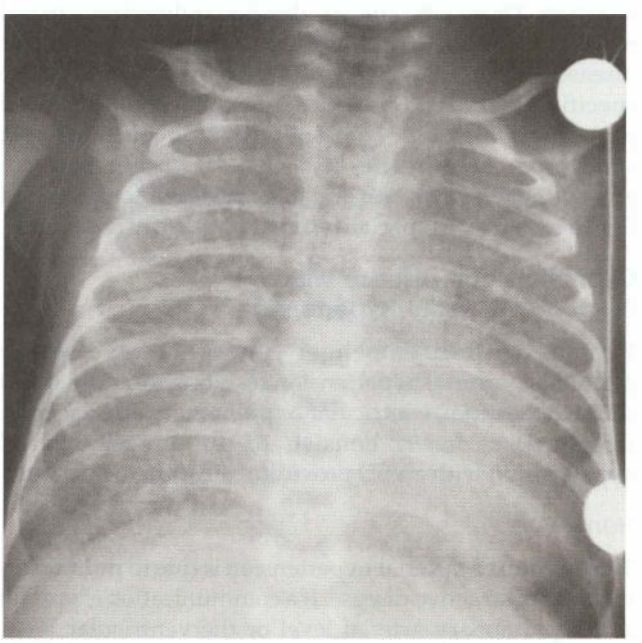

Fig. 15.32: Chest X-ray from a newborn with obstructed infracardiac total anomalous pulmonary venous connection. Note the characteristic ground glass appearance

"ground glass" lung fields. The diagnosis of non-obstructive TAPVC should be suspected if the auscultatory features of atrial septal defect are associated with either cyanosis with or without congestive failure in the first two to three months of life.

Management

Operation is indicated as early as possible since 80% of infants die within the first 3 months of life without surgical help. Obstructed TAPVC needs surgery at short notice. The results of surgery for both forms of TAPVC are good in most modern centers but newborns and infants with obstructed TAPVC need a long time to recover after surgery. These patients are prone to develop pulmonary hypertensive crisis in the postoperative period. A small proportion of infants develop progressive pulmonary venous obstruction after repair of TAPVC that is often not easy to correct.

Additional Conditions with Cyanosis and High Pulmonary Flow

Apart from transposition of great vessels and total anomalous pulmonary venous connection, single ventricle without obstruction to pulmonary blood flow, persistent truncus arteriosus, tricuspid atresia with absence of obstruction to pulmonary blood flow and double outlet right ventricle without pulmonic stenosis present with cyanosis and increased pulmonary blood flow. Clinically patients present with congestive failure in the neonatal period and are characterized by cyanosis, cardiomegaly and failure to thrive. Almost 80% die within 3 months of life due to congestive cardiac failure or pulmonary infection. Those who survive develop pulmonary arterial hypertension due to pulmonary vascular obstructive disease. Echocardiography is necessary to arrive at the specific diagnosis. Since the mortality of unoperated patients is high and patients develop Eisenmenger syndrome early in life, it is necessary that patients presenting with cyanosis and increased pulmonary blood flow be referred to specialized centers as early as possible.

Cyanotic Heart Disease with Pulmonary Arterial Hypertension

Patients with Eisenmenger syndrome have severe pulmonary arterial hypertension resulting in a right to left shunt at the atrial, ventricular or pulmonary arterial level. *Eisenmenger complex* consists of pulmonary arterial hypertension with a VSD providing the right to left shunt.

Hemodynamics

The pulmonary arterial hypertension is due to pulmonary vascular obstructive disease. If a communication is present at the pulmonary arterial level or the ventricular level, the right ventricular pressure cannot go beyond the systemic pressure. The right to left shunt decompresses the right ventricle. The right ventricle has only concentric hypertrophy without significant increase in the size. In patients who have a PDA or VSD, there is only a mild parasternal impulse without significant heave. In patients who do not have a VSD or PDA, the right ventricle besides hypertrophy also dilates. The right to left shunt at the atrial level is an indication of right ventricular failure to accommodate this volume and push into the pulmonary artery. Patients of Eisenmenger syndrome with communication at the atrial level only, exhibit a parastemal heave and cardiac enlargement. The right ventricular pressure may even be higher than the systemic pressure.

A right to left shunt at the atrial level or the ventricular level reaches the ascending aorta and is thus distributed to the whole systemic circulation. This results in equal cyanosis of fingers and toes. A right to left shunt through a PDA is directed downwards into the descending aorta, which results in *differential cyanosis* affecting lower limbs, with pink upper limbs.

Clinical Features

Patients present with history of cyanosis, fatigue, effort intolerance and dyspnea. There may also be history of repeated chest infections in childhood. On physical examination they have cyanosis and clubbing. Differential cyanosis separates patients who have a PDA from those who have a VSD or atrial septal defect. The features indicative of pulmonary arterial hypertension consist of parasternal impulse and palpable second sound. The pulmonary component of the second sound is accentuated and louder than the aortic component. The splitting of the second sound remains wide and fixed in atrial septal defect. Due to superimposition of A2 and P2 the second sound is single in patients who have a VSD. Patients who have a PDA continue to have a normally split second sound. A constant pulmonary ejection click, unlike in patients of valvar pulmonic stenosis, is well heard both during inspiration and expiration at the second left interspace. A functional pulmonary regurgitation murmur can be present along the left sternal border. Patients with atrial septal defect, in whom Eisenmenger physiology is uncommon, can develop tricuspid regurgitation (Fig. 15.33).

The electrocardiogram reveals right axis deviation and right ventricular hypertrophy, *P pulmonale* may be present. The chest radiograph is characteristic, showing prominence of the pulmonary arterial segment and large right and left main pulmonary arteries and their branches. The peripheral lung fields are oligemic. *Thus the hilar area suggests pulmonary plethora whereas the peripheral lung fields suggest pulmonary oligemia* (Fig. 15.34).

Treatment

Ideally pulmonary vascular obstructive disease should be prevented. This means early diagnosis and correction of all CHD associated with increased pulmonary blood flow. Patients with cyanosis and increased pulmonary blood flow develop Eisenmenger physiology very early and

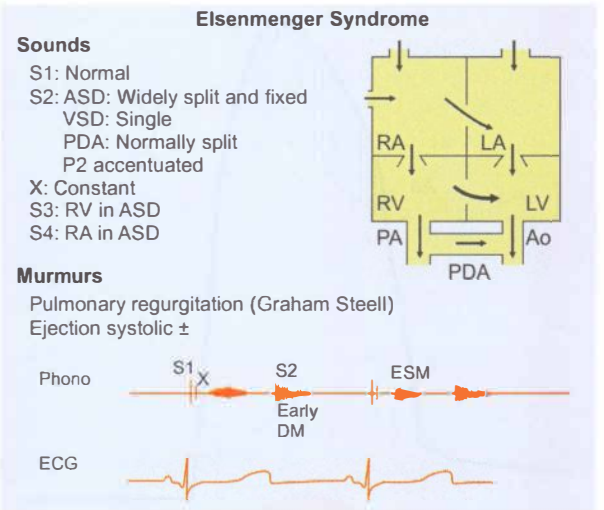

Fig. 15.33: Summary of auscultatory findings in Eisenmenger syndrome

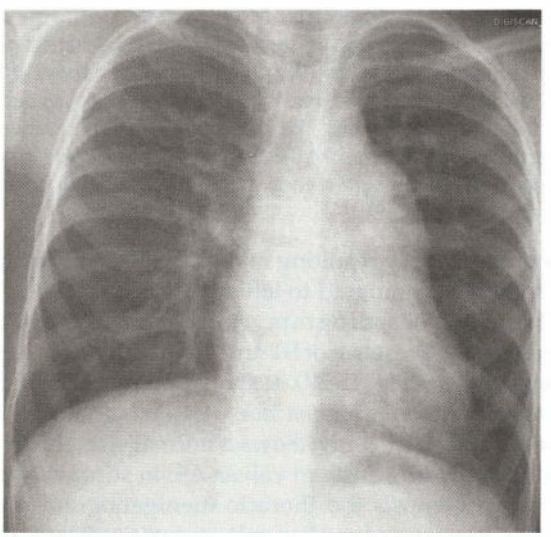

Fig. 15.34: Chest X-ray in Eisenmenger syndrome following ventricular septal defect. The proximal right pulmonary artery is enlarged. There is a relative paucity of vasculature in the periphery with a sudden tapering of caliber of the right pulmonary artery (pruning)

need to be operated by 2–3 months of age. Medications are available for the management of pulmonary hypertension (*see* later section on pulmonary hypertension).

OBSTRUCTIVE LESIONS

Aortic Stenosis

Pathologically the site of obstruction may be at valve level, above the valve (supravalvar) or below the valve (subvalvar). At the valve level the aortic stenosis results from either an unicuspid or a bicuspid aortic valve. Rarely the aortic valve annulus may itself be small. ***Supravalvar aortic stenosis*** results from obstruction in root of aorta, above the aortic valve, as in Williams syndrome. ***Subvalvar aortic stenosis*** may be discrete (membranous), fibromuscular or muscular (hypertrophic obstructive cardiomyopathy).

Hemodynamics

Valvar obstruction is overcome by raising the systolic pressure of the left ventricle. This is brought about by concentric hypertrophy of the left ventricle. Because of a powerful, muscular left ventricle, the emptying of the left ventricle is complete but the duration of the systole is prolonged. The prolongation of left ventricular ejection time causes delayed closure of the aortic valve resulting in delayed A2. The flow across the obstruction results in the aortic ejection systolic murmur that is typically diamond shaped, starting after the first sound and ending before the aortic component of the second sound with a mid-systolic peak. The systolic murmur is always palpable as a thrill at the second right interspace, suprasternal notch and the carotid vessels. The powerful left ventricle can maintain a normal forward cardiac output. The prolonged ejection results in the characteristic pulse that can be best described as slowly rising to a peak that is sustained and then has a slow down-slope. The peak is low so that the pulse is of low amplitude and prolonged duration.

Concentric hypertrophy of the left ventricle results in decreased distensibility of the left ventricle in diastole-reduced compliance. In severe aortic stenosis (AS), with marked left ventricular hypertrophy, the left ventricular diastolic pressure also rises. With increase in left ventricular diastolic pressure, the left atrial pressure must increase to be able to fill the left ventricle during diastole. Hence, with severe AS accompanied with marked left ventricular hypertrophy, a forceful left atrial contraction results in a palpable as well as audible fourth sound (S4). When the left ventricle starts failing in AS, besides hypertrophy dilatation also appears and causes increase in heart size. With left ventricular failure a third sound (S3) becomes audible. In valvar AS there is post stenotic dilatation of ascending aorta, seen on posteroanterior chest radiograph. In supravalvar and subvalvar AS, this is absent. In valvar stenosis, the first sound is followed by an aortic ejection click that precedes the starts of the murmur; the click is heard at the apex, and along left sternal border.

Clinical Features

Patients with mild to moderate AS are asymptomatic. With severe stenosis, the initial symptom is generally dyspnea on exertion. The patients may also give history of angina on effort and syncope. Presence of any one of these three symptoms suggests severe AS. The blood pressure is normal with mild disease; the width of pulse pressure relates inversely with severity of AS resulting in low amplitude prolonged duration pulse. The cardiac size remains normal unless left ventricular failure is present.

The apical impulse is forcible or heaving. In severe AS the fourth sound may be palpable. If left ventricular failure is present the third sound may be palpable. A systolic thrill is palpable at the second right interspace, suprasternal notch and the carotid arteries. The first sound is normal and followed by an ejection click in valvar aortic stenosis. The aortic component of the *second sound (A2) is delayed but not diminished in intensity in* AS. The delay results in closely split, single or paradoxically split second sound according to the severity of obstruction. With severe AS, S4 is audible, while in patients with left ventricular failure, S3 is palpable and audible. The ejection systolic murmur starting after the ejection click reaches a peak in mid-systole (Fig. 15.35). With increasing severity the peak gets delayed so that the maximum intensity of the murmur is closer to the end rather than being midsystolic. With immobile valves, either due to severe fibrosis or calcification the systolic click as well as the A2 diminish in intensity and may become inaudible (Fig. 15.36).

Subvalvar AS is differentiated from valvar lesions by absence of ejection click and the post stenotic dilatation of the ascending aorta in the thoracic roentgenogram. An aortic regurgitation murmur may be audible. The maximum intensity of the systolic murmur and thrill may be in the third or fourth left interspace.

Supravalvar AS (William syndrome) is associated with elfin facies, mental retardation, dental abnormalities, strabismus and peripheral pulmonary arterial stenosis. Since the obstruction is above the aortic valve, the pressure in the segment of the aorta before the obstruction is elevated and results in loud A2. The jet through the supravalvar narrowing may be directed toward the innominate artery resulting in higher systolic pressure in the right arm compared to left arm.

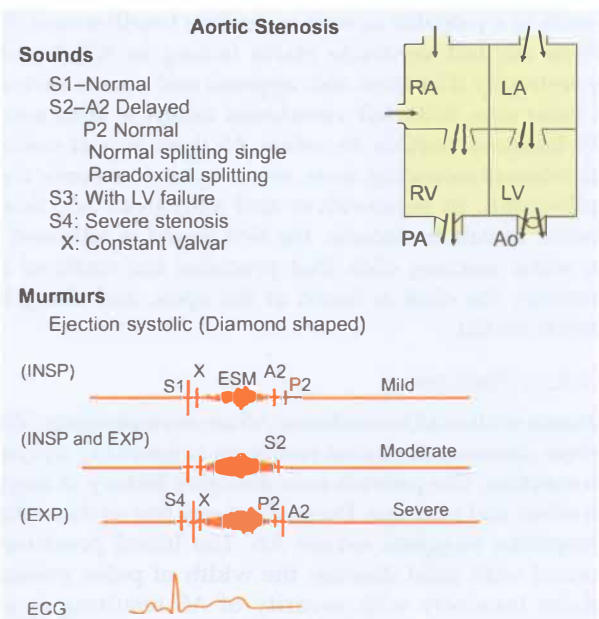

Fig. 15.35: Summary of auscultatory findings in aortic stenosis: S4 fourth sound; X aortic click

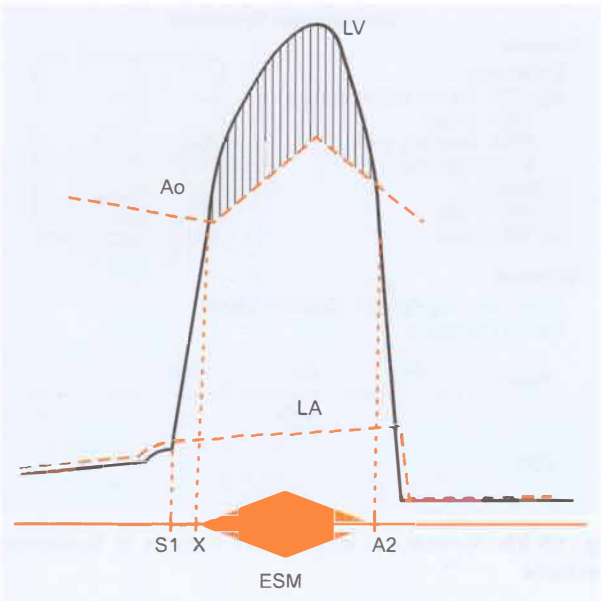

Fig. 15.36: Aortic stenosis: Diagrammatic portrayal of the hemodynamic basis for aortic stenosis murmur. The first sound (S1) occurs as the left ventricular (LV) pressure increases above left atrial (LA) pressure. This is followed by the ejection click (X) occurring after the aortic valve opens. The shape of the gradient between LV and aorta (Ao) corresponds to the shape of the aortic ejection systolic murmur (ESM). The murmur ends before the aortic components of the second sound (A2)

The electrocardiogram reveals left ventricular hypertrophy. Presence of ST and T wave changes suggest severe disease (Fig. 15.37). It should be remembered that *a normal electrocardiogram does not exclude severe aortic stenosis*. The chest X-ray shows a normal sized heart with dilated ascending aorta in valvar AS. In supravalvar and subvalvar stenosis the thoracic roentgenogram may be normal. Presence of cardiac enlargement indicates severe AS. Echocardiogram can not only identify the site of stenosis, but using Doppler assess the gradient across the obstruction fairly accurately.

Assessment of Severity

The severity of AS should be determined, based on the following:

i. Symptomatic patients have severe AS; lack of symptoms does not exclude severe disease
ii. Narrower the pulse pressure, the more severe the AS
iii. Systolic thrill at second right interspace suggests at least moderately severe AS
iv. The later the peak of the ejection systolic murmur, the more severe the narrowing
v. The delay in A2 correlates well with severity. With mild AS, the S2 is normally split, with moderate AS it is closely split, with severe or critical AS it is single or paradoxically split

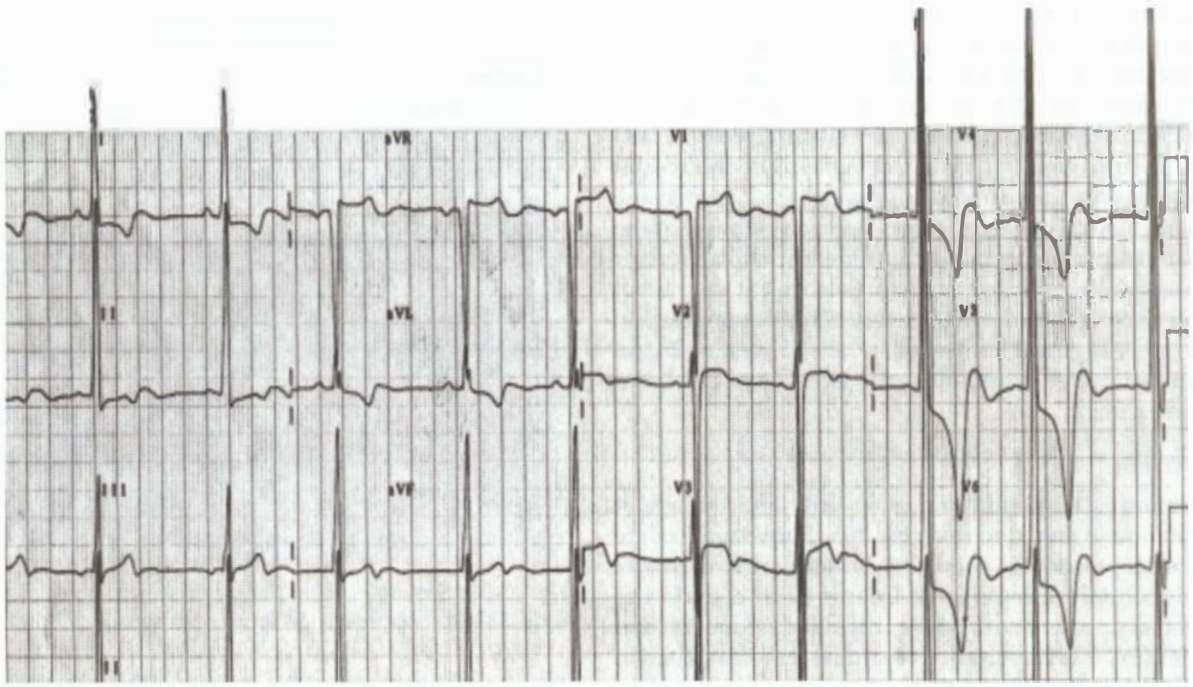

Fig. 15.37: Electrocardiogram from a patient with severe aortic stenosis showing prominent left ventricular voltages together with ST segment depression and T wave inversion in lateral leads (strain pattern)

vi. Presence of S4 is indirect evidence for severe AS
vii. Presence of S3 indicates severe AS and congestive cardiac failure
viii. ST and T changes in the electrocardiogram suggest severe stenosis
ix. Cardiac enlargement on chest radiograph indicates severe AS with left ventricular failure
x. Doppler can quantitate the gradient across the aortic valve accurately. Two-dimensional echo reveals concentric left ventricular hypertrophy; ventricular dysfunction is associated with heart failure.

Treatment

Patients with AS should be followed closely, with 6–12 monthly electrocardiogram. Symptoms should be carefully evaluated. Doppler echo can be used to quantitate the gradient at each visit and ventricular function should be monitored. Severe AS is risk for *sudden death*. Patients should be discouraged from outdoor games, athletics, competitive sports and strenuous exercises if AS is significant (gradient of 50 mm Hg or more).

Balloon aortic valvuloplasty is the procedure of choice for valvar AS. A balloon introduced through the femoral artery can be placed at the aortic valve and inflated to tear the valve along the commissure. It is indicated if the gradient is above 75 mm Hg. Supravalvar and subvalvar AS do not respond to balloon dilation; the procedure should also be avoided in patients with significant aortic regurgitation. Surgical options include aortic valve repair and replacement with a prosthetic valve. Patients need to be administered anticoagulants if they have a prosthetic valve replacement and careful followup to prevent/detect complications, such as restenosis, thrombus or pannus formation and infective endocarditis.

Coarctation of the Aorta

Coarctation of the aorta is located at the junction of the arch with the descending aorta. It is a sharp indentation involving the anterior, lateral and posterior wall of the aorta; the medial wall is spared. It may be distal or proximal to the ductus or ligamentum arteriosus and also the left subclavian artery. *Forty to 80% patients have a bicuspid aortic valve.*

Hemodynamics

In fetal life, the right ventricular output passes down the descending aorta through a wide ductus arteriosus. The left ventricular output empties into the innominate, left carotid and left subclavian arteries and little output reaches the descending aorta. The portion of the aorta distal to the left subclavian and before the portion where the ductus arteriosus joins is called the isthmus. At birth, the isthmus is the narrowest part of the aorta. Following closure of the ductus arteriosus, the descending aorta must receive its total supply from the left ventricle *via* the ascending aorta. Neonates with severe coarctation therefore become symptomatic immediately as the duct starts to close. However, a significant proportion present late.

The exact mechanism for the production of systemic hypertension in coarctation is not known. The aortic

obstruction is certainly partly responsible for it. The narrow pulse pressure in the descending aorta distal to the coarctation has been implicated in the renal mechanism for the causation of hypertension in coarctation. The obstruction stimulates growth of collateral vessels between the proximal and distal segments. The intercostal vessels also participate in decompressing the hypertensive upper segment. They enlarge and become palpable at the lower borders of the ribs often later in childhood or adolescence. Palpable collaterals are also felt at the medial and inferior angle of scapula. Because of the decompression of the upper segment by the collaterals, the resting blood pressure in upper extremities may even be normal, but rises on exercise.

Clinical Features

Coarctation has a continuum of severity and the age at presentation is linked to severity. Newborns with severe coarctation presents as soon as the duct start to close (*see* duct dependent circulation). Infants with coarctation occasionally present with left ventricular dysfunction and heart failure. It is important to examine femoral pulses in newborns and infants with heart failure. Later in life, coarctation is often not associated with symptoms.

The only symptoms in uncomplicated coarctation may be intermittent claudication, pain and weakness of legs and dyspnea on running. Examination shows delayed and weak femorals compared to strong brachial arteries. The heart size remains normal with a left ventricular forcible or heaving apex. A systolic thrill may be palpable in the suprasternal notch. There are prominent arterial pulsations in the suprasternal notch and the carotid vessels. The first sound is accentuated and sometimes followed by a constant ejection click. The second sound is normally split with a loud aortic component. A variable intensity ejection systolic murmur is heard with the point of maximum intensity over the back in the interscapular area. The murmur starts late in systole after a considerable gap from the first sound and click. It may appear to go through the second sound suggesting a continuous murmur. This is because of delay in the transmission of pulse from the heart to the site of coarctation. Continuous murmurs may be audible over collaterals in the chest wall but are uncommon. An aortic ejection systolic murmur and/or an aortic regurgitation murmur may also be present because of the commonly associated bicuspid aortic valve (Fig. 15.38).

The electrocardiogram shows left ventricular hypertrophy; ST and T wave changes below the age of 15 yr suggests additional aortic stenosis or endocardial fibroelastosis. Chest X-ray shows a normal sized heart with prominent ascending aorta and the aortic knuckle. In an overpenetrated film, the site of coarctation can be well localized as the proximal segment is dilated and there is post stenotic dilatation of the distal segment. Barium swallow shows the characteristic 'E' sign and confirms

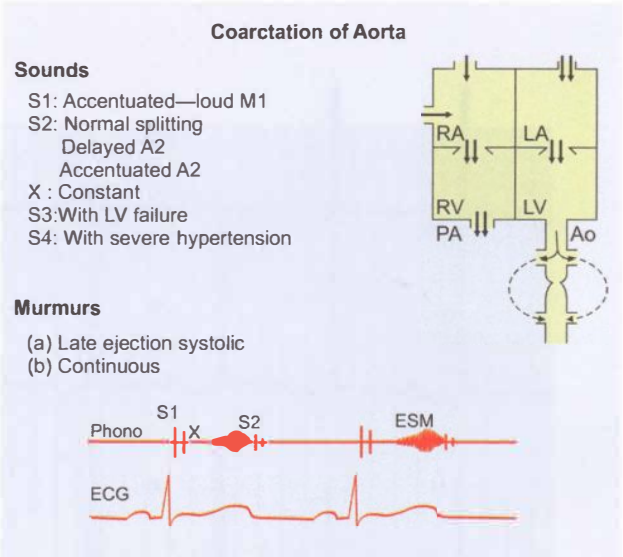

Fig. 15.38: Summary of auscultatory findings in coarctation of the aorta. S3 third heart sound, S4 fourth heart sound

the site of coarctation. The characteristic notching of the lower borders of ribs tends to appear beyond the age of 10 yr. Using suprasternal approach coarctation can be seen on echocardiogram and the gradient estimated.

Course and Complications

Coarctation may result in congestive failure in infancy. If congestive failure does not occur in infancy, it is unlikely to occur throughout the pediatric age group unless complicated by infective endocarditis or anemia. The complications of coarctation include rupture of berry intracranial aneurysm and dissection of aorta. These complications are rare in children. Infective endarteritis may in occur the wall of aorta distal to coarctation or there could be endocarditis involving the bicuspid aortic valve.

Treatment

Relief of coarctation is recommended as soon as diagnosis is made when coarctation is severe. In newborns and infants surgery is preferred. In older children, adolescents and adults, balloon dilation is often undertaken. The recurrence rates of balloon dilation in newborns is over 90% and this procedure should only be done as interim palliation in the face of heart failure and severe ventricular dysfunction. Prostaglandin E1 is used to maintain ductal patency prior to surgery in the first few weeks of life.

It is likely that coarctation is not a localized disease at the junction of arch and descending aorta and there is perhaps generalized weakness of the arterial media. Resection of coarctation does not guarantee freedom from complications like dissection of aorta. Systemic hypertension can persist following operation and recoarctation of aorta can also occur, requiring repeat balloon angioplasty.

Pulmonic Stenosis (Pure Pulmonic Stenosis or Pulmonic Stenosis with Intact Ventricular Septum)

Pulmonic stenosis (PS) is usually valvar or subvalvar (infundibular PS). Uncommonly pulmonic stenosis may be in the pulmonary artery above the valve or in the main right or left branches or the peripheral branches.

Hemodynamics and Clinical Features

Flow across the narrow pulmonary valve results in a pulmonary ejection systolic murmur and a thrill in the left second interspace. To keep the flow normal the right ventricle increases its systolic pressure and develops concentric right ventricular hypertrophy. The pulmonary artery beyond the obstruction shows poststenotic dilatation visible on the thoracic roentgenogram as a dilated pulmonary arterial segment. Because of the obstruction, the right ventricular systole is prolonged resulting in delayed closure of the pulmonic component (P2) of second sound. The delay in P2 results in a wide and variably split second sound. In valvar PS, a pulmonary ejection click is audible, soon after S1 and just before the onset of murmur, during expiration but disappears or becomes softer during inspiration. With increasing severity of stenosis the duration and intensity of the murmur increase and the peak gets delayed; the click disappears and P2 becomes softer. With moderate PS, the murmur ends just short of the aortic component of the second sound. The concentric right ventricular hypertrophy results in maintaining a normal heart size, but reduces its distensibility. In severe PS with marked right ventricular hypertrophy, the ventricular diastolic pressure also increases. The right atrial pressure increases to be able to fill the right ventricle and results in a right atrial fourth sound (S4) as well as prominent 'a' waves in the JVP (Fig. 15.39).

Patients with mild to moderate PS are asymptomatic; with severe stenosis, dyspnea on effort appears. If foramen ovale is patent, a right to left shunt at the atrial level may occur in severe PS and result in cyanosis. Palpitation, easy fatigability and rarely chest pain may occur. Features of Noonan syndrome should be looked for. The cardiac size is normal and the hypertrophied right ventricle results in left parasternal heave. If the right ventricle fails, a right ventricular third sound may be audible. Rarely with right ventricular failure, tricuspid regurgitation may appear. Since the right atrium offers less resistance to flow of blood than obstruction at the pulmonary valve, the flow through the pulmonary valve diminishes reducing the intensity as well as the duration of ejection systolic murmur.

Infundibular stenosis is distinguished from valvar PS by: (i) absence of click; (ii) absence of post stenotic dilatation; and (iii) a relatively lower point of maximum intensity of systolic murmur in 3–4th left interspace. Isolated pure infundibular PS is rare.

The electrocardiogram shows right axis deviation and right ventricular hypertrophy. PS results in systolic overload for the right ventricle, suggested by pure 'R' or 'qR' complex in V4R and V1 leads. *P pulmonale* suggests severe PS. Chest X-ray shows a normal sized heart with normal pulmonary vasculature in mild, moderate as well as severe PS. Pulmonary oligemia occurs if the patients develop a right to left shunt at the atrial level in severe or critical PS. The main pulmonary artery exhibits poststenotic dilatation. Echocardiography can identify the site and severity of obstruction and helps in planning catheter intervention.

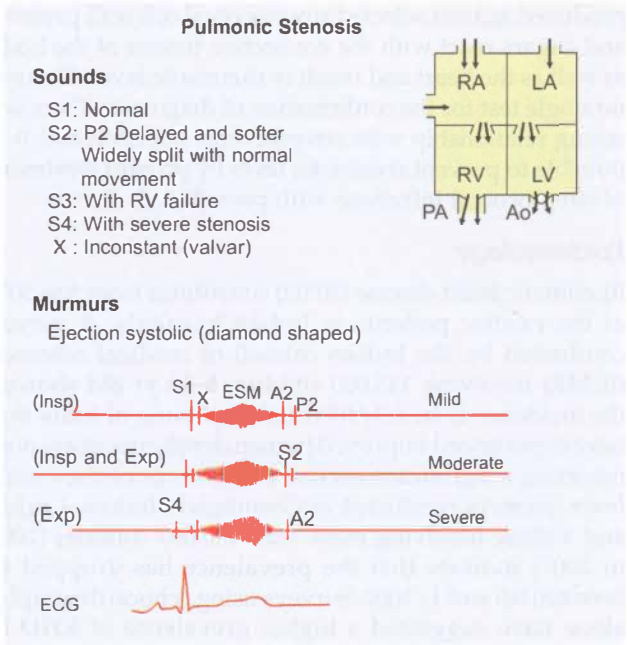

Fig. 15.39: Summary of auscultatory findings in pulmonic stenosis

Treatment

Valvar PS generally does not increase in severity with time unless it is severe or diagnosed in the newborn period. Patients with mild PS (gradients of 50 mm Hg or less) need annual review. Balloon pulmonary valvuloplasty is the treatment of choice for isolated valvar PS. The procedure is sometimes technically challenging in newborn with critical PS. Surgical treatment is indicated only if balloon valvotomy is unsuccessful, as in patients with dysplastic valves or small pulmonary valve annulus. Infundibular PS requires surgical resection.

Suggested Reading

Allen HD, Shaddy RE, Driscoll DJ, Feltes TF, Moss Adams' Heart disease in infants, children and adolescents, 7th Edition, Kluwer/Lippincott William and Wilkins, Philadelphia, USA, 2008

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Rheumatic Fever

Rheumatic fever is an immunological disorder initiated by group A beta hemolytic streptococci. Antibodies

produced against selected streptococcal cell wall proteins and sugars react with the connective tissues of the body as well as the heart and result in rheumatic fever. There is no single test for the confirmation of diagnosis. There is a strong relationship with streptococcal infection and it is possible to prevent rheumatic fever by prompt treatment of streptococcal infections with penicillin.

Epidemiology

Rheumatic heart disease (RHD) constitutes from 5 to 50% of the cardiac patients in Indian hospitals. A survey conducted by the Indian council of medical research (ICMR) involving 133,000 children 6–16 yr old showed the incidence to be 5.3/1000. Selected parts of India that have experienced improved human development are now reporting a significant decline in incidence of rheumatic fever. Surveys conducted at Chandigarh, Indore, Cochin and Vellore involving more than 100,000 children (2004 to 2007) indicate that the prevalence has dropped to between 0.5 and 1/1000. Surveys using echocardiography alone have suggested a higher prevalence of RHD in selected regions (as high as 20/1000).

Age and sex. The incidence of rheumatic fever following streptococcal throat infection is 0.3% in the general population and 1 to 3% in presence of epidemics of streptococcal sore throat. The commonest age group involved is 5–15 yr, and first episodes of RF are rare before 3 yr or after 30 yr age. Although the sexes are nearly equally affected, mitral valve disease and chorea is more common in girls whereas aortic valve involvement is more often seen in boys.

Predisposing factors. Poor socioeconomic conditions, unhygienic living conditions and overcrowded households predispose to streptococcal infections. However, an epidemic in United States occurred in upper middle class families in the absence of overcrowding and with good medical facilities in the mid 1980s.

Etiopathogenesis

The etiology of rheumatic fever is unknown. A strong association with beta hemolytic streptococci of group A is indicated by a number of observations:

i. History of preceding sore throat is available in less than 50% patients
ii. Epidemics of streptococcal infection are followed by higher incidence of rheumatic fever
iii. The seasonal variation of rheumatic fever and streptococcal infection are identical
iv. In patients with established RHD streptococcal infection is followed by recurrence of acute rheumatic fever
v. Penicillin prophylaxis for streptococcal infection prevents recurrences of rheumatic fever in those patients who have had it earlier
vi. More than 85% of the patients with acute rheumatic fever show elevated levels of anti-streptococcal antibody titer

Streptococci have never been isolated from rheumatic lesions in joints, heart or the blood stream. Considerable evidence suggests that rheumatic fever is an antigen-antibody reaction. Following streptococcal sore throat, there is a latent period of 10 days to several weeks before the onset of rheumatic fever. This latent period is similar to other antigen-antibody diseases like serum sickness. Streptococcal cell wall proteins as well as carbohydrates have the capacity to produce antibodies capable of reacting with human connective tissue, resulting in rheumatic fever. Rheumatic fever appears to be the result of the host's unusual response at both the cellular and humoral level to *Streptococcus*. There is no marker that identifies genetic susceptibility to rheumatic fever.

Only heart valves are permanently damaged during an episode of rheumatic fever. All other affected tissues typically heal without residua: pericarditis, chorea and arthritis resolve completely without constriction, longterm neurologic consequences or joint disability, respectively. Concepts about the pathogenesis of rheumatic fever and RHD are summarized in Fig. 15.40.

Clinical Features

The clinical features of rheumatic fever consists of streptococcal sore throat with fever followed 10 days to a few weeks later by recurrence of fever and the various manifestations of acute rheumatic fever. The history of sore throat is available in less than 50% of the patients. Guidelines for the clinical diagnosis of acute rheumatic fever, originally suggested by T. Duckett Jones have been revised by the American heart association and WHO. The guidelines consist of major, minor and essential criteria (Table 15.16). *Two major or one major and two minor criteria are required in the presence of essential criteria to diagnose acute rheumatic fever.* It is important to emphasize that these guidelines are meant to help a physician in making a firm diagnosis of rheumatic fever and do not mean that a physician should not use his clinical judgment in making a diagnosis in the absence of these criteria.

Major criteria These include:

(i) *Carditis.* It is an *early* manifestation of rheumatic fever. Studies utilizing echocardiography indicates that carditis occurs in almost 90% patients. In 60–70% it is clinically obvious whereas in the remaining, the diagnosis is based on echocardiographic findings labeled as subclinical carditis. Rheumatic carditis is designated as a pancarditis involving the pericardium, myocardium and endocardium, although studies indicate limited myocardial component. Almost 80% of those patients who develop carditis do so within the first two weeks of onset of rheumatic fever.

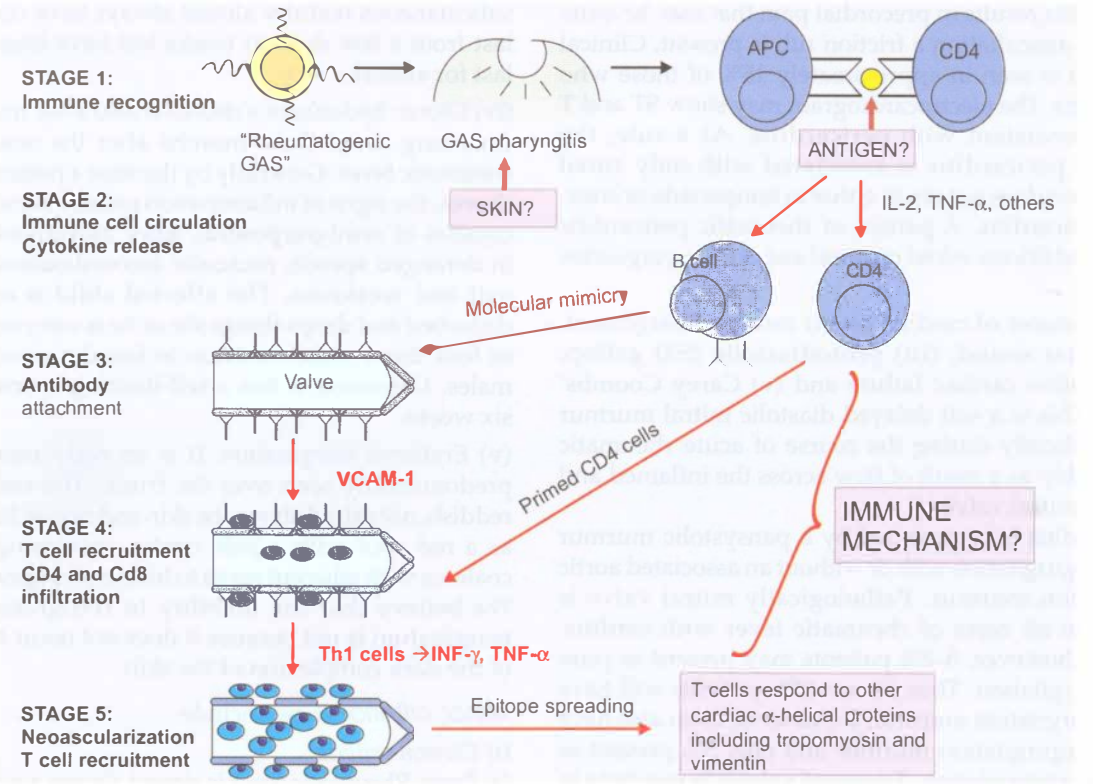

Fig. 15.40: Presumed pathogenesis of rheumatic fever; It is likely that the endothelium suffers initial damage due to a humoral immune response, the damage resulting in vascular cell adhesion molecule 1 (VCAM-1) being expressed on the endothelium. This is followed by activation of cellular immune response. As a result CD4+, CD8+ T lymphocytes and macrophages get attached to the valvar endothelium and migrate to the connective tissue core. This sets up an inflammatory response. The inflammation is accompanied by neovascularization of the valve substance. GAS group A streptococcus, INF-γ gamma Interferon, TNF-α tumor necrosis factor alpha, Th1 T helper cells 1

Table 15.16: WHO criteria for diagnosis of rheumatic fever (RF) and rheumatic heart disease (based on the revised Jones criteria)

Major manifestations: Carditis, polyarthritis, chorea, erythema marginatum, subcutaneous nodules

Minor manifestations: Clinical (fever, polyarthralgia); Laboratory (elevated erythrocyte sedimentation rate, leukocyte count), Electrocardiogram (prolonged P-R interval)

Supporting evidence of preceding streptococcal infection within last 45 days: Elevated or rising antistreptolysin O or other streptococcal; antibody, or a positive throat culture, or rapid antigen test for group A streptococci, or recent scarlet fever

Primary episode of RF: Two major or one major and two minor manifestations plus evidence of a preceding group A streptococcal infection

Recurrent attack of RF in a patient without rheumatic heart disease: Two major or one major and two minor manifestations plus evidence of a preceding group A streptococcal infection

Recurrent attack of RF in a patient with established rheumatic heart disease: Two minor manifestations plus evidence of a preceding group A streptococcal infection

Rheumatic chorea, insidious onset rheumatic carditis: Other major manifestations or evidence of group A streptococcal infection not required

Chronic valve lesions of rheumatic heart disease: Patients do not require any other criteria to be present if diagnosed for the first time as having rheumatic heart mitral stenosis, mixed mitral valve and/or aortic valve disease

Patients that present with polyarthritis, polyarthralgia or monoarthritis and ≥3 minor manifestations along with evidence of recent group A streptococcal infection should be considered as *probable rheumatic fever* once other diagnoses are excluded, particularly in vulnerable age groups in high incidence settings. They require close followup and regular secondary prophylaxis.

Pericarditis results in precordial pain that may be quite severe. On auscultation a friction rub is present. Clinical pericarditis is seen in approximately 15% of those who have carditis. The electrocardiogram may show ST and T changes consistent with pericarditis. As a rule, the rheumatic pericarditis is associated with only small effusions and does not result either in tamponade or constrictive pericarditis. A patient of rheumatic pericarditis *always has additional mitral or mitral and aortic regurgitation murmurs.*

Other features of carditis are (i) cardiac enlargement, (ii) soft first sound, (iii) protodiastolic (S3) gallop, (iv) congestive cardiac failure and (v) Carey Coombs' murmur. This is a soft delayed diastolic mitral murmur heard transiently during the course of acute rheumatic fever possibly as a result of flow across the inflamed and thickened mitral valve.

Endocarditis is represented by a pansystolic murmur of mitral regurgitation with or without an associated aortic regurgitation murmur. Pathologically mitral valve is involved in all cases of rheumatic fever with carditis. Clinically, however, 5–8% patients may present as pure aortic regurgitation. Thus almost 95% patients will have mitral regurgitation murmur, a quarter of them also have an aortic regurgitation murmur and only 5% present as pure aortic regurgitation. Tricuspid valvulitis resulting in tricuspid regurgitation occurs in 10–30% of cases. Isolated tricuspid valvulitis as a manifestation of acute rheumatic endocarditis does not occur. Clinical evidence of pulmonary valve involvement in acute rheumatic fever is never seen. The acute hemodynamic overload resulting from acute mitral regurgitation and/or aortic regurgitation leads to left ventricular failure and is the main reason for the morbidity and mortality of rheumatic fever and RHD.

(ii) *Arthritis.* Rheumatic arthritis is a polyarthritis involving large joints that include knees, ankles and elbows. Uncommonly smaller joints may also be involved. It is a migratory polyarthritis with the affected joints showing redness, warmth, swelling, pain and limitation of movement. It is an *early* manifestation and occurs in 70–75% of cases according to western literature. However, the figures from India indicate that arthritis is seen in 30 to 50% of patients. The pain and swelling appear rather quickly, last 3 to 7 days and subside spontaneously to appear in some other joint. There is no *residual damage to the joint.* Arthritis tends to be commoner in older patients.

(iii) *Subcutaneous nodules.* Subcutaneous nodules appear on bony prominences like elbows, shins, occiput and spine. They vary in size from pinhead to an almond. They are non-tender. Subcutaneous nodules are a *late* manifestation and appear around 6 weeks after the onset of rheumatic fever though they have been described as early as 3 weeks from the onset. They occur in about 3 to 20% of cases of rheumatic fever in India. Patients who have subcutaneous nodules almost always have carditis. They last from a few days to weeks but have been known to last for almost a year.

(iv) *Chorea.* Sydenham's chorea is also a *late* manifestation occurring about three months after the onset of acute rheumatic fever. Generally by the time a patient manifests chorea, the signs of inflammation usually subside. Chorea consists of semi-purposeful, jerky movements resulting in deranged speech, muscular incoordination, awkward gait and weakness. The affected child is emotionally disturbed and drops things she or he is carrying. It is three to four times more common in females as compared to males. Untreated, it has a self-limiting course of two to six weeks.

(v) *Erythema marginatum.* It is an early manifestation, predominantly seen over the trunk. The rash is faintly reddish, not raised above the skin and non-itching. It starts as a red spot with a pale center, increasing in size to coalesce with adjacent spots to form a serpiginous outline. We believe that the inability to recognize erythema marginatum is not because it does not occur but because of the dark complexion of the skin.

Minor criteria These include:

(i) *Clinical criteria*

(a) *Fever.* Rheumatic fever is almost always associated with fever. The temperature rarely goes above 39.5°C.

(b) *Arthralgia.* Arthralgia is defined as subjective pain whereas arthritis means subjective symptoms as well as objective signs of joint inflammation. Whereas arthritis is a major manifestation, arthralgia is a minor manifestation. Figures from India indicate that arthritis and arthralgia together occur in about 90% of the patients

(c) *Previous rheumatic fever or rheumatic heart disease.* This minor criterion is applicable only for a second attack of rheumatic fever.

Laboratory Manifestations

(a) *Acute phase reactants* consist of polymorphonuclear leukocytosis, increased sedimentation rate and C-reactive protein. The leukocyte count usually lies between 10,000 to 15,000/cu mm. The sedimentation rate is elevated during acute rheumatic fever and remains so for 4 to 10 weeks in almost 80% of patients. In a small proportion of patients it may remain elevated even beyond 12 weeks. Although congestive cardiac failure tends to bring the sedimentation rate down toward normal, it is unlikely that a patient of acute rheumatic fever in congestive cardiac failure will have a normal sedimentation rate. C-reactive protein is increased in all patients of acute rheumatic fever. It subsides rapidly if the patient is on steroids. While absence of C-reactive protein is strongly against the diagnosis of acute rheumatic fever, its presence is non-specific.

(b) *Prolonged PR interval in the electrocardiogram.* Prolonged PR interval is a non-diagnostic criterion since it can get

prolonged in many infections. It is also not diagnostic of carditis. Higher grades of block like second degree atrioventricular block specially of the Wenckebach type may also be seen. Complete atrioventricular block is extremely rare.

Essential Criteria

These include evidences of recent streptococcal infection. The commonest in use is the antistreptolysin 'O' titer (ASO). Elevated levels of ASO only indicate previous streptococcal infection and not rheumatic fever. Although generally the higher the level the more likely one can conclude a recent streptococcal infection, lower levels considered "normal" do not necessarily exclude a recent streptococcal infection. If the basal ASO titer of an individual is 50 units and it goes up to 250 units, it is indicative of recent streptococcal infection. Rising titer of ASO is a strong evidence for a recent streptococcal infection.

Positive throat culture for streptococci is relatively uncommon, when a patient presents with acute rheumatic fever. Positive throat culture can also not be equated with the diagnosis of rheumatic fever. Positive throat culture means that streptococci are present in the throat. The patient may or may not have rheumatic fever.

The third feature suggestive for the diagnosis of recent streptococcal infection is the presence of residua of scarlet fever. The desquamation of skin of palms and soles indicates that the patient has had scarlet fever within the previous two weeks. Scarlet fever is rare in India.

Echocardiography. Although the revised Jones criteria do not include echocardiographic findings for the diagnosis of carditis, this is a sensitive investigation for diagnosis of rheumatic carditis. The features indicative of rheumatic carditis consist of annular dilatation, elongation of the chordae to the anterior leaflet of the mitral valve causing a prolapse and lack of coaptation of the two leaflets resulting in mitral regurgitation. There is focal nodular thickening of the tips of the mitral leaflets, which do not have an independent chaotic movement seen with infective endocarditis. In addition, there is variable degree of increase in the left atrial and ventricular size. Involvement of the aortic valve is recognized as aortic regurgitation. Occasionally, the leaflet tip of the mitral valve becomes flail during an episode of rheumatic fever because of chordal rupture resulting in severe mitral regurgitation.

Echocardiography has improved recognition of the presence of carditis, which at times is not possible clinically by auscultation. This has lead to the recognition of the entity of subclinical carditis in which although there are no clinical findings to suggest mitral regurgitation, the echocardiograpic findings indicate mitral regurgitation. While the course of patients with subclinical carditis is not clear, most patients are advised longterm penicillin prophylaxis.

Treatment

Management is symptomatic combined with suppressive therapy.

Bed rest. Bed rest is generally recommended for acute rheumatic fever. Patients who do not have cardiac involvement can be ambulant in two to three weeks whereas when carditis is present, immobilization may have to be continued for one to three months specially in the presence of congestive failure.

Diet. In the absence of cardiac involvement there should be no restriction in salt intake. Even in the presence of cardiac involvement, salt restriction is not necessary unless congestive cardiac failure is present and not responding well to treatment.

Penicillin. After obtaining throat cultures the patient should be put on penicillin. A single injection of benzathine penicillin can be administered when the diagnosis of rheumatic fever is made. Penicillin V (250 mg four times a day for 10 days) is another alternative; erythromycin (250 mg qid for 10 days) can be administered for those with penicillin allergy.

Suppressive therapy *Aspirin* or *steroids* are given as suppressive therapy. Since untreated rheumatic fever subsides in 12 weeks in 80% of the patients, either of the two suppressive agents is given for 12 weeks. Steroids are a more potent suppressive agent as compared to aspirin. However, there is no proof that the use of steroids results in less cardiac damage as compared to aspirin. A number of observations indicate that steroids act faster and are superior at least in the initial phases. Pericardial friction rub tends to disappear within three to five days after starting the steroids and a new friction rub does not appear. Despite adequate doses of aspirin having been given, a new friction rub may still make its appearance. Subcutaneous nodules tend to disappear faster with the use of steroids as compared to aspirin. Patients who have carditis with congestive cardiac failure have a higher mortality if aspirin is used compared to steroids. In selecting the medication, the following guidelines are followed:

- Carditis with congestive cardiac failure: use steroids
- Carditis without congestive cardiac failure: One may use either steroids or aspirin, however, steroids are preferred
- If the patient does not have carditis, it is preferable to use aspirin.

The total duration of course for the suppressive agent, aspirin or steroids, is 12 weeks. Aspirin is given at a dose of 90–120 mg/kg/day (in 4 divided doses) for 10 weeks, and then tapered in the next two weeks. Alternatively, prednisolone (2 mg/kg daily; maximum dose 60 mg) is given for three weeks and then tapered gradually in next 9 weeks. The management of congestive cardiac failure is based on principles discussed above.

Surgical replacement of the mitral and/or aortic valve is indicated if the patient is deteriorating despite aggressive decongestive measures. Acute hemodynamic overload due to mitral or aortic regurgitation is the main cause of mortality due to rheumatic fever.

Management of chorea. The patient as well as the parents should be reassured and told about the self-limiting course of the disease. The signs and symptoms of chorea do not respond well to anti-inflammatory agents or steroids. Supportive measures such as rest in a quiet room and medications such as haloperidol, diazepam and carbamazepine are effective.

Prevention of Rheumatic Fever

Primary prevention requires identification of streptococcal sore throat and its treatment with penicillin. For primary prevention, it is necessary to educate the community regarding the consequences of streptococcal sore throat. Logistically it is difficult since it requires (i) identification of sore throat that is dependent on education of parents, (ii) rapidly confirming that sore throat is streptococcal: requires availability of microbiological facilities, and (iii) medical help and availability of penicillin. Data from recent epidemics of rheumatic fever indicates that anywhere from 30 to 80% of sore throats resulting in rheumatic fever can be asymptomatic. Because asymptomatic streptococcal pharyngitis can result in rheumatic fever, primary prevention can only be possible by using an anti-streptococcal vaccine, which is not available.

Secondary prevention consists in giving long-acting benzathine penicillin. The dose is 1.2 million units once every 3 weeks or 0.6 million units every alternate week. The injection is painful and since some patients get fever for 24 to 36 hr following the injection, it is preferable to give the injection on a weekend to avoid school absence. While the responsibility of continuing penicillin prophylaxis is on parents, the physician should explain the seriousness of the problem and the need for prolonged treatment (Table 15.17).

Duration of Secondary Prophylaxis

Recommendations of the WHO are widely accepted. Patient without proven carditis should receive prophylaxis for 5 yr after the last episode, or until they are 18-yr-old (whichever is longer). Patient with carditis (mild mitral regurgitation or healed carditis) should receive prophylaxis for 10 yr after the last episode, or at least until they are 25-yr-old (whichever is longer). Patients with established RHD disease or following valve surgery or balloon mitral valvotomy should receive lifelong prophylaxis. Some cardiologists recommend discontinuation of prophylaxis after the age of 40 yr, since the likelihood of recurrence beyond this age is minimal.

Table 15.17: Secondary prophylaxis following an episode of rheumatic fever

Antibiotic	*Mode of administration, dose*
Benzathine penicillin	Single intramuscular injection every 3 to 4 weeks*, 1200 000 units for patients ≥30 kg; and 600 000 units for <30 kg
Penicillin V	250 mg orally twice daily
Erythromycin (for penicillin allergy)	250 mg orally twice daily

*In high prevalence regions, 3 wk injections are recommended for prophylaxis, in patients >30 kg and every 2 weeks in patients <30 kg

Rheumatic Heart Disease

The sequelae of rheumatic fever consist of mitral, aortic and tricuspid valve disease. Mitral valve involvement manifests predominantly as mitral regurgitation (MR) and much less commonly as mitral stenosis (MS). Aortic valve and tricuspid valve involvement presents as aortic (AR) and tricuspid regurgitation (TR), respectively. Rheumatic aortic stenosis (AS) is very rare in childhood or adolescence.

Mitral Regurgitation

Mitral regurgitation (MR) is the commonest manifestation of acute as well as previous rheumatic carditis. In our study of 850 patients of RHD below the age of 12 yr, 750 had pure or dominant MR.

Hemodynamics

Mitral regurgitation results in a systolic leak of blood to the left atrium. The regurgitant volume of blood reaches the left atrium during ventricular systole at almost systolic pressure. However, during diastole it can pass freely across the mitral valve. Thus, although the left atrial pressure increases during systole, it drops during diastole. The mean left atrial pressure, therefore, stays normal or is only slightly increased. There is thus only a minimal increase in pulmonary venous pressure and no pulmonary congestion. The increased volume of blood handled by the left atrium and left ventricle results in an increase in the size of both these chambers. Mitral regurgitation provides two exits for the left ventricular blood—the forward flow through the aortic valve into the systemic circulation and the backward leak into the left atrium. The forward output becomes insufficient during exertion. This decrease in the systemic output results in fatigue, the commonest symptom of significant MR. Absence of pulmonary congestion prevents occurrence of dyspnea unless the MR is severe or the left ventricular myocardium is failing. With failing left ventricle, the left ventricular diastolic pressure increases, the left atrial and pulmonary venous pressure increase and pulmonary congestion appears. There is an increase in pulmonary arterial pressure and features of pulmonary arterial hypertension appear. Thus presence of features of pulmonary arterial hypertension in a patient having pure MR suggests (i) severe MR or (ii) failing left ventricular myocardium.

MR developing during acute rheumatic fever is of sudden onset. It results in an acute hemodynamic overload

over the left ventricle. The features of left ventricular failure can occur even with relatively moderate leaks during the acute illness. The size of the left atrium also plays a significant role in MR. With acute MR the left atrial size is normal and the increased volume reaching the left atrium increases the left atrial and the pulmonary venous pressure, resulting in pulmonary congestion and features of left ventricular failure. With long-standing MR the left atrium increases in size to accommodate the regurgitant volume without increasing the left atrial pressure and features of left ventricular failure are absent. Another important adjustment consists of *decrease in the systemic vascular resistance to help increase the forward flow*. The maximum ejection of blood into the aorta takes place during early systole. The combination of these two factors results in an increased systolic and decreased diastolic pressure in the systemic circuit. The pulse pressure is, therefore, increased resulting in the *small water hammer pulse* of MR.

Clinical Features

The resting pulse rate is increased to maintain an adequate cardiac output. In absence of pulmonary congestion the respiratory rate is normal. Features of left ventricular failure are absent and appear late unless the MR is *acute, severe* or left ventricular *myocardium is failing*. The heart size is dependent on the severity of MR as well as the status of the left ventricular myocardium. The cardiac apex is displaced downward and outward with forcible apex and hyperkinetic precordium. Less than 10% of patients have a systolic thrill because of posterior direction of the regurgitant stream. The first sound may be soft as it is masked by the systolic murmur. The second sound is normally split with mild MR. With moderate or severe MR the second sound is widely and variably split. The wide split is due to an early aortic component of the second sound. With failing left ventricle the wide splitting disappears. Except with very mild MR, *a third sound is audible at the apex and indicates increased early rapid filling* of the left ventricle. With severe MR a delayed diastolic mitral murmur starting with the third sound is audible. The delayed diastolic murmur is *secondary to a large flow* across the mitral valve during diastole. Not infrequently this *delayed diastolic murmur* may be palpable as a short diastolic thrill. In pure MR, the delayed diastolic murmur always ends somewhere in *mid-diastole* and there is *no late diastolic (presystolic) accentuation*. The classical diagnostic sign is the pansystolic murmur, best heard at the apex and widely radiating to the axilla and back as well as to the left sternal border (Fig. 15.41).

The electrocardiogram shows sinus tachycardia and a normal axis. Signs of left ventricular hypertrophy may be present with long-standing and severe MR. The thoracic roentgenogram shows cardiac enlargement secondary to left ventricular enlargement, the size depending on the severity of MR. Left atrial enlargement may be inferred

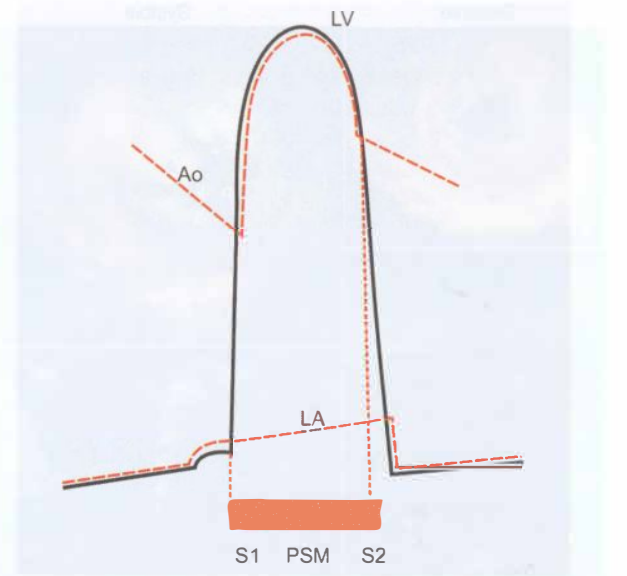

Fig. 15.41: The characteristic pansystolic murmur. As the left ventricular (LV) pressure exceeds the left atrial pressure (LA) the first sound (S1) occurs. However, the murmur of mitral regurgitation will also start at the same time masking the S1. Since the maximum difference in the LV and LA pressure is quickly reached and maintained throughout systole, the murmur maintains the same intensity throughout systole appearing pansystolic. Finally as the LV pressure drops below the aortic (Ao) pressure, A2 occurs. The LV pressure is higher than LA pressure at this time and the murmur goes beyond, A2 thus masking both the S1 and A2. (PSM pansystolic murmur)

from the elevation of left bronchus. In the absence of left ventricular failure, there is absence of prominence of pulmonary veins as well as features of pulmonary congestion. Echocardiogram shows enlarged left atrium and ventricle. The specific findings of pathology of mitral valve affliction can be demonstrated vividly by two-dimensional and three-dimensional echocardiography, and this is essential to plan treatment. Color Doppler can quantify MR non-invasively (Fig. 15.42).

Differential Diagnosis

Other causes of MR in childhood include: (i) atrial septal defect of the primum variety; (ii) coarctation of the aorta with MR (congenital); (iii) left ventricular fibroelastosis; (iv) congenital corrected transposition of great arteries; (v) papillary muscle dysfunction in dilatation of left ventricle from any cause including myocarditis; (vi) atrial septal defect of the secundum type with floppy mitral valve; (vii) Marfan and Hurler syndrome, and (*viii*) anomalous origin of left coronary artery from pulmonary artery.

Treatment

Mild to moderate MR is well tolerated for long periods. However, its severity increases with time. Medical management consists of the use of digitalis and diuretics

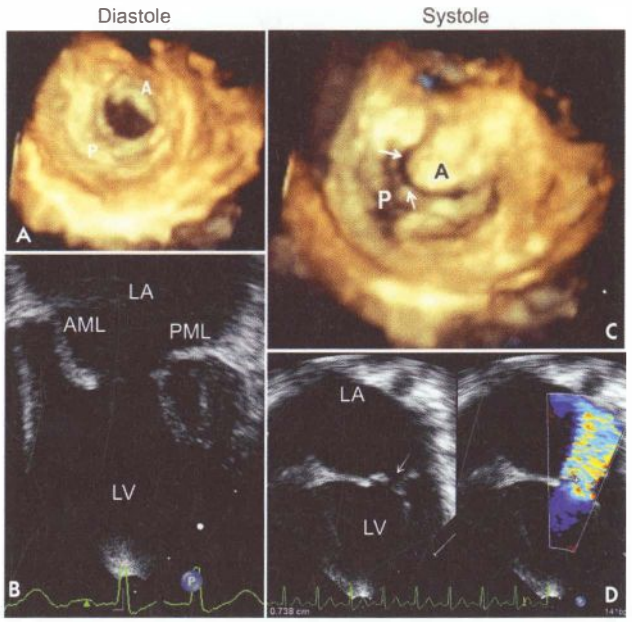

Fig. 15.42: Rheumatic mitral valve disease with mitral stenosis and regurgitation. These frames are from a 10 yr old child with rheumatic heart disease with severe affliction of the mitral valve. Although the predominant lesion is mitral regurgitation, there is also some mitral stenosis. Three dimensional (3D) echocardiograms are shown in the upper panel and equivalent two dimensional frames obtained from apical four chamber views are in the lower panel; (A) The diastolic frame in the 3D image shows the mitral valve from its left atrial aspect. Note that the leaflet substance is seen in diastole; (B) Equivalent diastolic frame on 2D shows several features rheumatic affliction. The anterior mitral leaflet (AML) is thickened. The tip of the AML is oriented horizontally and does not point downwards suggesting restriction of mobility of diastolic motion. The posterior mitral leaflet (PML) is also thickened and mobility is restricted to a greater degree. The chordae tendinae beneath the PML are visibly thickened; (C) During systole the PML stays in a relatively fixed position. The free edge of the AML moves to a position above the optimal zone of coaptation between the two leaflets. The resultant regurgitation orifice is shown by white arrows in both the 3D and 2D frames. This orifice is typically crescentic and extends along the length of the AML; (D) The resultant color Doppler jet of mitral regurgitation is directed posteriorly and laterally

besides penicillin prophylaxis for prevention of recurrences. The role of systemic vasodilators, most commonly ACE inhibitors and calcium channel blockers, to reduce afterload in isolated MR and aortic regurgitation is controversial. An important additional consideration in RHD is the presence of varying degrees of mitral stenosis that accompanies MR.

There are no clear guidelines for the timing of mitral valve surgery (particularly replacement) in children. The natural history of MR is quite different in children and standard guidelines for mitral valve surgery in adults might not apply to children. Persistent symptoms, in spite of maximally tolerated medications, warrant consideration of surgery especially in the presence of pulmonary artery hypertension. For an asymptomatic child, evidence of even the slightest ventricular dysfunction merits consideration for surgery. The treatment of choice is mitral valve repair. At present the commonest surgical approach is prosthetic valve replacement because rheumatic mitral valves are difficult to repair. It is necessary to emphasize that valve replacement is not a cure and patients need to receive anticoagulants on the longterm, which might be a challenge in young children.

Rheumatic Mitral Stenosis (MS)

Rheumatic MS is less common than MR in children. Juvenile MS (<18 yr) is typically seen in regions with high prevalence of RHD.

Hemodynamics (Fig. 15.43)

MS results in obstruction to flow of blood across the mitral valve during left ventricular diastole. The left atrium compensates for this obstruction by increasing its pressure. This increase in pressure results in hypertrophy of the left atrial wall. Unfortunately, the left atrium is a thin walled chamber and the capacity for hypertrophy of the left atrial wall is limited. The increase in left atrial pressure prevents decrease in the blood flow across the mitral valve. The increased left atrial pressure is transmitted to pulmonary veins and results in pulmonary capillary engorgement and pulmonary congestion, which produces dyspnea, the commonest symptom of MS. The pulmonary arterial pressure increases to maintain forward flow from the pulmonary artery to the left side of the heart. In the absence of tricuspid regurgitation the right ventricular hypertrophy is concentric without an increase in the size of right ventricular chamber. The heart size usually stays normal.

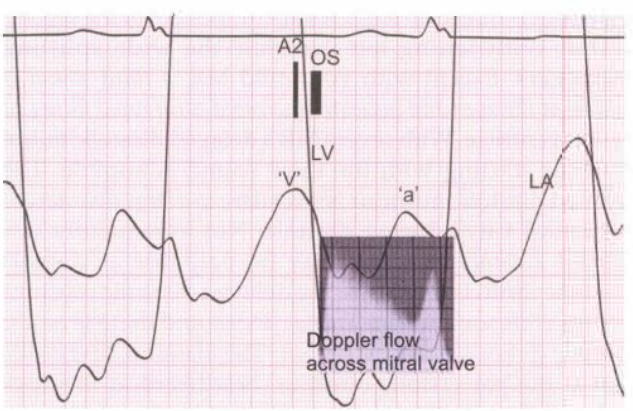

Fig. 15.43: Hemodynamics of mitral valve stenosis: A cardiac catheterization tracing with simultaneous recording of left atrial (LA) with 'a' and 'v' waves and left ventricular (LV) waveforms is shown. A continuous wave Doppler record is superimposed during diastole; note the two peaks in flow acceleration-the second peak coincides with pre-systolic accentuation. The flow patterns reflect the pressure gradients across the mitral valve in diastole. A2 aortic component of second heart sound; OS opening snap

With mild or moderate MS, the forward flow through the mitral valve remains normal. With severe obstruction the forward flow is diminished with reduced cardiac output resulting in a small volume pulse and cold extremities.

Clinical Features

Boys are twice as commonly affected as girls in the age group up to 12 yr. Juvenile rheumatic MS has been described in children as young as 5 yr. Patients with MS give history of shortness of breath on exertion or even at rest depending on the severity. Other important symptoms consist of cough, hemoptysis, paroxysmal nocturnal dyspnea, attacks of acute pulmonary edema and atypical angina. On examination, the pulse volume is small. The respiratory rate is increased except in patients with mild mitral obstruction. Depending on the severity, there may or may not be signs of right-sided congestion, in the form of engorged neck veins and enlarged tender liver. The liver may have systolic pulsations if there is associated tricuspid regurgitation; the jugular venous pulse shows prominent 'a' waves. If tricuspid regurgitation is present, the jugular veins show dominant 'V waves. With moderate or severe MS, signs of pulmonary congestion in the form of rales are present.

Examination of the precordium reveals a normal sized heart with a tapping apex beat, parasternal impulse and an apical diastolic thrill. The second sound may be palpable at the second left interspace. On auscultation the first sound is accentuated, the second sound normally split with a loud pulmonary component. An opening snap of the mitral valve is best audible just medial to the apex. The delayed diastolic mitral murmur starts immediately following the opening snap, diminishes somewhat in intensity during mid diastole and accentuates again at the end of diastole. The late diastolic accentuation is always present in the presence of MS. Absence of late diastolic accentuation of murmur is against the diagnosis of dominant MS.

The electrocardiogram shows right axis deviation with right ventricular hypertrophy. In addition, there is evidence for *P mitrale*. Thoracic roentgenogram shows a normal sized heart with features of pulmonary venous and arterial hypertension, as well as left atrial enlargement. Echocardiogram shows decreased EF slope, paradoxical posterior leaflet motion, left atrial enlargement and pulmonary arterial hypertension. 2D echo can identify the narrowed mitral opening. Doppler echo provides accurate information on transmitral gradient.

Assessment of severity The minimum criteria for the clinical diagnosis of MS are *accentuated first sound, the mitral opening snap and delayed diastolic murmur with late diastolic accentuation*. The closer the openings snap to the second sound, the more severe the mitral obstruction. The intensity or the duration of the diastolic murmur does not correlate with the severity since mild as well as severe MS may result in very soft murmurs. The duration of the murmur depends on the heart rate. Whereas mild pulmonary arterial hypertension may be present with mild, moderate or severe mitral obstruction, severe pulmonary arterial hypertension can occur only with severemitral obstruction. Echocardiogram (determination of cross-sectional area) combined with Doppler gradient gives more precise assessment of severity. Atrial fibrillation is rare in the pediatric age group.

Differential Diagnosis

Very few conditions can be considered in the differential diagnosis in children. Isolated congenital MS is very rare. The opening snap is less commonly heard in congenital MS. Cortriatriatum, obstruction of individual pulmonary veins and left atrial myxoma should be considered in the differential diagnosis.

Treatment

The management of MS is essentially catheter based or surgical. Beta blockers or digoxin work equally well by reducing resting and exercise heart rates thereby improving diastolic filling. Diuretics help by reducing pulmonary venous congestion. Balloon mitral valvotomy (BMV), also known as percutaneous trans-septal mitral commissurotomy (PTMC) has largely replaced closed or open mitral commissurotomy for MS in children. Improvement in mitral valve area following these procedures largely results from splitting of the fused commissures. The sub-valvar pathologic abnormalities of MS remain after valvotomy, so the mitral valve area does not normalize. The balloon, introduced through the femoral vein is passed through the atrial septum, positioned in the mitral valve and inflated to open the stenotic valve.

Longterm followup after valvotomy is mandatory because of significant risk of restenosis with time. Restenosis is typically associated with significant residual MS following balloon mitral valvotomy. A repeat procedure is an option for restenosis and helps postpone mitral valve surgery. Closed mitral valvotomy (CMV) is an inexpensive and equally effective surgical alternative to BMV.

Aortic Regurgitation (AR)

Aortic valve involvement in RHD results in AR. Clinically pure AR, without associated mitral valve disease, is rare and occurs in 5 to 8% patients. Pathologically pure rheumatic aortic valve disease is almost unknown.

Hemodynamics

AR is a backward leak from the aorta into the left ventricle during diastole. This increases the volume of blood reaching the left ventricle. The left ventricle increases in size to accommodate the extra volume. The size of the left ventricle is thus directly related to the degree of aortic leak,

unless there is myocardial disease. Because of the backward flow of blood the forward flow is impaired. This is compensated by peripheral vasodilatation as well as increased ejection from the left ventricle during early part of the systole. However, significant AR results in low forward output. Signs of wide pulse pressure in the form of exaggerated arterial and arteriolar pulsations are present unless the AR is mild. Slowing of heart rate increases the diastolic period and increases the regurgitant volume of blood in AR. With good left ventricular myocardial function, even moderate AR is tolerated well for long periods. If the left ventricular myocardium is failing the left ventricular diastolic pressure goes up and results in an increase in left atrial pressure and pulmonary congestion.

Clinical Features

Aortic valve disease is more common in boys compared to girls. The main symptom is palpitation, related to the large stroke volume. With mild to moderate AR the forward flow can be raised effectively on exercise. Thus fatigue is not an early symptom.

The pulse pressure is wide. The wider the pulse pressure, the more severe the aortic leak. The diastolic blood pressure may be recorded as zero with severe AR. Prominent carotid pulsations (*Corrigan sign*), visible arterial pulsations over extremity vessels (*dancing peripheral arteries*) and visible pulsations of the abdominal aorta are evidences of wide pulse pressure from any cause. Holding the middle of the forearm or leg and elevating it discloses a sharply rising and abruptly falling pulse (*Corrigan pulse* or *water hammer pulse*). Nodding of head may be present with each systole (*de Musset sign*) due to sudden filling of carotid vessels in severe AR. Arteriolar pulsations may be seen over the nail bed, uvula, lips, ear lobes and in the eye grounds. There is also exaggeration of the systolic pressure difference between the brachial and femoral arteries (*Hill sign*). Normally the difference between the pressures in brachial artery and femoral artery is less than 20 mm Hg, the femoral systolic pressure being higher. Systolic pressure difference between 20 to 40 mm Hg suggests mild AR, 40 to 60 mm moderate AR, and more than 60 mm Hg severe AR. If a stethoscope is put over the brachial or the femoral artery without applying pressure *pistol shot sounds* may be heard in moderate or severe AR. A systolic murmur may be heard if pressure is applied to partially occlude the artery proximal to the chest piece, and diastolic murmur if pressure is applied distally; the combination of systolic and diastolic murmurs is the *Duroziez sign*.

The apex is displaced downward and outward and is forcible or heaving. A diastolic thrill is unusual. The first sound is soft and the aortic component of the second sound may be audible or may be masked by the regurgitant diastolic murmur. The murmur of AR is a high-pitched, decrescendo diastolic murmur starting with the aortic component of the second sound. The intensity and the length of the murmur do not correlate with the severity of AR. The murmur is heard along the left sternal border and radiates to the apex and even beyond. With large aortic leaks there is also an ejection systolic murmur at the second right interspace, conducted to the neck and not infrequently associated with a systolic thrill. The systolic murmur is the result of a large stroke volume, passing across rough valves. It does not indicate aortic stenosis if the pulse pressure is wide and the carotid upstroke is brisk.

The electrocardiogram shows increase in left ventricular voltages with deep S waves in V1 and tall R waves in V6. There are also deep Q waves in left chest leads accompanied with tall T waves; this is called diastolic overloading pattern of the left ventricle. The thoracic roentgenogram shows cardiac enlargement of the left ventricular type and dilated ascending aorta. Echocardiogram identifies enlarged left ventricle, dilated aorta and flutter of anterior mitral leaflet. Doppler echo can quantitate the severity of AR.

Differential Diagnosis

The differential diagnosis of rheumatic AR includes two sets of conditions: (i) *conditions associated with a wide pulse pressure* like patent ductus arteriosus, arteriovenous fistulae, ventricular septal defect with AR, ruptured sinus of Valsalva, anemia and thyrotoxicosis, (ii) *conditions associated with a non-rheumatic regurgitant diastolic murmur* like pulmonary regurgitation, AR with ventricular septal defect, ruptured sinus of Valsalva and congenital aortic valve disease. As a rule congenital aortic valve disease is either a leaking bicuspid aortic valve or aortic stenosis. Pure congenital AR is extremely rare. Other conditions that may result in AR include Marfan syndrome, Hurler syndrome and Takayasu aortoarteritis.

Management

Mild to moderate AR is well tolerated for years. There is role for therapy with calcium channel blockers. Significant AR, if associated with either chest pain or left ventricular failure, should be treated surgically. Surgical treatment consists of aortic valve replacement either by homograft or prosthetic valve; valve repair is not feasible for rheumatic AR. Better surgical results are obtained before onset of significant ventricular dysfunction.

Patients planned for valve replacement should be screened for: (i) rheumatic activity; (ii) ability of the family to take lifelong anticoagulants. Aortic valve replacement has fewer longterm complications when compared to mitral valve replacement.

Tricuspid Regurgitation (TR)

Features indicative of TR are seen in 20 to 50% patients of RHD in children in our country. It is often difficult to determine whether TR is organic (due to involvement of the tricuspid valve by the rheumatic process) or functional (due to pulmonary hypertension).

Hemodynamics and Clinical Features

TR results in a systolic backflow of blood from the right ventricle to the right atrium. The systolic leak thus results in a systolic murmur and a volume load of the right atrium as well as the right ventricle. As a rule, almost all patients who have TR also have features of pulmonary arterial hypertension. The systolic backflow under pressure results in a prominent systolic wave, the V wave, in the jugular venous pulse as well as the liver. Both the systolic as well as the diastolic murmurs at the tricuspid valve become louder during inspiration. In patients of rheumatic heart disease the TR may be associated either with MS or with MR. If the TR is associated with MS it may be either organic or functional due to pulmonary arterial hypertension. If, on the other hand, the TR is associated with dominant or pure MR it is most likely organic. This is because MR of a severity to result in pulmonary arterial hypertension of a degree to cause functional TR is rare.

There are no specific symptoms of TR. It is possible that with onset of TR the dyspnea may be relieved to some extent in patients of MS. The patients may give history of pain in right hypochondrium due to a congested liver and of fatigue due to a decrease in systemic output. In addition to features of TR there are signs of pulmonary arterial hypertension and those of mitral valve disease. In association with MS, severe TR may result in marked dilatation of the right ventricle and the whole of the anterior surface, including the apex may be formed by the right ventricle. In such patients the apex beat is not only displaced outward but also downward. This should not be mistaken for left ventricular enlargement. In these cases the pansystolic murmur of TR may be heard from the lower left sternal border to the apex. Since the left ventricle is displaced backwards, the MS murmur may be audible only in the axilla or may not be made out at all. It is not uncommon for these patients to be diagnosed as those of MR. Besides peripheral signs of TR, the electrocardiogram is helpful in separating these cases from those of MR. Patients of TR of this severity almost always show severe right ventricular hypertrophy in the electrocardiogram. Echocardiography and color Doppler can document and identify the nature (organic vs. functional) and quantitate severity of TR.

Management

Decongestive measures will help in reducing the severity of TR. Further management depends on the associated mitral valve lesion. TR may resolve following mitral valvotomy. In those patients undergoing surgery for the MR, the tricuspid valve can be inspected and tricuspid annuloplasty or repair performed if needed.

Clinical Problems in Patients with Rheumatic Heart Disease

Two major problems that clinicians face in patients of RHD are discussed below.

Active or Inactive Rheumatic Fever?

A lot of 'judgment' or personal bias is generally involved in this decision. For the diagnosis of activity one has to fall back on the Jones criteria. Presence of cardiac involvement cannot be used as a major criterion since the carditis may be the result of a previous attack of rheumatic fever. However, presence of a pericardial friction rub is evidence of active carditis. If the patient has well documented cardiac findings then the appearance of a new murmur or a significant increase in a pre-existing murmur is very suggestive for active rheumatic fever. History of arthralgia or arthritis within a period of less than 12 weeks is suggestive of active rheumatic fever specially if associated with elevated sedimentation rate and ASO titer. Despite congestive cardiac failure, it is unusual for the sedimentation rate to be normal in a patient of active rheumatic fever. All patients of RHD should show elevated ASO titer before they can be labeled as *active* rheumatic fever. The difficulty arises in those patients who have relatively low levels of the ASO titer. In such cases, unless serial serum samples are available it is difficult to decide whether there is rise in level of ASO liter. An ASO titer of 250 units may indicate a significant rise if the baseline was 50 units.

In a Febrile Patient, Is it Active Rheumatic Fever or Infective Endocarditis?

At times separation of rheumatic activity from infective endocarditis can be very difficult. The arguments used above for separating active from inactive rheumatic fever can be used for diagnosis of active rheumatic fever. A detailed description of endocarditis follows.

Suggested Reading

Bland EF, Jones TD. Rheumatic fever and rheumatic heart disease. A twenty year report on 1000 patients followed since childhood. Circulation 1951; 42:836

Narula J, Virmani R, Reddy KS, Tandon R. Rheumatic fever. Amer Registry Path AFIP. Washington DC, 1999

Rheumatic fever and rheumatic heart disease. Report of a WHO expert consultation. World Health Organization, Geneva, 2004 (Technical Report Series No. 923)

INFECTIVE ENDOCARDITIS

Infection of the endocardial lining of the heart is called infective endocarditis, and may involve the endocardium of the valves, the mural endocardium or the endothelium of blood vessels (infective endarteritis). The commonest site of infection is a diseased valve from where the infection can spread along the endothelium. The injection has significant morbidity.

Etiopathogenesis

Infective endocarditis predominantly occurs in a diseased heart. The commonest substrate is a damaged endothelium or endocardium resulting from contact with a high

velocity jet together with the presence of a significant bacteremia. Endocarditis can occur following a surgical shunt as in Blalock-Taussig shunt. Other congenital lesions, associated with endocarditis are patent ductus arteriosus, pulmonic stenosis and mitral valve prolapse syndrome. It is rare in atrial septal defect of the secundum type unless associated with mitral valve prolapse and mitral regurgitation.

Infective endocarditis occurs over the mitral valve or the aortic valve in patients with rheumatic heart disease. Patients with prosthetic valves or those who have had a recent cardiac operation are also especially prone to endocarditis. Infections anywhere in body like boils or furuncles, tooth abscess, ear infection, urinary tract infection or osteomyelitis may result in endocarditis. Although interventions like dental procedures, cardiac catheterization, genitourinary procedures or bronchoscopy can be followed by endocarditis, it is rare to be able to identify a predisposing event. An important predisposing cause is poor dental hygiene. Parenteral drug abuse is a frequent cause of right-sided endocarditis involving the tricuspid or the pulmonary valve. Occasionally it can result in mitral and/or aortic valve disease as well.

15

Pathogenesis

The pathogenesis of endocarditis depends on the invasiveness and virulence of the infective organisms. The infection generally starts at a jet lesion, where the high-pressure jet strikes the endocardium or the endothelium. The right ventricular mural endocardium or the tricuspid valve in VSD, aortic endothelium in AS or coarctation of the aorta, ventricular surface of the aortic valve in AR are the usual sites. Endocarditis results in immune mediated vasculitis and thrombocytopenia.

Bacteremia resulting from an infection such as a boil, furuncle, otitis media or initiated by an intervention such as cardiac or urinary catheterization or dental extraction is necessary for initiation of endocarditis. Bacteremia may also result from simple events such as brushing teeth. Bacteria that are deposited on the endocardium are covered by fibrin and platelets forming vegetations. Almost any species of bacteria and some species of fungi can cause endocarditis. *Streptococcus viridians, S. aureus,* enterococci, *P. aeruginosa* and some gram negative bacilli are responsible for most episodes. Fungal endocarditis typically results in the setting of chronic hospitalization with indwelling central venous catheters.

Diagnosis

Any fever in a patient with known heart disease raises the question of endocarditis. *The minimum criteria for the diagnosis of endocarditis consist of unexplained fever of 7 to 10 days duration in a patient with known heart disease.* If this is associated with other clinical manifestations of endocarditis the diagnosis becomes more likely.

Endocarditis has been subdivided into acute and subacute types, depending on whether the patient presented with a chronic illness or as septicemia. Endocarditis is also identified by the infective organism, for example viridans endocarditis, staphylococcal endocarditis and enterococcal endocarditis. *S. viridans* results in the sub-acute form of illness while *S. aureus* and other pyogenic organisms cause a fulminant (acute) and rapidly progressive illness. It is possible, for an organism like staphylococcus to cause a subacute or acute type of illness. Identification of the organism is necessary, as it helps determine the choice of antibiotics.

Clinical Features

Infective endocarditis is uncommon below the age of two years. The clinical features of endocarditis may be grouped into those (i) indicating the presence of an infection; (ii) indicating involvement of the cardiovascular system; and (iii) indicating the presence of an immunological reaction to infection. The features indicating the presence of infection consist of fever, chills, rigors, night sweats, general malaise, weakness, loss of appetite, weight loss and amenorrhea in females. Loss of appetite is a very persistent and important symptom. Arthralgia and diffuse myalgia can occur, however, arthritis does not occur except in acute endocarditis as part of septicemia when it is likely to be monoarticular.

Features indicative of the involvement of the cardiovascular system may be absent in the initial stages. Appearances of left or right heart failure, development of a new murmur or change in a pre-existing murmur, presence of embolic episodes to various parts of the body (like stroke from central nervous system embolism, hematuria from renal infarct, left flank pain from splenic infarct, gastrointestinal hemorrhage from mesenteric embolism etc.) indicate involvement of the cardiovascular system. As damage to the valve tissue occurs, regurgitant lesions appear. These regurgitant lesions, aortic, mitral or tricuspid, progress rapidly causing hemodynamic changes that result in congestive failure.

Features of immunological response presenting as vasculitis consist of arthralgia, myalgia, clubbing, splenomegaly and microscopic hematuria. Splinter hemorrhages are hemorrhagic spots under the nails, though suggestive, are not specific for endocarditis as they can result from minor injuries. Petechiae over the skin or mucous membranes and conjunctiva are seen in about 50% patients. Petechiae in the retina are called Roth spots. Osler nodes are tender erythematous nodules over the pulp of fingertips, but are relatively rare. Janeway lesions are non-tender erythematous patches on the palms and soles. Clubbing and splenomegaly tend to appear 3 weeks after the onset of endocarditis.

In the acute form, the symptoms appear early and progress rapidly with hectic fever, chills and rigors. Perforation of valve cusps may result in appearance of

acute regurgitant lesions like acute tricuspid, aortic or mitral regurgitation. With inadequate treatment, the course is downhill and death within 6-weeks from the onset. Metastatic lesions causing abscesses in the central nervous system, spleen, mesentery, bones and joints are common. Metastatic abscesses are rare in subacute endocarditis.

Patients with endocarditis of the right side, such as tricuspid or the pulmonary valve, throw emboli to the lungs. The embolic episodes to lungs may present as repeated episodes of pneumonitis or septic infarcts resulting in lung abscesses. It is more common in patients with indwelling central catheters, intravenous drug abuse and with VSD. Fever may occasionally present in some patients with right-sided endocarditis. Some patients remain afebrile for several days at a time and yet have large vegetations and elevated acute phase reactants.

Postoperative endocarditis. Postoperative endocarditis is classified as early (<12 months) and late. Early endocarditis is usually due to pyogenic organisms such as staphylococcus, pseudomonas or gram negative bacilli introduced at the time of operation. These patients have high fever with chills and rigors and features of septicemia. Late endocarditis is more like native valve endocarditis and the commonest organisms are *S. viridans* and gram negative bacilli; these patients have a subacute course. Cardiac operations are an important predisposing factor for gram negative endocarditis. Prosthetic valve endocarditis may also be early or late and behaves as above.

Fungal endocarditis. With extensive use of broad-spectrum antibiotics, yeast and fungal infections occur more frequently than before specially following cardiac operations and in intensive care settings. Candida is by far the commonest fungus responsible; others include *Histoplasma, Blastomyces, Aspergillus, Cryptococcus* and *Mucor*. Fungemia is high and the organism is easily cultured from the peripheral blood. Predisposing factors for fungal endocarditis include intravenous drug abuse, indwelling catheters, intensive antibiotic therapy, prolonged steroid administration, radiation, immunosuppressive therapy and prosthetic valves. Incidence of embolism is higher since the fungal vegetations tend to be very large. Despite intensive therapy, mortality is high.

Laboratory Diagnosis

Blood culture is essential for diagnosis. A positive blood culture in a patient with underlying heart disease, suspected to have endocarditis is confirmatory. Three sets of cultures, each containing adequate volumes of blood, taken every half-hour are appropriate and detect 95% cases. The commonest cause for negative cultures is prior antibiotic therapy or unsatisfactory culture technique. Infection with unusual organisms, anerobic organisms and fungi require special mediums and incubation for 2–3 weeks before declaring that the culture is negative. Arterial sampling does not offer any advantage over venous samples. Other investigations, which provide supportive evidence for the diagnosis, include:

i. Normocytic normochromic anemia
ii. Moderately elevated total leukocyte count
iii. Reduced platelet count
iv. Elevated sedimentation rate and C-reactive protein
v. Microscopic hematuria and albuminuria in more than 95%.

Echocardiography

Echocardiography is a valuable diagnostic tool, especially in patients with culture negative endocarditis. The investigation identifies complications like ruptured chordae, perforated cusps and flail cusps resulting from endocarditis. Vegetations more than 2 mm can be identified on echocardiography, but its sensitivity is dependent on the site of involvement. For aortic and mitral valves, the sensitivity is more than 90%, while for tricuspid and pulmonary valves it is 70%. The presence of vegetations has high negative as well as positive predictive value for confirming the diagnosis of infective endocarditis. However, the procedure is highly operator dependent. Limitations of echocardiography can be overcome by transesophageal echocardiography, especially in patients with prosthetic valve endocarditis and if valve ring abscess is suspected.

Complications

Damage to valve cusps or perforation, rupture of chordae tendinae result in acute regurgitant lesions causing hemodynamic deterioration. Migration of vegetations may result in embolic neurological deficit, renal infarcts with hematuria, mesenteric infarct and melena, loss of fingers or toes due to obstruction of blood supply. Damage to the vasa vasorum of blood vessels due to vasculitis may result in the formation of mycotic aneurysms that can rupture and result in massive bleeding. The kidneys suffer in many ways in endocarditis. They may have embolic infarct with hematuria. There may be focal or diffuse membranoproliferative glomerulonephritis resulting in albuminuria and microscopic hematuria. The finding of IgG, IgM and complement deposits on the glomerular basement membrane indicate that it is an immune complex nephritis. Renal insufficiency tends to appear beyond three weeks of the onset of endocarditis and is progressive until the endocarditis is cured; hematuria can persist for three to six months. Even advanced renal insufficiency tends to regress and renal function returns to normal after the endocarditis has been cured. Hence, presence of mild to moderate renal insufficiency should not be viewed as a poor prognostic sign.

Treatment

The main principles in management consist of: (i) identification of organism; (ii) finding out its antibiotic sensitivity; and (iii) prompt, appropriate and prolonged

antimicrobial treatment to cure and prevent relapse. If the blood culture is positive the choice of antibiotics is dictated by the antibiotic sensitivity. If the culture is negative empirical therapy covering a wide range of organisms is necessary. If the culture is positive, the culture plate should not be discarded. After starting the antibiotic treatment, patient's serum diluted to 1:8 parts or more should be used to determine if it inhibits the growth of the organism in subculture, to indicate the efficacy of treatment. Common organisms causing endocarditis, antibiotic of choice and duration of treatment is shown in Table 15.18.

Fungal endocarditis. Fungal endocarditis is very resistant to treatment. The patient should recieve amphotericin B combined with 5-flucytosine if it is sensitive to both. After two to three weeks the patient should be operated to remove the fungal mass with the valve. The antifungal agents should be continued postoperatively for a minimum period of 6 weeks. The dose of amphotericin B is 1.0 mg/kg/day (maximum 1.5 mg/kg/day) intravenously and flucytosine 50 to 150 mg/kg/day given in 4 divided doses orally. Relapse following apparently successful treatment can occur even up to two years.

Culture negative endocarditis. Patients with culture negative endocarditis need to be treated empirically. The choice of treatment is dictated by circumstances anticipating the most likely organism. If the patient seeks help late and has significant renal insufficiency the treatment has to be modified.

Prophylaxis

There have been major changes in the recommendations for prevention of endocarditis patients with congenital heart defects such as ventricular septal defect, bicommissural aortic valve and valvar pulmonary stenosis, do not routinely require prophylaxis. According to the new guidelines of the American Heart Association, since the absolute lifetime risk of endocarditis is small, prophylaxis is only recommended for patients with conditions associated with increased risk of adverse outcome from endocarditis (Table 15.19).

The focus of prophylaxis has shifted from prophylactic antibiotics for a dental procedure to the prevention of dental caries, which reduces the incidence of bacteremia from daily activities and is therefore, more important. These guidelines need validation in developing countries where oral hygiene is unsatisfactory and regular dental health screening is not pursued avidly.

Table 15.19: Conditions where antibiotic prophylaxis is definitely recommended

Prosthetic cardiac valve or use of prosthetic material for valve repair
Past history of infective endocarditis
Unrepaired cyanotic heart disease, including palliative shunts and conduits
During first 6 months following complete repair of congenital heart disease by surgery or catheter intervention using prosthetic material or device
Repaired congenital heart disease with residual defects at or adjacent to the site of repair
Cardiac transplantation recipients with cardiac valvulopathy

The antibiotic recommendations for those who need prophylaxis are as follows:

Dental treatment

a. Penicillin V 2 g given orally on an empty stomach 1 hr before dental treatment, followed by 0.5 g every 6 hr for 3 days, *or*
b. Crystalline penicillin G 1,000,000 U mixed with 600,000 U of procaine penicillin 30–60 min before dental treatment, followed by oral penicillin as above, *or*
c. Single dose of amoxicillin 50 mg/kg orally 1 hr before the procedure.
d. Patients with prosthetic heart valves: Injectable penicillin with streptomycin or gentamicin IM 1 hr before the procedure

Genitourinary and gastrointestinal procedures

- Amoxicillin 25 mg/kg by mouth 1 hr before, with gentamicin 2 mg/kg IM 30 min before procedure; both are repeated at least for 2 more doses after the procedure
- Gastrointestinal surgery: Add metronidazole

Infective endocarditis is a life threatening disease with significant mortality and morbidity. The treating physician should advise patients and parents regarding prevention of endocarditis. The maintenance of good oral hygiene is

Table 15.18: Choice of antibiotics and duration of treatment for infective endocarditis

Organism	*Option I*	*Option II*	*Duration, weeks*
Streptococcus viridians	Penicillin, aminoglycoside	Ceftriaxone, aminoglycoside	4
Group A streptococci	Penicillin, aminoglycoside	Ceftriaxone, aminoglycoside	4
Streptococcus fecalis	Ampicillin, aminoglycoside	Vancomycin, aminoglycoside	4–6
Staphylococcus aureus	Cloxacillin/cefazolin, aminoglycoside	Vancomycin, aminoglycoside	6
Escherichia coli	Ceftriaxone, aminoglycoside	Ampicillin, aminoglycoside	6
Pseudomonas spp.	Ticarcillin, aminoglycoside	Meropenem, aminoglycoside	6
Culture negative	Ampicillin, aminoglycoside	Ampicillin, aminoglycoside	6

The choice of antibiotics should ideally be guided by culture results and organism sensitivity

encouraged. Careful attention to prophylaxis on the longterm is useful in preventing relapses.

Suggested Reading

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. Guidelines from American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia. Circulation 2007;116(15): 1736–54

MYOCARDIAL DISEASES

Myocarditis

Myocarditis usually viral infections, including ECHO, Coxsackie B, rubella, herpes and influenza viruses. Diphtheritic myocarditis is occasionally noted in South Asia. The presentation may be abrupt, with cardiovascular collapse, or insidious development of heart failure. Arrhythmias and conduction disturbances may be present. Examination shows cardiac enlargement, tachycardia, muffled heart sounds and features of congestive cardiac failure. The electrocardiogram shows low voltages, and nonspecific ST-T changes. Chest X-ray reveals cardiac enlargement with pulmonary venous congestion.

Treatment includes management of congestive failure. Digoxin should be used cautiously, preferably in half to three quarters of the standard dose. Steroids are of uncertain value and perhaps should be avoided in the acute phase of viremia. ACE inhibitors are a useful adjunct to therapy. The utility of IV immunoglobulin infusion is not proven.

Cardiomyopathies

The term cardiomyopathy is an intrinsic disease of the myocardium which is not associated with a structural deformity of the heart. It is considered *primary cardiomyopathy* when the etiology is unknown, and secondary, if the myocardial disease is attributed to a systemic disease. Myocardial diseases are classified clinically as (i) dilated, (ii) restrictive, and (iii) hypertrophic type of cardiomyopathy.

A significant proportion of patients have correctible causes of left ventricular dysfunction that mimics dilated cardiomyopathy (Table 15.20). A diagnosis of idiopathic dilated cardiomyopathy can only be made after these causes are excluded.

Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy is the commonest form of myocardial disease. The onset of cardiac failure may be acute or insidious. Cardiomegaly and S3 gallop are present. Murmur of MR and uncommonly, that of tricuspid regurgitation, may be present. The patients are prone to embolic phenomena. The electrocardiogram may show non-specific ST and T changes with or without left ventricular hypertrophy, conduction disturbances, arrhythmias or pseudo-infarction pattern. Chest X-ray shows cardio-

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Table 15.20: Correctable causes of left ventricular dysfunction in children

Condition	*Clues to diagnosis*
Congenital cardiovascular disease	
Anomalous left coronary artery from pulmonary artery	ECG changes of myocardial infarction in I, avL, V4-6; 2D, Doppler echocardiography
Severe coarctation of aorta	Weak femoral pulses; echocardiography
Critical aortic stenosis	Auscultation; echocardiography
Acquired cardiovascular diseases	
Takayasu arteritis	Asymmetric pulses, bruit, Doppler, scintigraphy, angiography
Tachyarrhythmia	Disproportionate tachycardia
Ectopic atrial tachycardia	ECG
Permanent junctional re-entrant tachycardia	Esophageal electrophysiology
Chronic atrial flutter	
Severe hypertension	Blood pressure; fundus examination
Metabolic and nutritional causes	
Hypocalcemia	Setting (newborns; severe hypoparathyroidism); Chvostek, Trousseau signs; prolonged QTc on ECG
Infantile beri-beri	Prominent edema, diarrhea and vomiting; documented thiamine deficiency in mother (if breastfed)
Carnitine deficiency	Hypoglycemia, congestive heart failure; coma; ventricular hypertrophy; high ammonia, low carnitine
Hypophosphatemia	Poorly controlled diabetes; following hyperalimentation, nutritional recovery syndrome; recovery from severe burns; hyperparathyroidism; vitamin D deficiency; hypomagnesemia, Fanconi syndrome; malabsorption
Selenium deficiency	Keshan disease (endemic in parts of China); chronic parenteral nutrition, AIDS

megaly with pulmonary venous hypertension. Echocardiogram confirms dilated ventricular cavity without hypertrophy of the free wall of the left ventricle or the septum. The left ventricular contractility is reduced.

Treatment consists in decongestive therapy with vasodilators, especially ACE inhibitors. Beta-blockers control the heart rate, reduce vasoconstriction caused by catecholamines and upgrade beta-receptors. These agents are expected to prevent or retard myocardial damage related to high catecholamine levels. Carvedilol, a beta-blocker with peripheral vasodilator effect, has shown utility in the management of CCF. Though experience in children is limited, it should be considered in presence of disproportionate tachycardia. The starting dose is 0.1 mg/kg/day once daily, which is gradually increased up to 0.5 mg/kg/day.

Gradual improvement occurs in a significant proportion of patients. The prognosis for individual patients cannot be predicted and treatment should continue for prolonged periods.

Despite aggressive therapy, about a third of children with cardiomyopathy continue to deteriorate with time and eventually become refractory. Intermittent (weekly or biweekly) dopamine or dobutamine infusions may be used effectively in some patients. It is important to consider a number of correctable conditions that can masquerade as cardiomyopathy (Table 15.23) and correct them.

Clues to presence of these conditions may be obtained from clinical examination, laboratory profile or ECG (Fig. 15.44).

Anomalous Left Coronary Artery from Pulmonary Artery (ALCAPA)

ALCAPA needs specific mention as a cause of congestive cardiomyopathy. The diagnosis is likely in a patient with congestive cardiomyopathy with or without a murmur suggesting MR and a pattern on electorcardiogram that suggests anterolateral myocardial infarction (Fig. 15.45). Echocardiography shows a large right coronary artery and absence of the origin of left coronary artery from the aorta. The left coronary artery is seen to arise from the pulmonary artery and shows flow in the reverse direction in the left anterior descending artery and the left circumflex artery. This flow reversal results from collateral flow into the left coronary system from the right coronary artery. Angiography is rarely necessary for the diagnosis. The treatment is surgical and requires mobilization and translocating the origin from pulmonary artery to aorta.

Restrictive Cardiomyopathy (RCM)

It is relatively uncommon in children. Restriction to ventricular filling is usually associated with either endomyocardial fibrosis or endocardial fibroelastosis with a normal or smaller than normal left ventricle. Endomyocardial fibrosis was previously endemic in the state of Kerala and is now quite rare anywhere in the country. Pathologically, there is dense fibrosis in the apical and inflow regions of the left and right ventricles. Fibrosis restricts the ventricular filling in diastole. Papillary muscles and chordae may be tethered by the connective tissue, resulting in severe mitral or tricuspid regurgitation.

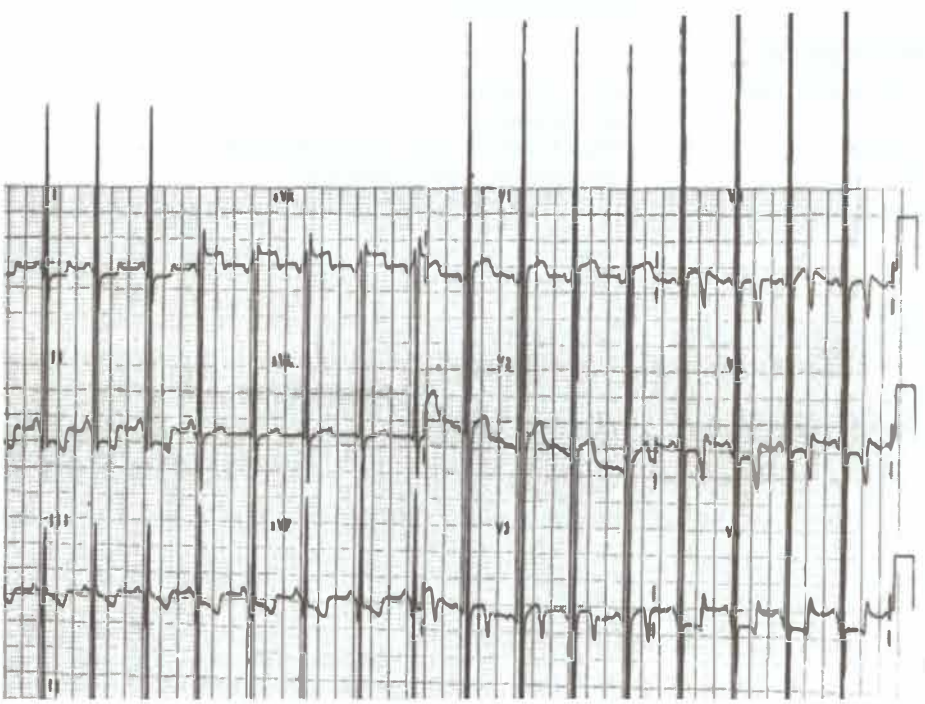


Fig. 15.44: Pompe disease; Note the characteristically tall QRS voltages and very short PR interval

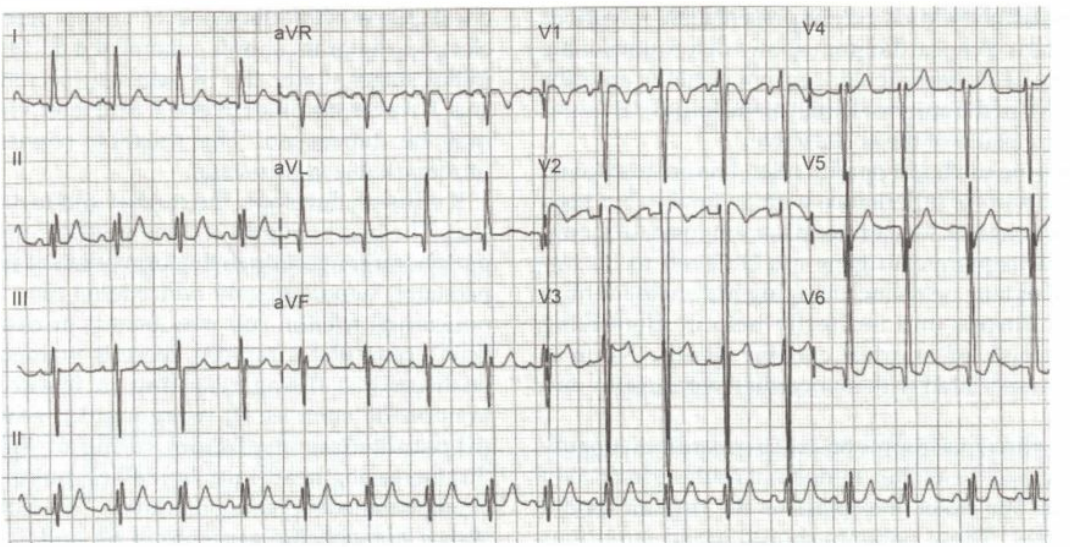


Fig. 15.45: ECG obtained from an infant with heart failure and ventricular dysfunction. He was labeled as having dilated cardiomyopathy. The leads I, aVL and V6 show 'q' waves suggesting of myocardial infarction suggesting. There is subtle ST segment elevation in lead aVL. The echocardiographic diagnosis of anomalous left coronary artery from pulmonary artery was confirmed at surgery. The ventricular function recovered over the next 3 months

Patients with predominant left sided involvement have symptoms of dyspnea, orthopnea, hemoptysis and embolic phenomena. On examination, there is cardiomegaly with or without findings of MR. Cardiac output is low and there are features of pulmonary venous and arterial hypertension. With predominant right-sided involvement, patients present with fatigue, pedal edema and ascites. There is cardiomegaly with prominent cardiac pulsations in the second, third and fourth left interspace from a dilated right ventricular outflow. S3 gallop and tricuspid regurgitation murmur may be present. The electrocardiogram and chest X-ray do not show-specific changes. Treatment consists of decongestive therapy. Decortication or stripping of the endocardium with mitral valve replacement has been tried with variable success.

Restrictive cardiomyopathy of other uncommon varieties is characterized by a combination of features of left and right-sided failure with a normal sized heart. Clinically, or even following cardiac catheterization, it may be difficult to distinguish it from constrictive pericarditis. However, children with restrictive cardiomyopathy tend to have dominant left sided involvement and disproportionate pulmonary hypertension. Echocardiogram can be useful in excluding constrictive pericarditis. Treatment consists in bed rest and anticongestive therapy.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy may occur (a) without outflow obstruction, or (b) with outflow obstruction. Obstructive cardiomyopathy is also known as idiopathic hypertrophic subaortic stenosis (IHSS) or asymmetrical septal hypertrophy (ASH) or hypertrophic obstructive cardiomyopathy (HOCM).

Hypertrophic cardiomyopathy with obstruction (HOCM) is uncommon in children. Pathologically there is asymmetrical hypertrophy of the ventricular septum. The free walls of the left and right ventricles are hypertrophied to a lesser extent. The ventricular septum bulges into the left ventricle, and the malaligned anterior mitral valve leaflet causes obstruction in the left ventricular outflow during systole. Uncommonly, there is right ventricular outflow obstruction as well. The abnormally oriented mitral valve may regurgitate.

Patients usually present with exertional dyspnea, anginal chest pain, palpitation and syncope; sudden death can occur. The pulse has a sharp upstroke with a bisferiens character. The apex beat is forcible or heaving. The fourth sound may be palpable at the apex. Double or triple apical impulse may be present. The second sound may be normally split, single or paradoxically split, depending on the severity of the left ventricular outflow obstruction. An ejection systolic murmur of varying intensity is heard at left sternal edge. A pansystolic murmur or MR and a fourth sound may be heard at the apex.

The ejection systolic murmur increases in intensity with maneuvers which increase the myocardial contractility or decrease the volume of the left ventricle. The murmur decreases in intensity with procedures that increase left ventricular volume or decrease the myocardial contractility. Thus, sudden squatting tends to decrease the intensity of the murmur whereas standing upright from sitting position by decreasing the venous return tends to decrease the left ventricular size and increases the intensity of the ejection systolic murmur. The electrocardiogram shows left ventricular hypertrophy, with or without ischemic changes. Prominent initial R in right precordial leads and deep Q

waves in the left chest leads may be present with or without a WPW pattern. Echocardiogram shows disproportionate hypertrophy of the ventricular septum, systolic anterior motion (SAM) of the anterior leaflet of the mitral valve and mid-systolic closure of the aortic valve.

Hypertrophic cardiomyopathy often has an autosomal dominant pattern of inheritance with a variable but high degree of penetrance. Mutations in beta-myosin, troponin T and alpha-tropomyosin gene are believed to be responsible. Magnetic resonance imaging may help identify myocardial fibrosis and indirectly help in identifying patients at risk of sudden cardiac death. Noonan syndrome is associated with myocardial hypertrophy and ASH.

Patients with hypertrophic obstructive cardiomyopathy should have a 24 hr Holter to document the presence of arrhythmias. The effect of exercise on the rhythm should be ascertained. These patients should avoid strenuous games and exercise. Digitalis and other inotropic drugs as well as diuretics and nitrates are contraindicated in these patients.

The prognosis is variable; young age of onset predicts poor prognosis. The disease may be progressive and sudden death may occur in spite of medical and/or surgical treatment. Beta-blockers decrease the myocardial contractility and thus decrease the obstruction.

PERICARDIAL DISEASES

Inflammatory diseases of the pericardium may present as acute dry pericarditis, pericarditis with effusion or chronic constrictive pericarditis (Table 15.21).

Acute Pericarditis

Acute pericardial inflammation causes precordial pain, which may be dull, sharp or stabbing in character. Occasionally, the pain may be felt over the neck and shoulder and may worsen on lying down. The child becomes dyspneic and has cough. The pattern of fever and toxemia depends on the etiology. The bedside diagnostic physical sign is the presence of pericardial friction rub, which is a rough scratchy sound, with three components, a systolic, diastolic and a presystolic scratch. It can be heard anywhere over the precordium, is unrelated to the respiratory cycle and increases on pressing the chest piece of stethoscope over the precordium. The electrocardiogram shows generalized ST elevation in the initial stages. Later the ST segment becomes isoelectric and T waves become inverted. Still later, the ST segment may be depressed. The thoracic roentgenogram is unremarkable at this stage.

If effusion develops, the cardiac silhouette increases in size. The heart sounds become muffled and evidence of peripheral congestion in the form of raised jugular venous pressure, hepatomegaly and edema may develop. The pericardial friction rub may persist or disappear. If the fluid accumulates rapidly, there is marked interference with cardiac filling resulting in features of cardiac tamponade such as: (i) rising jugular venous pressure; (ii) paradoxical inspiratory filling of the neck veins; (iii) increasing heart rate; (iv) falling pulse pressure; and (v) appearance of pulsus paradoxus. The electrocardiogram shows non-specific generalized ST and T changes with low voltage tracings. The chest X-ray shows cardiomegaly with smooth outline and blunting of the cardiohepatic angle. The lung fields are clear. Echocardiogram shows an echo-free space behind the posterior left ventricular wall.

Evidence of right atrial or right ventricular diastolic collapse indicates a hemodynamically significant effusion. Pericardiocentesis should be done to determine the etiology as well as to relieve cardiac tamponade if present. Treatment will depend on the etiology. Surgical drainage is indicated when pyopericardium is suspected.

Table 15.21: Etiology of pericardial diseases

Acute	*Chronic*
Bacterial	Constrictive pericarditis
Viral	Tuberculous
Tuberculous	Idiopathic
Rheumatic fever	Post-pyogenic
Collagen disorders	Post-traumatic
Uremic	
Postoperative	
Idiopathic	

Chronic Constrictive Pericarditis

Constrictive pericarditis is not uncommon in our country, tuberculous infection and, less commonly, often following a pyogenic pericarditis. Fibrous thickening of both layers of the pericardium encases the heart and restricts filling of both the ventricles equally; calcification is rare in childhood. The myocardium is not involved initially, but the fibrous process later infiltrates the myocardium, making surgical correction difficult. Dyspnea, fatigue and progressive enlargement of the abdomen are common.

Jugular venous pressure is always elevated with equally prominent 'a' and '*v*' waves and a prominent 'y' descent. Inspiratory filling of neck veins (Kussmaul sign) is seen in about one-half. Liver is enlarged and pulsatile; ascites with unilateral or bilateral pleural effusion is common. Splenomegaly may also be present. Pulse is fast and of low volume and pulsus paradoxus may be present. The precordium is quiet with a normal sized heart. First and second sounds are normal. An early third heart sound (pericardial knock) is commonly heard. The EKG shows low voltage in 75% patients and non-specific ST-T changes in all cases. *Normal electrocardiogram is against the diagnosis of constrictive pericarditis.* Occasionally, there is right axis deviation or right ventricular hypertrophy pattern.

The chest X-ray shows normal sized heart with ragged or shaggy borders and prominent superior vena cava

shadow merging with the right atrial margin. The lungs may show pleural effusion and plate atelectasis. Fluoroscopy shows reduced cardiac pulsations and may help reveal pericardial calcification. Hemodynamic studies reveal elevation of right atrial mean pressure, right ventricular end-diastolic pressure, pulmonary artery diastolic pressure and the pulmonary artery wedge pressures, which are identical. The right ventricular end-diastolic pressure is more than one-third of the systolic pressure. The cardiac index may be normal or reduced, but the stroke volume is low. In some cases, acute digitalization may improve the hemodynamics indicating presence of myocardial dysfunction.

Surgical decortication of the pericardium results in normalization of the hemodynamic abnormalities in most cases. Some cases of long-standing constrictive pericarditis with myocardial dysfunction may improve slowly or have residual myocardial dysfunction. Except post-pyogenic pericarditis, most patients in India receive 6-weeks' therapy with antitubercular agents before surgery, since majority of cases are post-tuberculous. A full course of antitubercular treatment follows pericardiectomy.

SYSTEMIC HYPERTENSION

Essential (primary) hypertension is the most common form of hypertension in adults and is recognized more often in adolescents than in younger children. Systemic hypertension is rare in infants and young children, but when present, it is usually due to an underlying disease (secondary hypertension). With age, the prevalence of essential hypertension increases and becomes the leading cause of elevated blood pressure in adolescents. Approximately 4% of children and adolescents have hypertension and 10% have pre-hypertension.

Etiopathogenesis

The etiology of essential hypertension is multifactorial. Obesity, insulin resistance, activation of sympathetic nervous system, disorders in sodium homeostasis and renin-angiotensin system, vascular smooth muscle structure and reactivity, uric acid levels, genetic factors and fetal programming have been implicated. Primary hypertension is often associated with a family history of hypertension.

Approximately 90% of secondary hypertension in children are due to renal or renovascular abnormalities. The major renal causes include chronic glomerulonephritis, reflux or obstructive nephropathy, polycystic or dysplastic renal diseases and renovascular hypertension. Coarctation of the aorta and Takayasu aortoarteritis are leading vascular causes. Hyperthyroidism, hyperparathyroidism, congenital adrenal hyperplasia, Cushing syndrome, primary aldosteronism, pheochromocytoma and neuroblastoma are endocrine causes of secondary hypertension in children.

Certain conditions can result in transient or intermittent hypertension. Renal causes include postinfectious glomerulonephritis, rapidly progressive (crescentic) glomerulonephritis, Henoch-Schönlein purpura, hemolytic uremic syndrome, acute tubular necrosis, and renal trauma. Raised intracranial pressure, Guillain-Barré syndrome, burns, Stevens-Johnson syndrome, porphyria, poliomyelitis, encephalitis, drugs (e.g. sympathomimetic agents, steroids, cyclosporine), heavy metal poisoning (e.g. lead, mercury) and vitamin D intoxication result in elevations of blood pressure.

Definition and Staging

The Fourth Report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents provided normative data on distribution of blood pressure in healthy children. Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is ≥ 95th percentile for age, sex and height on ≥3 occasions. Prehypertension is defined as SBP or DBP that are ≥90th percentile but <95th percentile. Adolescents having blood pressure between 120/80 mm Hg and the 95th percentile are also considered as having prehypertension. Children with blood pressure between the 95th percentile and 99th percentile plus 5 mm Hg are classified as stage I hypertension and children with blood pressure above the 99th percentile plus 5 mm Hg have stage II hypertension. Figures 15.46 and 15.47A and B indicate blood pressure cut off for stage I and stage II hypertension in girls and boys with stature at median for age.

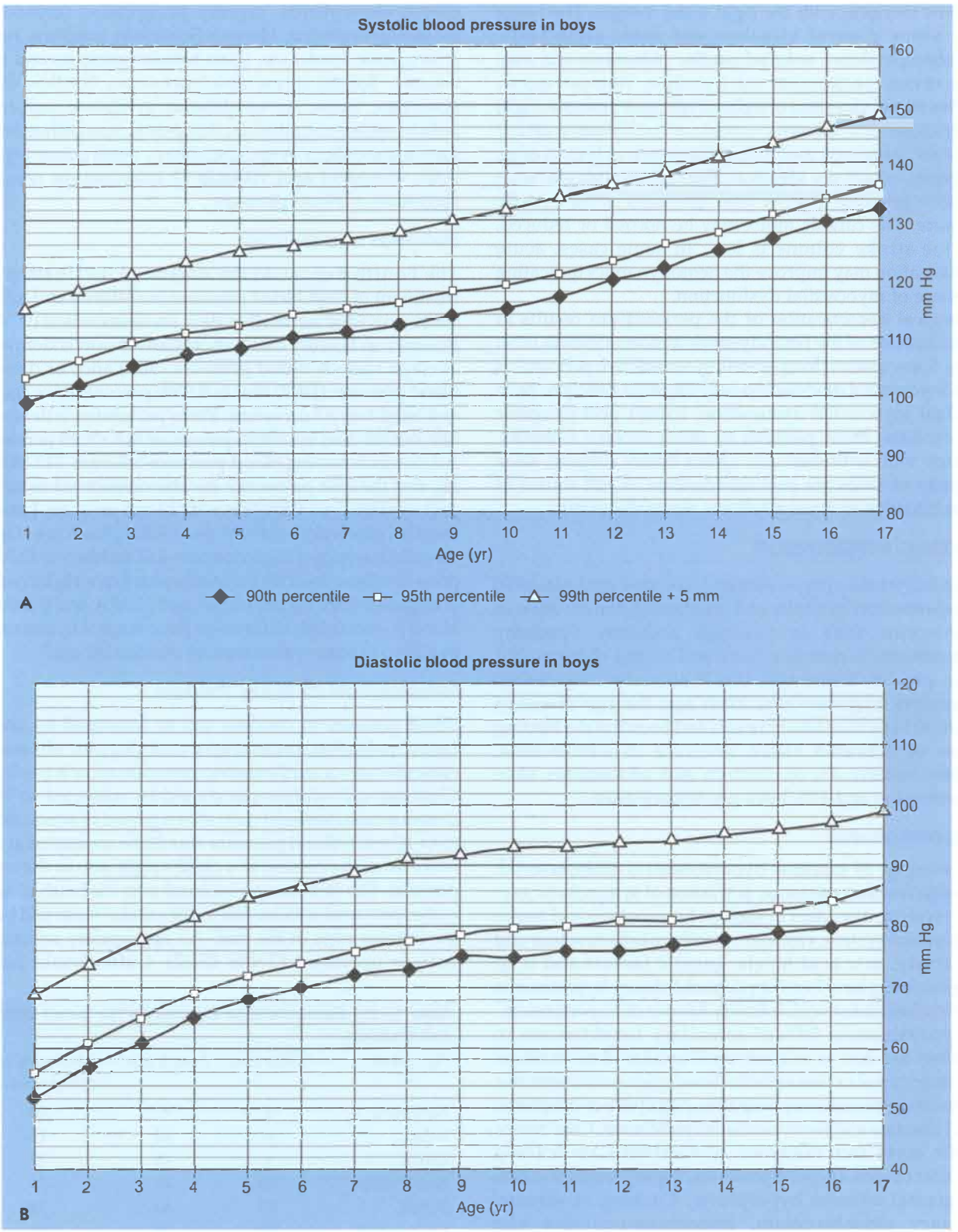
Measurement of Blood Pressure

Blood pressure in children can be measured by auscultation, palpation, oscillometry and Doppler ultrasound. Auscultation or oscillometric determination is preferred. Children and adolescents should be subjected to blood pressure measurement only after a period of adequate rest (5 to 10 min). Blood pressure should be measured at least twice on each occasion in a child's right arm in the seated position. The stethoscope is placed over the brachial artery pulse, proximal and medial to the cubital fossa and below the bottom edge of the cuff. An appropriate selection of cuffs is necessary (Table 15.22). Cuffs should have a

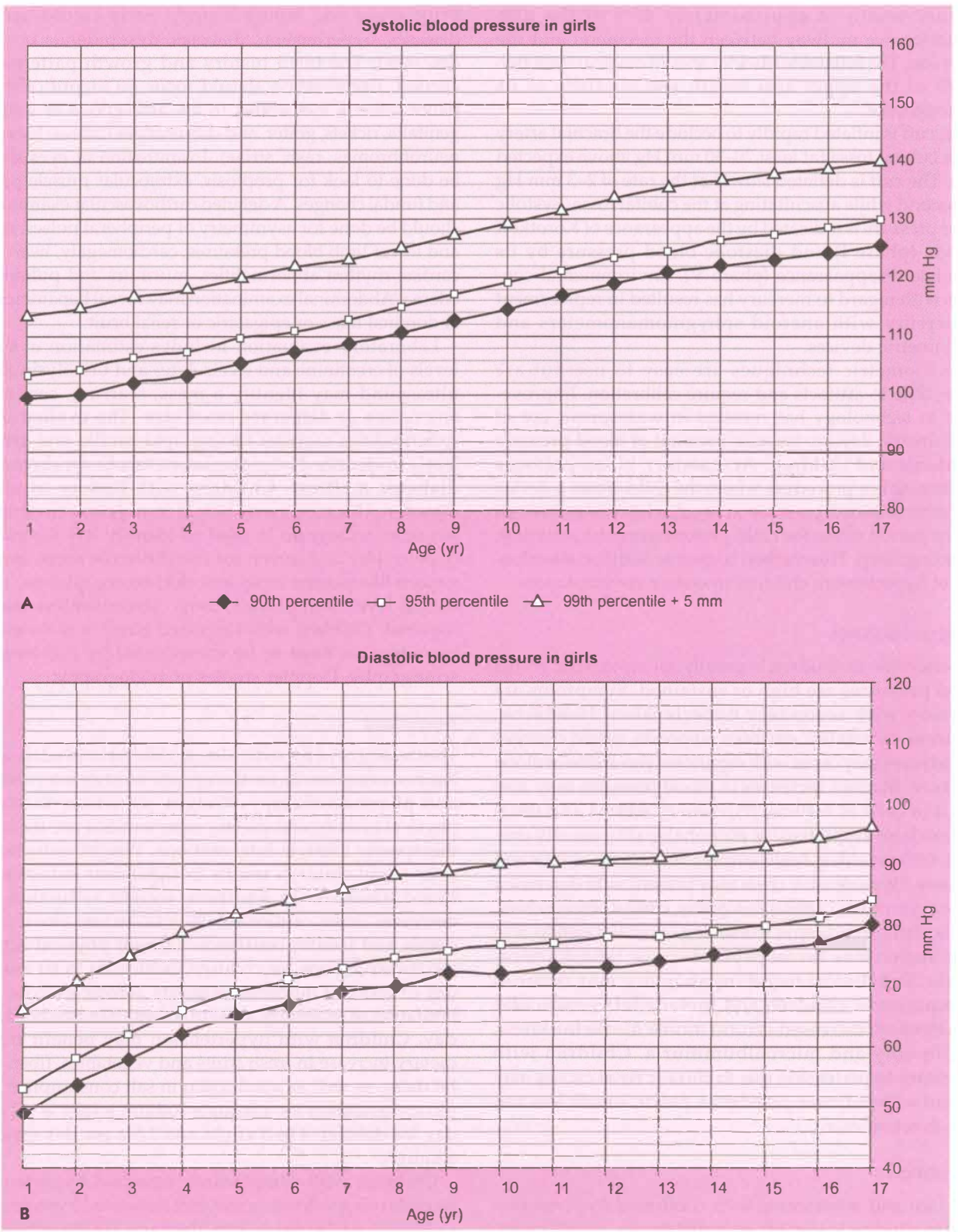
Table 15.22: Recommended dimensions for blood pressure cuff bladders

Age group	*Width (cm)*	*Length (cm)*	*Maximum arm circumference (cm)*
Newborn	4	8	10
Infant	6	12	15
Child	9	18	22
Small adult	10	24	26
Adult	13	30	34
Large adult	16	38	44
Thigh	20	42	52

Maximum arm circumference is calculated such that the largest arm would still allow bladder to encircle arm by at least 80% (Adapted from Fourth Task Force report)



Figs 15.46A and B: Blood pressure levels for boys at 50th precentile for height. Chart depicting 90th (closed diamonds), 95th (open squares) and 99th + 5 mm (open triangles) percentile values for (A) systolic and (B) diastolic blood pressures, representing cut off values for the diagnosis of pre-hypertension, stage I and stage II hypertension, respectively, in boys (based on the Fourth US Task Force Report on Hypertension). *With permission from Indian Pediatrics 2007;44:103–21*



Figs 15.47A and B: Blood pressure levels for girls at 50th precentile for height. Chart depicting 90th (closed diamonds), 95th (open squares) and 99th + 5 mm (open triangles) percentile values for (A) systolic and (B) diastolic blood pressures, representing cut off values for the diagnosis of pre-hypertension, stage I and stage II hypertension, respectively in girls (based on the Fourth US Task Force Report on Hypertension).
With permission from Indian Pediatrics 2007;44:103–21

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bladder width of approximately 40% of the arm circumference midway between the olecranon and the acromion. The inflatable bladder should cover at least two thirds of the upper arm length and 80–100% of its circumference.

The cuff is inflated rapidly to occlude the brachial artery in the cubital fossa (at least 20–30 mm Hg above expected SBP). The cuff is deflated slowly at the rate of 2–3 mm Hg per second while auscultating at the cubital fossa. Systolic blood pressure is indicated by the appearance of Korotkoff sounds (phase I) and diastolic blood pressure by its complete disappearance (phase V). Environmental concerns with regard to mercury has resulted in replacement of mercury with aneroid sphygmomanometers and oscillometric devices.

Oscillometric techniques are easy to use but are susceptible to artifacts and require calibration. Improvement in technology has resulted in widespread use of oscillometric devices for measurement of blood pressure in infants and children. Ambulatory blood pressure monitoring is a procedure where the child wears a device that records blood pressure at regular intervals, through a 24 hr period while the child performs regular activities, including sleep. This method is used as additional evaluation of hypertensive children in certain circumstances.

Clinical Features

Hypertension in children is usually asymptomatic unless blood pressures are high or sustained. Symptoms are common with secondary hypertension. Headache, dizziness, irritability, epistaxis, anorexia, visual changes and seizures may occur with significant elevations of blood pressure. Marked increases in blood pressure may also result in cardiac failure, pulmonary edema and renal dysfunction. Hypertensive encephalopathy usually presents with vomiting, high temperature, ataxia, stupor and seizures. Hypertensive crisis may present with decreased vision, symptoms of encephalopathy, cranial nerve palsies, cardiac failure and rapid worsening of renal function. Eye examination may reveal papilledema or retinal hemorrhages. Subclinical target organ injury may occur in asymptomatic children and include left ventricular hypertrophy, increased carotid intima media thickness, retinopathy and microalbuminuria. Children with secondary hypertension due to chronic renal causes may present with polyuria, polydipsia, pallor, weight loss and growth retardation.

Evaluation

Children and adolescents with confirmed hypertension need evaluation to identify potential causes, identification of co-morbidities and extend of target organ damage. All cases of hypertension require a detailed history and physical examination. The history should include sleep history, treatment history, smoking and alcohol intake, drug abuse and family history (early cardiovascular diseases, hypertension, diabetes, dyslipidemia or renal diseases). The birth history and growth patterns are elicited. Examination should focus on identification of pallor, edema, syndromic facies, ambiguous or virilized genitalia, rickets, goiter, and skin changes (café au lait spots, neurofibromas, rash, striae). Examination of eyes should be done to look for proptosis, extraocular muscle palsies and fundal changes. A detailed cardiovascular examination should be done for asymmetry of peripheral pulses, upper and lower limb blood pressures, cardiomegaly, heart rate, cardiac rhythm abnormalities, murmurs and pulmonary edema. Abdominal examination may reveal hepatomegaly, abdominal mass or epigastric or renal bruit.

Laboratory evaluation includes estimation of blood levels of creatinine and electrolytes and urinalysis. Renal ultrasound may identify a mass, scarring, congenital anomalies or disparate renal size. The evaluation of comorbidities requires fasting lipid profile and glucose levels to identify dyslipidemias, metabolic syndrome and diabetes mellitus. Children with history of sleep-disordered breathing may benefit from polysomnography. An echocardiogram is used to identify left ventricular hypertrophy and screen for coarctation of aorta. Investigations like plasma renin and aldosterone, plasma/urine steroid levels and plasma/urine catecholamines may be required. Children with suspected renal or renovascular hypertension need to be investigated by radionuclide scintigraphy, Doppler studies or angiography.

Treatment

The treatment of hypertension in children and adolescents has two components, i.e. therapeutic lifestyle interventions and pharmacotherapy. Weight reduction, increased physical activity and dietary interventions are the major therapeutic lifestyle interventions. Weight reduction in overweight children results in significant reductions of blood pressure. In addition, weight reduction also decreases other cardiovascular risk factors like dyslipidemia and insulin resistance. Current physical activity recommendations for children include 30 to 60 min per day or more of moderate intensity aerobic exercise plus limitation of sedentary activity to less than two hours per day. Children with hypertension may benefit from a dietary increase in fresh fruits and vegetables, fiber, non-fat dairy, as well as a reduction in salt consumption. The recommendation for adequate sodium intake is 1.2 g per day for children 4 to 8 yr old and 1.5 g per day for older children.

Children with symptomatic essential hypertension, secondary hypertension, diabetes associated hypertension, evidence of target-organ damage (left ventricular hypertrophy), or failed non-pharmacologic interventions require pharmacologic therapy. Agents approved for management of hypertension include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor

blockers (ARB), beta blockers, calcium channel blockers and diuretics (Table 15.23). ACE inhibitors and calcium-channel blockers are commonly used in children. ACE inhibitors or ARB are preferred in patients with diabetes or chronic kidney disease.

The goal of therapy for pediatric hypertension should be to reduce blood pressure below 95th percentile, except in the presence of chronic kidney disease, diabetes or target organ damage, when the goal is to reduce blood pressure to less than 90th percentile. Pharmacotherapy is done in a stepped-care approach and usually starts with a low dose of a single agent (step 1). If blood pressure control is not achieved, the dose is titrated every two weeks until blood pressure goals are achieved or the maximum dosage for the drug is reached (step 2). If adequate blood pressure control is not achieved with a single agent, a second agent with a complementary mechanism of action should be added and dose titrated until adequate control or dosage limit is reached (step 3). If adequate blood pressure control is not achieved with a two-drug regime, a third agent from a different drug class should be added as mentioned earlier (step 4).

In the case of hypertensive emergencies, the safest way is to lower blood pressure using an antihypertensive medication that is administered by continuous intravenous infusion in an intensive care unit, where the patient can be monitored appropriately. In general, the pressure should be reduced by up to 25% over the first 8 hr (10% in the first hour), followed by a further gradual reduction in blood pressure over the next 36-48 hr. Too rapid a reduction in blood pressure may lead to cerebral ischemia. Drug choices include labetalol, nicardipine and sodium nitroprusside of which nicardipine is the preferred drug in children due to its efficacy and safety (Table 15.24). Many patients in hypertensive crisis are volume depleted because of a combination of decreased oral intake and pressure natriuresis. Volume repletion in such conditions will help restore tissue perfusion and prevent a precipitous fall in BP that may occur with intravenous anti-hypertensive therapy.

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Table 15.23: Dosage of common antihypertensive medications for outpatient management

Agents	*Dose; frequency*	*Comments*
ACE inhibitors, angiotensin receptor blockers		
Captopril	0.3–6 mg/kg/day; tid	Use cautiously if GFR <30 ml/min/1.73 m^2; avoid in renal artery stenosis
Enalapril	0.1–0.6 mg/kg/day; qd or bid	
Lisinopril	0.06–0.6 mg/kg/day; qd	Use smaller doses in neonates
Ramipril	6 mg/m^2; qd	Monitor serum potassium, creatinine regularly
Irbesartan	4–5 mg/kg/day	Hyperkalemia, impaired renal functions; anemia, neutropenia, dry cough infrequent
Losartan	0.7–1.4 mg/kg/day; qd	
Calcium channel blockers		
Amlodepine	0.05–0.5 mg/kg/day; qd-bid	Extended release nifedepine must be swallowed whole
Nifedipine (extended release)	0.25–3 mg/kg/day; qd-bid	Side effects: headache, flushing, dizziness, tachycardia; lower extremity edema , erythema
Isradipine	0.15–0.8 mg/kg/day; tid	
Beta-blockers		
Atenolol	0.5–2 mg/kg/day; qd or bid	Decrease dose by 50% at GFR <50 ml/min/1.73 m^2; give on alternate days at GFR <10 ml/min/1.73 m^2; sleep disturbances with propranolol, metoprolol; hyperlipidemia; avoid in asthma, heart failure; blunt symptoms of hypoglycemia
Metoprolol	1–6 mg/kg/day; bid	
Labetalol	10–40 mg/kg/day; bid or tid	
Alpha agonists		
Clonidine	5–25 µg/kg/day; tid or qid	Abrupt cessation may cause rebound hypertension; sedation
Prazosin	0.05–0.5 mg/kg/day; bid or tid	May cause 'first dose' hypotension, syncope
Vasodilators		
Hydralazine	1–8 mg/kg/day; qid	Hypertension refractory to other drugs;
Minoxidil	0.1–1 mg/kg/day; qd or bid	Side effects: headache, palpitation, fluid retention, congestive heart failure; pericardial effusions and hypertrichosis with minoxidil
Diuretics		
Frusemide	0.5–6 mg/kg/day; qd or bid	Monitor electrolytes, fluid status periodically
Spironolactone*	1–3 mg/kg/day; qd or bid	Thiazides: dyslipidemia, hyperglycemia, hyperuricemia, hypokalemia, hypomagnesemia
Metolazone	0.2–0.4 mg/kg/day; qd	
Hydrochlorothiazide	1–3 mg/kg/day; qd	Loop diuretics: metabolic alkalosis, hypokalemia, hypercalciuria
Amiloride*	0.4–0.6 mg/kg/day; qd	*Use cautiously with ACEI, angiotensin receptor blockers

qd once daily; bid twice daily; tid thrice daily; qid four times qd

Table 15.24: Antihypertensive agents for management of severe hypertension

Medication	*Onset*	*Duration of effect*	*Route*	*Dose*	*Side effects*
Sodium nitroprusside	30 sec	<10 min	IV infusion	0.5–8 µg/kg/min (made in 5% dextrose)	Nausea, vomiting, headache, tachycardia, cyanide toxicity (dizziness, confusion, seizures, jaw stiffness and lactic acidosis)
Labetalol	5–10 min	3–6 hr	IV infusion	0.25–3 mg/kg/hr	Orthostatic hypotension, bradycardia, pallor, abdominal pain, diarrhea
			IV bolus	0.2–1 mg/kg/dose q 5–10 min (max 40 mg)	
Nicardipine	1–10 min	3 hr	IV infusion	0.5–4 µg/kg/min (max 5 mg/hr)	Flushing, reflex tachycardia, phlebitis, nausea, increased intracranial pressure, headache
			IV bolus	30 µg/kg (max 2 mg/dose) q 15 min	
Nitroglycerine	2–5 min	5–10 min	IV infusion	1–3 µg/kg/min	Methemoglobinemia, headache, tachycardia
Phentolamine	10 min	30–60 min	IV bolus	0.1–0.2 mg/kg (max 5 mg) q 2–4 hr if required	Reflex tachycardia, abdominal pain
Nifedipine	10–30 min	1–4 hr	Oral	0.2–0.5 mg/kg (max 10 mg) q 4 to 6 hr	Excessive hypotension, peripheral edema
Clonidine	15–30 min	2–4 hr	Oral	0.05–0.1 mg/dose, may repeat q hr; max 0.8 mg total dose	Somnolence, dry mouth

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Prevention

The prevention of high blood pressure in children can be achieved by preventing childhood obesity. Regular physical activity, consumption of fruits and vegetables, moderation of salt intake, low consumption of processed food items and animal fats and reducing sedentary activities will aid in reducing the prevalence of high blood pressure in children and adolescents.

Suggested Reading

National High Blood Pressure Education Program Working Group on High Blood pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114(2 Suppl 4th Report): 555–76

Raj M, Sundaram KR, Paul M, Deepa AS, Kumar RK.,Obesity in children – time trends and relationship with hypertension, Natl Med J India, 2007;20:288–93

PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) is defined as resting mean pulmonary arterial pressure greater than 25 mm Hg, or mean pulmonary artery pressure following exercise that exceeds 30 mm Hg. PAH occurs in an idiopathic form or in association with other etiologies. The condition is a critical determinant of morbidity and mortality in diverse pediatric cardiac, lung, hematologic, and other diseases.

Etiology

PAH may be associated with a number of congenital heart diseases. Idiopathic PAH is rare in children. In a small proportion mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*) gene, the activin receptor-like kinase type 1 (*ACVRL1*), or endoglin are identified.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

At birth, pulmonary vascular resistance is high, it normally falls rapidly throughout the first week of life. By 6 to 8 weeks, pulmonary vascular resistance usually has reached a normal adult level of 1 to 3 Wood units. These changes are accompanied by a gradual dilation of the smaller and then the larger muscular pulmonary arteries and development of new arteries and arterioles. PPHN develops when pulmonary vascular resistance remains elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways. The common associations include congenital diaphragmatic hernia, meconium aspiration syndrome and perinatal asphyxia. These newborn patients typically require mechanical ventilatory support and those with underlying lung disease may benefit from high-frequency oscillatory ventilation or extracorporeal membrane oxygenation (ECMO). Pulmonary vasodilators, such as inhaled nitric oxide, improve the outcome and reduce the need for ECMO. Sildenafil is increasingly used for PPHN as an alternative to inhaled nitric oxide.

Clinical Manifestations

The clinical features of PAH are related to the degree of pulmonary hypertension and right ventricular function

and status of the right ventricle. Most common symptom is exertional breathlessness due to the inability of the right ventricle to raise cardiac output with exercise. Other symptoms are hemoptysis, atypical chest pain, congestive heart failure, dizziness or syncope and arrhythmias. Cyanosis and its complications are seen in Eisenmenger patients but not otherwise unless there is a patent foramen ovale. A comprehensive evaluation is advised before a diagnosis of idiopathic PAH is made. It is essential to rule out cardiac (congenital heart disease), respiratory, upper airway obstruction (Down syndrome, adenoids), neurogenic causes (sleep apnea) and liver disease (porto-pulmonary hypertension).

Management

Supplemental low-flow oxygen alleviates arterial hypoxemia in patients with chronic pulmonary parenchymal disease. Patients with Eisenmenger syndrome or idiopathic PAH do not exhibit resting alveolar hypoxia and do not require oxygen unless significantly hypoxic. Children with severe right ventricular failure and resting hypoxemia may require continuous oxygen therapy.

Diuretics are useful in patients with symptomatic right heart failure. The right ventricle is highly preload dependent, and care should be taken to avoid excessive diuresis since this can lead to a fall in cardiac output and compromise other pharmacologic measures, such as vasodilators. Patients are at higher risk of thromboembolic events due to sluggish pulmonary circulation and dilated right-sided cardiac chambers. Anticoagulants may have a role in select cases when the risk for thromboembolism outweighs the likelihood of hemoptysis.

The goal of vasodilator therapy for PAH is to reduce pulmonary artery pressure and increase cardiac output without causing systemic arterial hypotension. Sildenafil is an oral phosphodiesterase type 5 inhibitor that prevents the breakdown of cGMP and potentiates pulmonary vasodilation with inhaled nitric oxide. Symptomatic patients with PAH, PPHN and postoperative PAH benefit with sildenafil. Other agents including bosentan, an oral endothelin-receptor antagonist (ERA) and prostacyclin analogs.

Combined heart lung transplantation, or lung transplantation alone has been performed successfully in patients with PAH. The major limitations to its widespread use include the limited number of centers with the expertise to perform the procedure and care for patients and the limited availability of suitable donors and significant cost.

Prognosis

Prognosis is dictated by the underlying etiology and the right ventricular function. An overall 80% 5 yr survival has been reported in patients with Eisenmenger syndrome compared with a 2–3 yr mean survival after the diagnosis of idiopathic PAH.

Suggested Reading

Abman SH, Ivy DD. Recent progress in understanding pediatric pulmonary hypertension. Curr Opin Pediatr 2011;23:298–304

Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55–66

RHYTHM DISORDERS

The recognition of cardiac arrhythmias in children is challenging and requires a high index of suspicion. It is important to arrive at a precise diagnosis since the treatment is dictated by the specific arrhythmia. In some situations, it may be possible to affect a complete cure.

Clinical Features

These are listed in Table 15.25.

Irregular heart rate. The commonest cause of an irregular heart rate is physiological sinus arrhythmia. This can be recognised by an increase in heart rate with inspiration and decrease with expiration. Sinus arrhythmia is usual following a febrile illness and by drugs that increase vagal tone (such as digoxin). It is readily abolished by exercise. Irregularities of rhythm are commonly seen in premature infants especially bradycardia associated with periodic apnoea. Common causes of heart rate irregularity in children include atrial and ventricular premature beats and conduction disturbances (Table 15.26).

Inappropriate heart rate. A heart rate that is inappropriately fast or slow for the clinical condition should arouse the suspicion of an underlying arrhythmia. Inappropriately

Table 15.25: Clinical features in arrhythmias

Irregular heartbeat
Heart rate that is inappropriate for the clinical condition
Unexplained heart failure
Syncope, palpitations, chest discomfort
Underlying cardiac anomaly known to be associated with rhythm disorders
Family history of sudden cardiac events

Table 15.26: Causes of irregular heart beat

Sinus arrhythmia
Other common and usually benign causes
Supraventricular (atrial and junctional premature beats)
Ventricular premature beats
Transient conduction disturbances (Wenckebach type), atrioventricular and sinoatrial blocks
Transient bradycardia in a premature infant
Uncommon but potentially serious causes
Mobitz type II heart block
Ectopic atrial tachycardia; multifocal atrial tachycardia
Polymorphic ventricular tachycardia and Torsades
Atrial fibrillation, with or without WPW syndrome
Atrial flutter with variable conduction

slow heart rate in a child with fatigue, giddiness or syncope should arouse the suspicion of complete heart block. Inappropriately fast rates suggest tachyarrhythmias such as SVT.

Unexplained heart failure. Incessant arrhythmias such as ectopic atrial tachycardia (EAT), permanent junctional re-entrant tachycardia (PJRT) and some forms of ventricular tachycardia can present as heart failure. At the time of initial evaluation the heart rates may not be inappropriate for the degree of heart failure. Diagnosis may be missed and requires a high index of suspicion. These conditions should be considered in the differential diagnosis of childhood dilated cardiomyopathy, especially if the heart rate is relatively fixed.

Underlying conditions. A number of congenital and acquired heart diseases and certain systemic conditions are known to be associated with cardiac arrhythmias (Table 15.27). Ventricular and supraventricular arrythmias can follow cardiac surgery for correction of CHD. Operations resulting in scar formation in the right ventricle such as repair of tetralogy of Fallot are known to be associated with ventricular tachycardia. The Fontan operation for single ventricle physiology or the Senning or Mustard procedure for transposition is known to result in a particularly high incidence of re-entrant atrial arrhythmias. Organophosphate exposure, tricyclic antidepressant overdose, digoxin toxicity, antiarrhytmic drug treatment and substance abuse can be associated with a variety of arrhythmias.

Syncope. The commonest cause of syncope in children is mediated *via* the autonomic nervous system, known as the neurocardiogenic syncope or vasovagal syncope. A fraction of syncopal episodes result from cardiac arrhythmias. Life threatening ventricular tachycardia (VT), as associated with long QT syndrome characteristically results in syncope. It is important to differentiate them from vasovagal episodes. Vasovagal syncope occurs in specific situations like prolonged standing in a hot environment, sight of blood, painful stimulus, emotional stress or following a recent illness. Syncope secondary to arrhythmia are sudden, unpredictable, paroxysmal and usually have no predisposing cause or premonition. Duration of syncope depends upon the duration of arrhythmia. Some forms of long QT syndromes and catecholemenergic tachycardia are precipitated by exercise. Ventricular tachycardia secondary to *Brugada syndrome* may be precipitated during febrile illness.

Palpitations and chest discomfort. Older children may complain of episodic palpitations. Not infrequently, they have a sensation of chest discomfort or pain during tachyarrhythmia.

Table 15.27: Arrhythmias suggestive of specific congenital heart disease

Sick sinus syndrome	
	Sinus venosus, atrioventricular canal defect, Holt Oram syndrome with atrial septal defect (ASD)
Narrow QRS tachycardias	
	Ebstein anomaly; corrected transposition with Ebstein anomaly
	Atrioventricular canal, ASD. pulmonic stenosis, total anomalous pulmonary venous connection, tricuspid atresia (older patients)
Atrial fibrillation and flutter	
	Congenital mitral stenosis, total anomalous pulmonary venous connection, coronary AV fistula
WPW and pre-excitation syndromes	
	Ebstein anomaly; corrected transposition with Ebstein anomaly
Wide QRS tachycardias	
	Anomalous left coronary artery from pulmonary artery, coronary AV fistula, arrhythmogenic rightventricle, atrioventricular conduction defects, corrected transposition of great arteries; Ebstein anomaly
Postoperative patients	
	Supraventricular, ventricular arrhythmias

Basic Electrophysiology Concepts

Arrhythmia that originates at or above the bundle of His has narrow QRS morphology; that below this level (Purkinje fibers, ventricular muscles) have wide QRS morphology. Majority of tachycardia in children are regular. Common irregular tachycardia are ectopic atrial tachycardia, multifocal atrial tachycardia, atrial flutter with varying conduction, atrial fibrillation (rare in children) and ventricular fibrillation. During a regular narrow QRS tachycardia, if a P wave is identified and has normal morphology, axis and 1:1 P and QRS relation, it suggests sinus tachycardia. Absence of any of the three suggests supraventricular tachyarrhythmia.

Re-entrant vs. automatic tachyarrhythmias. Tachyarrhythmia is generally considered to result from one of the three mechanisms: re-entry, increased automaticity and triggered activity. In children, the first two mechanisms account for most important arrhythmias. Clinical and EKG features together with response to certain medications and maneuvres help distinguish re-entrant tachyarrhythmias from those due to increased automaticity. Re-entrant arrhythmias characteristically have a relatively sudden onset and termination. Successful termination with DC cardioversion or overdrive pacing (pacing at rates faster than the arrhythmia rate) strongly suggests a re-entrant mechanism. Automatic arrhythmias characteristically have a relatively slow onset. Gradual acceleration (warm-up) to the peak rates may be demonstrable at onset and gradual deceleration (cool down) at termination is seen.

Diagnostic Workup of Suspected Arrhythmia

Attempts should be made to answer all the questions listed in Table 15.28. This will allow the specific treatment strategy to be initiated. A 12 lead EKG should be obtained

Table 15.28: Initial assessment of arrhythmia

Can the clinical condition result from a cardiac arrhythmia?
Is there hemodynamic instability?
Is the arrhythmia incessant or episodic?
Is this a re-entrant arrhythmia or does it involve an automatic focus?
Where is the arrhythmic focus or circuit located?
Is there an underlying structural heart disease?

and cardiac rhythm monitoring should be initiated as quickly as possible.

Management of Hemodynamic Instability

All tachyarrhythmias and bradyarrhythmias influence hemodynamics adversely, manifesting with no detectable manifestations to circulatory collapse. Extreme hemodynamic instability is relatively rare in childhood arrhythmias, particularly in absence of structural heart disease. Hemodynamic instability necessitates emergency treatment. Most unstable tachyarrhythmias are broad QRS. Unstable narrow QRS tachycardia are quite uncommon, especially in the absence of structural heart disease. Low energy (0.5–2 J/kg) synchronized DC cardioversion should be performed. If and when possible cardioversion should always be preceded by administration of a short-acting benzodiazepine such as midazolam (0.1–0.2 mg/kg/dose). Emergency treatment options for bradyarrhythmias are shown in Table 15.29.

Diagnosis and Management of Tachyarrhythmia

A combined strategy that simultaneously addresses both diagnosis and treatment is appropriate. This is determined by the QRS duration on the initial EKG and presence or absence of hemodynamic instability. Based on the QRS duration arrhythmias can be classified as narrow and wide. This is a useful practical classification and serves as an excellent guide to initial treatment. Age specific normal values for QRS duration are given in Table 15.30. As a preliminary step, sinus tachycardia should be excluded. Rates as high as 240/min can occasionally be recorded during sinus tachycardia. There is always an underlying cause for sinus tachycardia and this is usually apparent during the initial evaluation. Fever, circulatory failure, extreme dehydration, accidental ingestion of drugs and toxic substances are common examples. Figure 15.48 depicts a useful treatment algorithm.

Table 15.30: Normal QRS duration at various age groups

Age group	*QRS duration in seconds*
0–6 months	0.03–0.07 (0.05)
1–5 yr	0.04–0.08 (0.06)
10–15 yr	0.04–0.09 (0.07)
>15 yr	0.06–0.09 (0.08)

Values represent range (mean)

Narrow QRS tachycardia. Most narrow QRS tachycardias (Table 15.31) are reasonably well tolerated and allow a preliminary diagnostic workup (Table 15.32). If a patient is seen during an episode of tachyarrhythmia, all attempts should be made to obtain quality data before terminating the arrhythmia. Information that should be specifically sought include the P wave morphology and P-QRS relationship. P waves that appear normal during the tachyarrhythmia suggest sinus tachycardia. Ectopic atrial tachycardia is suggested by abnormal P wave morphology. Inverted P waves may be seen when atria are activated in a retrograde fashion as in the case of re-entrant tachyarrhythmias involving accessory pathways (AV re-entrant tachycardia) (Fig. 15.49). Often P waves are not

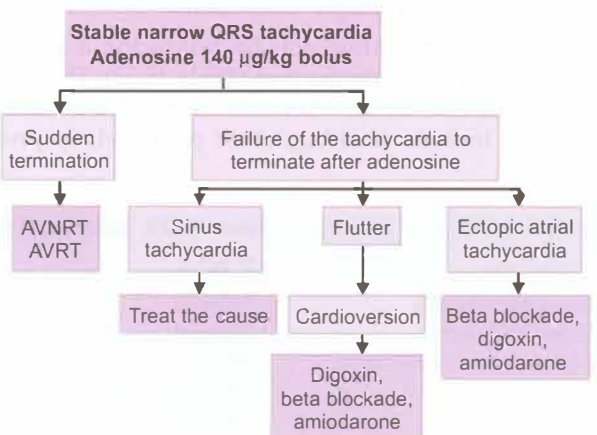

Fig. 15.48: Management algorithm for stable narrow QRS tachycardia. AVNRT atrioventricular nodal re-entrant tachycardia; AVRT atrioventricular re-entrant tachycardia

Table 15.29: Emergency treatment for bradyarrhythmias

Modality	*Indication*	*Dose*
Atropine	Severe sinus bradycardia, AV block with narrow QRS (supraventricular) escape	0.02 mg/kg IV bolus
Isoproterenol	Lack of response to atropine, AV block with wide QRS (ventricular) escape	0.1–2 µg/kg/min IV infusion
Transcutaneous pacing	Severe symptomatic bradycardia, asystole (not suitable for infants, young children)	Twice the capture threshold
Transvenous pacing	Alternative to transcutaneous pacing for infants and young children	Twice the capture threshold

Table 15.31: Causes of narrow QRS tachycardia

Site	*Re-entrant arrhythmias*	*Automatic arrhythmias*
Sinus node	Sinus node re-entry	Sinus tachycardia
Atrium	Intra atrial re-entrant arrhythmias following cardiac surgery (Fontan, Senning operations) Atrial flutter Atrial fibrillation	Ectopic atrial tachycardia Multifocal atrial tachycardia
AV node	AV node re-entry	Junctional ectopic tachycardia
Accessory pathway	Atrioventricular re-entry involving concealed or manifest (WPW) pathway Permanent junctional re-entrant tachycardia	

clearly seen on baseline EKG but are unmasked by adenosine. Evidence of 2:1 AV conduction as suggested by a 2:1 P-QRS ratio during a narrow QRS tachycardia indicates atrial flutter (Fig. 15.50). Evidence of complete AV dissociation (no consistent P-QRS relationship) indicates junctional ectopic tachycardia.

Adenosine administration acts by producing a marked slowing of AV node conduction (Table 15.32). The effect of adenosine lasts for a few seconds. Side effects are short-lived and include flushing, chest pain and dyspnea. Adenosine needs to be administered rapidly followed by rapid push of normal saline as a bolus. The recommended dose is 50–300 µg/kg. Most re-entrant tachycardias, where AV node is a part of the circuit (AV node re-entrant tachycardia, AV re-entrant tachycardia) will be terminated by adenosine. *Atrial flutter is seldom terminated by adenosine.* The transient AV block that results from adenosine administration can unmask flutter waves on the EKG thereby confirming the diagnosis (Fig. 15.51). Similarly transient slowing of AV conduction can unmask ectopic atrial tachycardia. If adenosine is not available, vagal maneuvres can be attempted. For infants and young children an ice filled plastic bag placed on the face is the most effective vagal maneuver. Older children can be encouraged to perform the Valsalva maneuver or carotid sinus massage can be attempted. *Eyeball pressure is contraindicated in infants.*

Wide QRS tachycardia. Wide QRS complex tachycardias usually result from foci or circuits in the ventricles. Some supraventricular tachycardias can also result in a wide QRS configuration. The overall approach is quite similar to narrow QRS tachycardias, with identification of P waves, defining P-QRS relationship and determining the QRS axis configuration (Fig. 15.52).

Demonstrable AV dissociation (inconsistent P-QRS relation) suggests ventricular tachycardia (VT). In most situations, however, it is not easy to distinguish VT from SVT. If the patient is stable, administration of adenosine will terminate or unmask SVT. If there is no response, treatment for VT should be initiated. In stable patients it is better to initiate pharmacologic treatment of VT before considering cardioversion since the response to initial

Table 15.32: Differential diagnosis of narrow QRS tachycardia

Arrhythmia	*P waves*	*P-QRS relationship*	*Response to adenosine*
Sinus tachycardia	Normal	1:1	Transient slowing; AV block
Sinus node-entry	Normal	Usually 1:1	No effect or transient AV block
Ectopic atrial tachycardia	Abnormal and different from baseline	Usually 1:1	No effect or transient AV block
Atrial flutter	Saw tooth appearance rates exceed 240/min	2:1 or 1:1	Transient AV block may unmask flutter waves; rarely arrhythmia terminates
Postoperative intra atrial re-entry*	Slow atrial flutter, P waves different from baseline	Variable, often 1:1	Transient AV block may unmask flutter waves; rarely arrhythmia terminates
Multifocal atrial tachycardia	Multiform	Usually 1:1	No effect or transient AV block
Junctional ectopic tachycardia	Normal (AV dissociation) or inverted (1:1 retrograde conduction)	Complete AV dissociation is diagnostic	No effect on rate; transient retrograde VA conduction block unmasks AV dissociation
AV nodal tachycardia	Usually not visible (masked by RS complexes)	1:1	Sudden termination is characteristic
AV re-entrant tachycardia	Inverted (retrograde VA conduction)	1:1	Sudden termination
Junctional re-entrant tachycardia	Inverted (long VA conduction time)	1:1	No effect or transient termination

*Postoperative intra atrial re-entry may follow surgery that results in atrial scarring, e.g. Fontan operation, Senning operation

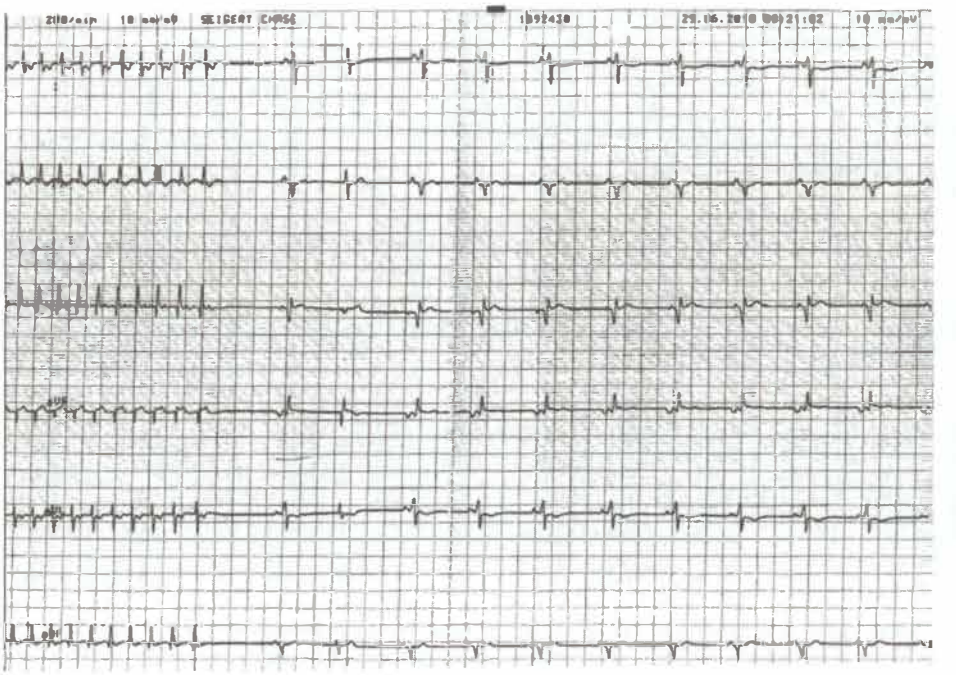

Fig. 15.49: Six lead ECG. Adenosine was administered to a child with regular narrow QRS supraventricular tachycardia. Note the tachycardia terminates with a P wave. Note delta waves with short PR interval that is prominently seen in lead I. Adenosine administration was therapeutic in this case

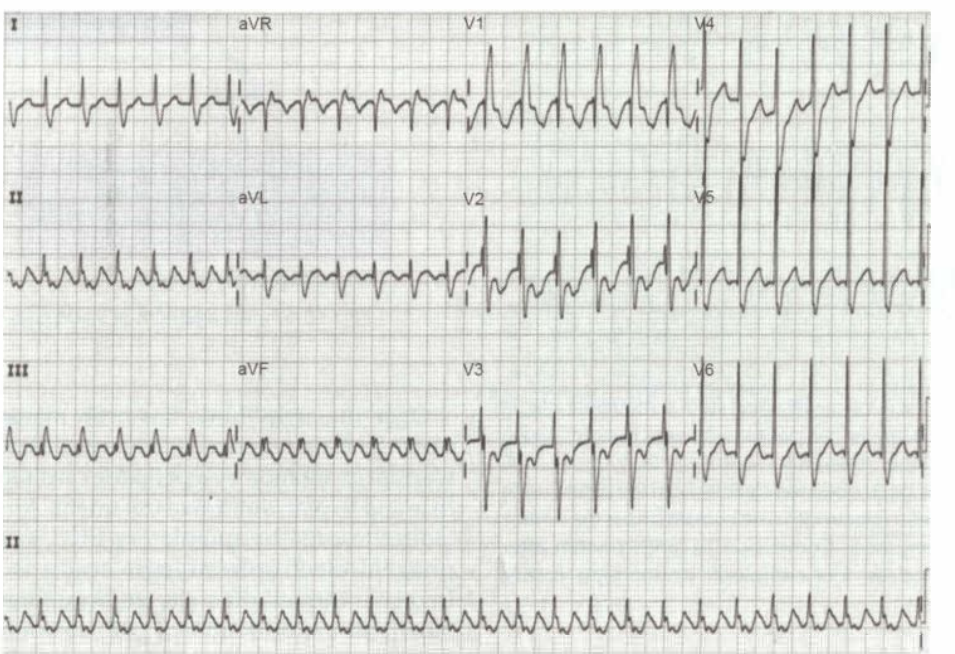

Fig. 15.50: Regular narrow QRS tachycardia at a heart rate of 150/min. Heart rate was fixed at 150/min for several hours that was suggestive of underlying arrhythmia. P waves were abnormally broad and tall

treatment can help decides longterm therapy. Lignocaine is the initial choice, while procainamide is an effective alternative; others include amiodarone, sotalol, mexeletine and flecanide.

Unstable wide QRS tachycardia. Wide QRS tachycardia with hemodynamic instability is a medical emergency. Synchronised cardioversion (0.5-2 J/kg) should be performed immediately. For pulseless patients, CPR

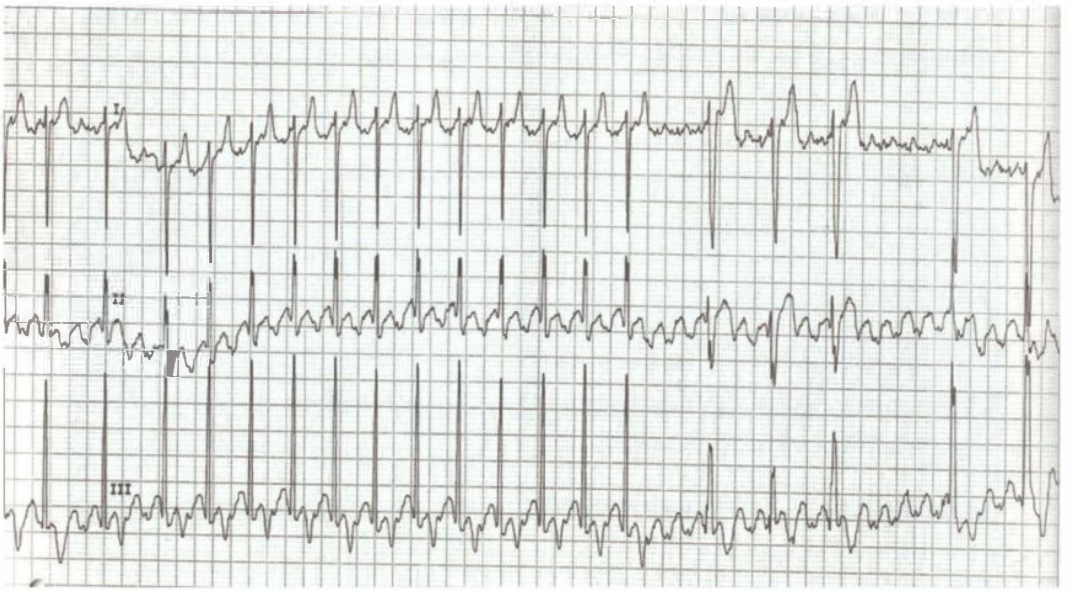

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Fig. 15.51: Response to adenosine administration to a child with atrial flutter. Note the unmasking of flutter waves that are prominently seen in lead II and III. P rate was 300/min. Before administration of adenosine, there was 2:1 AV conduction. The blocked P waves were hidden within the QRS complexes. After administration of adenosine, AV block increased and AV conduction block increased to 4:1 unmasking the flutter waves

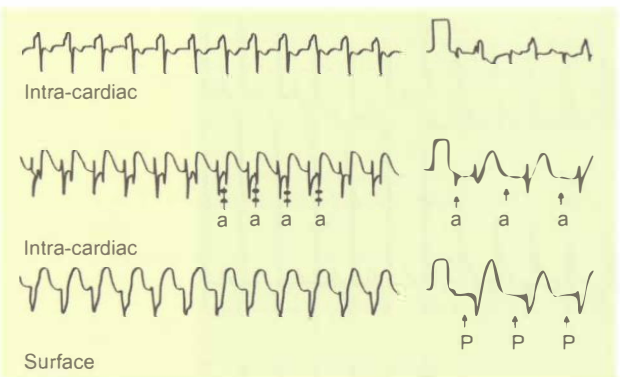

Fig. 15.52. Wide QRS tachycardia resulting from a re-entrant circuit involving an accessory pathway in a patient with right bundle branch block. Surface ECG, can be mistaken for ventricular tachycardia. ECG of the top two rows has been obtained directly from the atrium using postoperative atrial wires as electrodes. The bottom strip is the surface ECG from a monitoring lead. Conversion to sinus rhythm after adenosine is seen in the last four complexes on the right. a artial contraction, P p wave

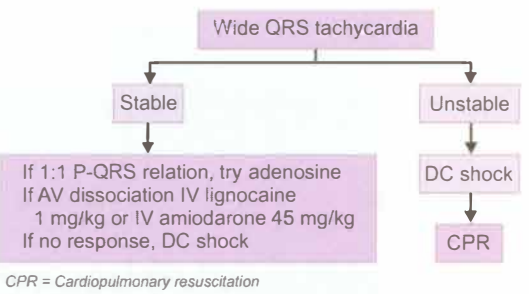

Fig. 15.53: Management of wide QRS tachycardia

should be initiated. Subsequent treatment should follow standard guidelines recommended for pulseless patients with VT (Fig. 15.53).

Irregular wide QRS tachycardia. Sustained and irregular wide QRS tachycardia is uncommon and usually suggests a diagnosis of Wolf Parkinson White (WPW) syndrome with atrial fibrillation. In presence of hemodynamic instability, synchronised cardioversion (1–2 J/kg) is indicated. If the patient is stable, procainamide infusion may be tried.

Once the arrhythmia has been managed, recurrences need to be prevented. Most childhood arrhythmias warrant evaluation by a pediatric cardiologist for followup care and to plan definitive treatment. An echocardiogram, Holter test (24 hr ambulatory EKG recording) and esophageal electrophysiologic study is often required. Invasive intracardiac electrophysiologic study is combined with radiofrequency (RF) ablation. Most accessory pathways are now treated by radiofrequency ablation, especially in older children (>4-yr-old). For younger children RF ablation is reserved for refractory situations.

PREVENTING ADULT CARDIOVASCULAR DISEASE

Major risk factors for cardiovascular disease in adulthood include cigarette smoking, hypertension, dyslipidemia, diabetes mellitus, obesity and physical inactivity. Some of these risk factors have genesis in childhood and are

Table 15.33: Pediatric diseases with high cardiovascular risk in adulthood

Category	*Diseases*	*Prevention oriented targets*
Tier I (high risk)	Homozygous familial hypercholesterolemia (FH); diabetes mellitus type 1; chronic kidney disease; post heart transplantation; Kawasaki disease with current coronary aneurysms	Maintain BMI <85th centile; blood pressure <90th centile; and LDL cholesterol (LDL-C) <100 mg/dl
Tier II (moderate risk)	Heterozygous FH; Kawasaki disease with regressed coronary aneurysms, diabetes mellitus type 2; chronic inflammatory disease	Maintain BMI <90th centile; blood pressure <95th centile; and LDL-C <130 mg/dl
Tier III (at risk)	Post cancer-treatment survivors; congenital heart disease; Kawasaki disease without detected coronary involvement	Maintain BMI ≤95th centile; blood pressure ≤95th centile plus 5 mm Hg; and LDL-C ≤160 mg/dl

All tiers require maintaining fasting blood sugar <100 mg/dl and glycosylated hemoglobin (Hb A1c) <7%.

amenable to modification, contributing to primary prevention of cardiovascular disease.

Childhood Obesity

Obesity influences major cardiovascular risk factors such as dyslipidemia, hypertension, glucose intolerance and inflammation. Emerging cardiovascular risk factors like carotid intima media thickness as well as carotid elasticity has also shown strong association with childhood obesity. Childhood obesity is managed by a combination of increased physical activity and dietary interventions.

Hypertension

Primary or essential hypertension is the most common form of hypertension in older children and adolescents. Childhood obesity is associated with hypertension in children, which often tracks into adulthood.

Dyslipidemia

Screening for dyslipidemia is recommended for children whose parents and/or grandparents required coronary artery bypass-surgery or balloon angioplasty before age 55, those with a family history of myocardial infarction, angina pectoris, peripheral or cerebral vascular disease, or sudden death before age 55 and those whose parents have dyslipidemia. Youth with dyslipidemia are treated with a diet low in total and saturated fats and cholesterol. The intake of complex carbohydrates is increased, whereas that of simple sugars is decreased. Drug therapy is used in patients with significantly elevated LDL-cholesterol.

Diabetes Mellitus

Diabetes mellitus is associated with cardiovascular complications, which develop early in childhood and adolescence. Endothelial dysfunction seen in both types of diabetes is recognized to aggravate cardiovascular risk in later life. Optimal daily and longterm glycemic control, maintenance of blood pressure and lipid levels in the normal values for age, regular exercise, healthy diet and avoidance of smoking are necessary.

Tobacco Consumption

Mechanisms by which smoking exerts its detrimental effects on cardiovascular system include endothelial dysfunction, increased oxidative stress, increased arterial stiffness, alterations in lipoprotein metabolism and induction of prothrombotic state. School based campaigns to prevent smoking and chewing tobacco are appropriate tools to contain this public health concern. Parents should be role models to children by avoiding or quitting smoking and chewing tobacco.

Early atherosclerotic disease has been documented in certain conditions in children. The risk category, group of diseases in each category and the prevention oriented treatment targets are shown Table 15.33.

Suggested Reading

Raj M. Obesity and cardiovascular risk in children and adolescents. Indian J Endocrinol Metab 2012;16:13–19

Raj M, Sundaram KR, Paul M, et al. Obesity in children – time trends and relationship with hypertension. Natl Med J India 2007; 20:288–93

16 Disorders of Kidney and Urinary Tract

Arvind Bagga, Aditi Sinha, RN Srivastava

RENAL ANATOMY AND PHYSIOLOGY

Each kidney is composed of approximately a million nephrons, each consisting of a glomerulus and renal tubule. The glomerulus is made of a tuft of capillaries and a central region of mesangium. The capillaries arise from the afferent arteriole and join to form the efferent arteriole, the entry and exit being at the hilum of the kidney. The capillary wall consists of fenestrated endothelium, glomerular basement membrane and foot processes (podocytes) of visceral epithelial cells. The basement membrane is made of type IV collagen, laminin and heparan sulfate proteoglycan. The Bowman space leads into the proximal tubule that has an initial convoluted portion, then the straight segment, descending and ascending limbs of the loop of Henle and the distal tubule. Six to eight distal tubules join to form the collecting ducts that finally enter the renal pelvis.

The renal artery divides into segmental arteries that branch to form interlobar and arcuate arteries. The latter give rise to the intralobar arteries, which provide the afferent arterioles for the glomeruli. The efferent arterioles from the glomeruli form a meshwork of peritubular venous capillaries that empty into intralobar veins. The early part of the distal tubule on its ascent from the medulla to the cortex lies near the glomerulus of the same nephron. The cells of the tubule in contact with the afferent arteriole are denser than the rest and called macula densa. The smooth muscle cells of the afferent arteriole, in this region, contain prominent cytoplasmic granules that are the site of renin activity. The juxtaglomerular apparatus (JGA) is composed of afferent and efferent arterioles, the macula densa and lacis cells located between these structures. The JGA is involved in systemic blood pressure regulation, electrolyte homeostasis and tubuloglomerular feedback.

Renal Physiology

Glomerular filtration depends upon the higher pressure in afferent arterioles. The filtration barrier is constituted by the endothelium with slit pores, basement membrane and podocytes of visceral epithelial cells. Filtration of solutes depends upon their molecular size, shape and electrical charge. The filtrate from the glomerular capillaries passes from the Bowman capsule into the proximal convoluted tubule, loop of Henle, distal tubule and collecting ducts. The filtrate contains all the diffusible and ultrafiltrable substances present in plasma. Small quantities of protein are usually present, but are reabsorbed in proximal tubule. Bulk of the glomerular filtrate is reabsorbed into the peritubular capillaries and only 0.5% is excreted as urine.

Tubular Reabsorption

The proximal tubules reabsorb about 80% of the glomerular filtrate. Approximately 65% of sodium is reabsorbed in the proximal tubule, through several active transport systems. Sodium transport is dependent on the parallel transport of bicarbonate, chloride, amino acids and glucose. Tubular reabsorption of sodium and other permeable solutes is promoted by the phenomenon of solvent drag during transport of water across the tubular epithelium. Figure 16.1 indicates the principal sites of reabsorption of sodium and potassium.

The glomerular filtration rate is regulated by tubuloglomerular feedback that depends upon the functional integrity of the JGA. Increased delivery of chloride to the macula densa results in local activation of renin-angiotensin mechanism. The renin-angiotensin-aldosterone system, prostaglandins and natriuretic peptides are involved in sodium handling. Potassium is completely reabsorbed in the proximal tubule; the amount seen in urine depends upon its secretion in the distal tubule.

Distal tubules and collecting ducts are responsible for urinary acidification, concentration and regulation of sodium balance. Exchange of potassium or hydrogen ions for sodium takes place in the distal tubules under the regulation of aldosterone. Antidiuretic hormone mediates

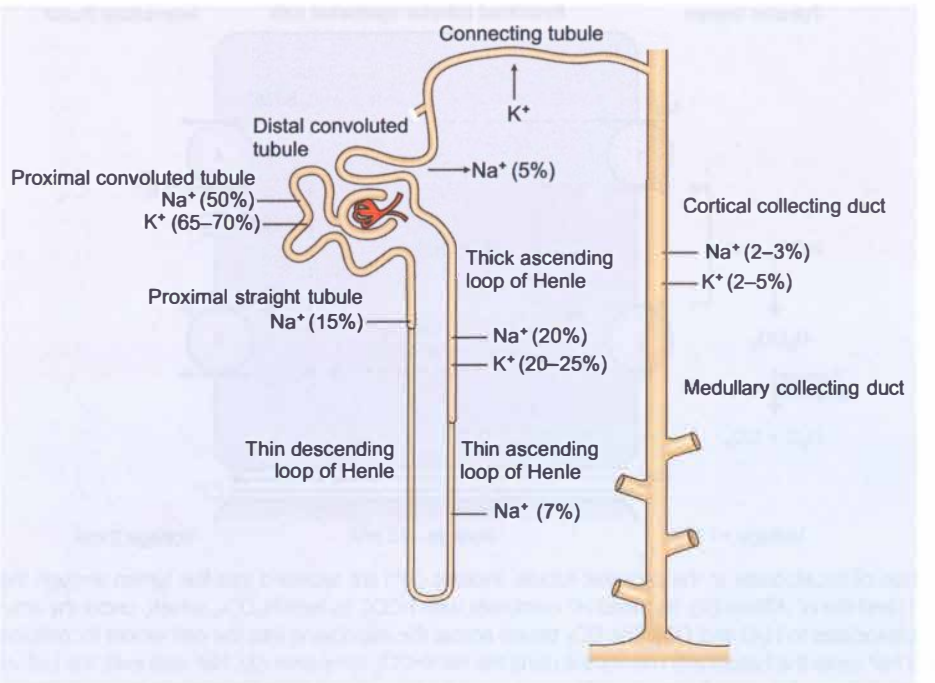

Fig. 16.1: Renal tubular handling of sodium and potassium. The major sites of reabsorption are shown, with percentage of filtered cation in parenthesis

absorption of water through insertion of 'water channels' (aquaporins) on the luminal surface of cells in the collecting tubules.

Renal acidification. The kidney helps in regulation of acid-base balance by maintaining plasma bicarbonate concentration at 24–26 mEq/l. Depending on dietary protein intake, children produce about 1–3 mEq/kg/day of nonvolatile acids. Filtered bicarbonate is almost completely reabsorbed, 85 to 90% in the proximal tubules and the rest in distal tubules and collecting ducts. Bicarbonate, consumed in the buffering of nonvolatile acids, is regenerated by the renal excretion of titrable acid and ammonia. Chronic acidosis augments the production of ammonia and thus elimination of acid. Figures 16.2 and 16.3 demonstrate the chief mechanisms involved in the reabsorption of bicarbonate and excretion of protons in the proximal and distal tubules, respectively. The reabsorption of filtered bicarbonate as well as excretion of acid is mediated by tubular secretion of hydrogen ions (H^+).

In the proximal tubule, filtered HCO_3^- combines with H^+ to form H_2CO_3 that rapidly dissociates to H_2O and CO_2 (catalyzed by carbonic anhydrase at the brush border of the tubular basement membrane) (Fig. 16.2). CO_2 diffuses along its concentration gradient into the tubular cell, combining with H_2O to generate HCO_3^- that is absorbed by the peritubular capillaries. The proximal tubule reabsorbs 80–90% of the filtered HCO_3^-; the remainder is reabsorbed distally. In the distal tubule, the secreted H^+ ions combine with the major urinary buffers, sodium hydrogen phosphate (Na_2HPO_4) and ammonia (NH_3) to form NaH_2PO_4 and NH_4^+ (measured in urine as titratable acidity and ammonium ion respectively) (Fig. 16.3). The distal nephron generates and maintains a steep pH gradient between the blood and urine, but its capacity to secrete H^+ ions is small. Thus, even a slight increase in distal HCO_3^- delivery results in increase in urine pH. Extracellular fluid volume and potassium balance also regulate H^+ secretion and HCO_3^- reabsorption.

Suggested Reading

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Development of Structure and Function

Differentiation of the primitive kidney is stimulated by penetration of the metanephros, during the fifth week of gestation, by the ureteric bud, which is an outgrowth of the lower portion of the mesonephric duct. Division of the ureteric bud within the metanephros induces the development of nephrons. The ureteric bud gives rise to the intrarenal collecting system, renal calyces, pelvis and ureter. The most active period of nephrogenesis is from 20–36 weeks. The full number of nephrons is present around 36 weeks. Partitioning of the cloaca during the 5th week results in the formation of the urogenital sinus anteriorly and the anal canal posteriorly. The upper part of the urogenital sinus differentiates to form the fetal bladder.

The fetal kidneys are lobulated structures that ascend from the pelvis to their normal position between 6 and

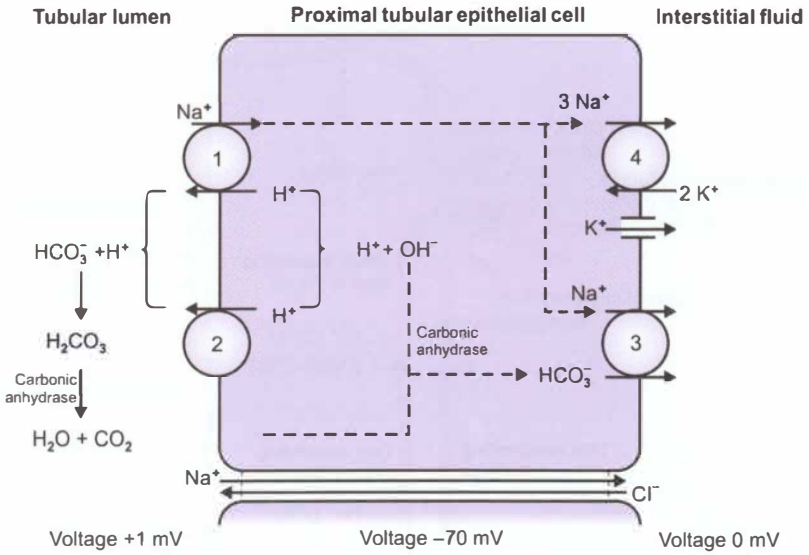
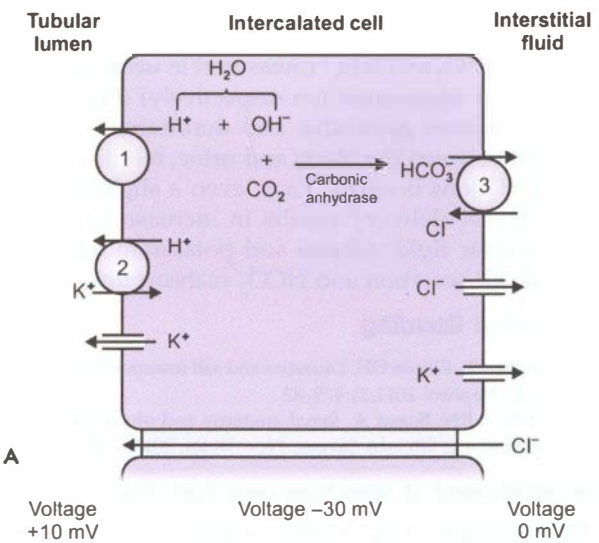
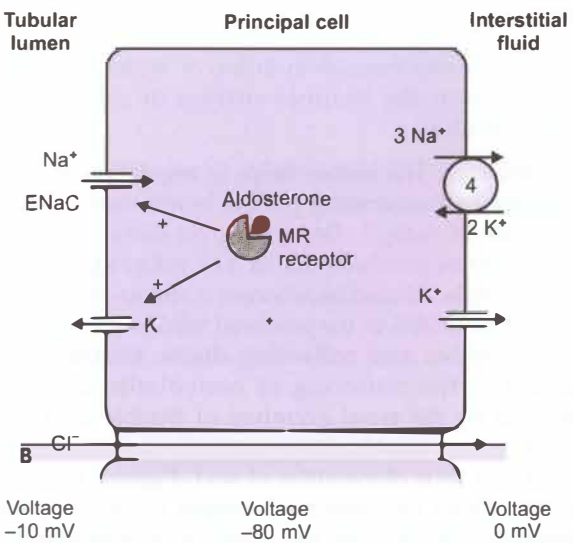


Fig. 16.2: Reabsorption of bicarbonate in the proximal tubule. Protons (H^+) are secreted into the lumen through the actions of the sodium (Na^+) H^+ antiporter (1) and the H^+ ATPase (2). Secreted H^+ combines with HCO_3^- to form H_2CO_3, which, under the action of luminal membrane carbonic anhydrase dissociates to H_2O and CO_2. The CO_2 travels across the membrane into the cell where it combines with OH^- to generate HCO_3^-. The HCO_3^- and Na^+ cross the basolateral membrane using the Na^+/HCO_3^- symporter (3). Na^+ also exits the cell via the Na^+/K^+ ATPase (4). Electrogenic H^+ secretion generates a small lumen positive voltage, which creates current flow across the paracellular pathway





Figs 16.3A and B Mechanism of acidification and potassium excretion in the distal renal tubules. (A) The intercalated cells of the cortical collecting ducts secrete H^+ through the H^+ ATPase (1) and H^+/K^+ ATPase (2), independent of Na^+ transport. The hydroxyl (OH^-) ions generated in the cell through H^+ secretion exit the cell by the HCO_3^-/Cl^- exchanger (3). The secreted H^+ is buffered by luminal ammonia forming NH_4^+ and phosphate (titrable acids), to prevent a drop in luminal pH that would prevent further H^+ secretion. (B) Principal cells mediate sodium (Na^+) absorption and potassium (K^+) transport. The apical membrane contains an amiloride sensitive Na^+ channel (epithelial sodium channel, ENaC); Na^+ exits basolaterally *via* Na^+/K^+ ATPase (4). Sodium transport creates a lumen negative transepithelial potential that increases the rate of H^+ secretion by intercalated cells. Aldosterone binds to the mineralocorticoid (MR) receptor and enhances Na^+ absorption and H^+ and K^+ secretion

9 weeks of gestation. These kidneys can be visualized on antenatal ultrasound by 12–13th week. The kidneys grow steadily in size between the 12th week and the 40th week, with the renal length increasing from about 1.0 cm to 2.7 cm. The fetal bladder is visualized by the 10–14th week, and its capacity increases steadily to about 50 ml at term. Beyond the 16th week, the amniotic volume is principally dependent on urine production.

Glomerular Filtration

Glomerular filtration begins at 5–9 weeks' gestation, initiating urine formation. The fetal kidney receives about

2–4% of cardiac output, which increases in neonates to 15–18%. Serum creatinine level is high at birth, reflecting maternal values, but falls rapidly to 0.3–0.5 mg/dl by the end of first week. Most (92%) neonates pass urine within the first 48 hr. The GFR is low at birth (15–20 ml/min/1.73 m^2 in the first 3 days in term, 10–15 ml/min/1.73 m^2 in preterm) but increases to 35–45 ml/min/1.73 m^2 at 2 weeks and 75–80 ml/min/1.73 m^2 by 2 months.

Tubular Function

Tubular function contributes to urine formation around 14 weeks' gestation. Postnatal tubular maturation follows a pattern similar to GFR but its maturation is delayed. Infants have reduced sodium and bicarbonate reabsorption and limited ability for hydrogen ion excretion. The pH of urine in newborns is inappropriately high for the degree of acidemia.

Plasma Osmolality

The capacity of the kidneys to concentrate or dilute urine is limited in neonates. An infant can concentrate his urine to a maximum of 700–800 mOsm/kg whereas the older child can achieve 1200–1400 mOsm/kg. Growing babies utilize most of the protein available for growth rather than catabolize to urea. Decreased production and excretion of urea result in a relatively hyposmolar interstitium and reduced urinary concentration. The newborn can dilute urine to a minimum of 50 mOsm/kg, like an older child. However, the time taken to excrete a water load is longer. Thus, delayed feeding and overdiluted or concentrated feeds are potentially harmful.

Maturation of Renal Function

Renal function continues to improve during the first two years of life, at the end of which, various parameters of renal function approach adult values, if corrected to standard surface area. Structural growth parallels the functional maturation.

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DIAGNOSTIC EVALUATION

Common manifestations of renal disorders include edema, hematuria, oligoanuria, dysuria and abnormalities of micturition, flank pain and ureteric colic. Serious renal disease may be present with subtle or no symptoms. With improvements in techniques and widespread availability of antenatal ultrasonography, several congenital anomalies of kidney and urinary tract (CAKUT) are detected. Appropriate imaging procedures are needed to confirm and define their severity. Abnormal urinary stream or dribbling of urine suggests an anomaly of the distal urinary tract. The causes of acute kidney injury in the newborn are different from those in older children.

During infancy, unexplained fever may be the only feature of urinary tract infection (UTI). UTI may be suggested by other nonspecific symptoms such as failure to thrive, diarrhea and vomiting. It is important to diagnose these infections since urinary tract anomalies may be present. An abdominal mass at this age is likely to be Wilms' tumor, hydronephrosis or multicystic renal dysplasia. An important cause of acute kidney injury, at this age, is hemolytic uremic syndrome. About 20% patients with minimal change nephrotic syndrome have onset of the disease between 2 and 3 yr. Renal tubular disorders such as renal tubular acidosis and Fanconi syndrome are usually diagnosed at this age.

Acute poststreptococcal glomerulonephritis (GN), rare below the age of 3 yr, is usual in older children. Rickets at this age is rarely due to vitamin D deficiency, unless there is malabsorption or chronic liver disease. Nephrotic syndrome beginning in adolescence may be of the non-minimal type. Acute-on-chronic renal failure, previously undetected chronic renal failure, symptomatic hypertension and collagen vascular diseases are common.

Clinical Features of Renal Disease

Hematuria

Gross hematuria in acute GN is typically smoky brown or cola colored. Bright red blood suggests a nonglomerular cause, as in renal or vesical calculi. Gross hematuria is rare in UTI. Other conditions, which might impart a red color to urine include hemoglobinuria, myoglobinuria, porphyria and ingestion of beetroot.

Edema

Acute GN presents with facial puffiness and gross hematuria; the edema does not pit readily on pressure. If fluid intake is not restricted, the edema may increase and involve hands, feet and legs. In nephrotic syndrome, edema develops insidiously, starting with eyelid puffiness most noticeable in the morning. Over a period of several days, there is pitting edema over the feet and legs. Facial swelling is often mistaken for allergy or insect bite.

Oliguria

Oliguria, defined as urine volume less than 0.5 ml/kg per hr, commonly results from gastroenteritis and hypovolemia. Oliguria is an important feature of moderate or severe acute GN, acute tubular necrosis and conditions causing severe glomerular injury (e.g. HUS, vasculitis).

Abnormalities of Micturition

A poor urinary stream in boys, especially in presence of a full bladder, suggests obstruction, most commonly due

to posterior urethral valves. Persistent dribbling indicates abnormal ureteric insertion distal to bladder neck. Infants with meningomyelocele should be evaluated for bladder dysfunction. Dysuria, flank pain or ureteric colic suggest UTI or urinary tract calculi.

Polyuria, Polydipsia

Impaired urinary concentration is a feature of obstructive uropathy and primary or secondary tubulointerstitial disorders. Polyuria is also present in conditions associated with deficiency or resistance to antidiuretic hormone, diabetes mellitus, hypokalemia (e.g. distal renal tubular acidosis) and hypercalcemia.

Enuresis

Primary monosymptomatic enuresis needs to be distinguished from patients with dysfunctional voiding. Most children with nocturnal enuresis have no evidence of renal disease. Urinalysis and culture are recommended in patients with secondary enuresis.

Hypertension

Assessment of blood pressure is necessary in all children, and especially those with disorders of the kidneys or urinary tract. Symptomatic hypertension is chiefly due to a renal parenchymal or renovascular cause; endocrine conditions are uncommon.

Growth Retardation, Anemia

Physical retardation is a feature of chronic kidney disease (stage 3–5) and tubular disorders. Normocytic normochromic anemia is striking in patients with chronic kidney disease (stage 3–5). Patients with unexplained anemia should be evaluated for a renal disease.

Abdominal Mass

Multicystic renal dysplasia, polycystic kidneys, renal vein thrombosis, hydronephrosis (due to pelviureteric or lower urinary tract obstruction) and Wilms' tumor may result in palpable masses.

Examination of Urine

Urinalysis is an important step for diagnosis of renal disease. Evaluation includes microscopic examination of the uncentrifuged as well as centrifuged specimen and semiquantitative or quantitative detection of different substances.

Collection of Specimen

The first morning specimen is preferred since it is relatively concentrated. While a clean container is sufficient, specimens for culture should be collected in a sterile container. After cleaning the perineum with soap and water, a 'clean catch' sample is collected. If facilities for immediate processing are not available, the specimen is stored at 4°C for 12–14 hr.

It is difficult to obtain satisfactory specimens in children below 2-yr-old. Urine may be collected using a sterile bag that is applied after local cleaning and removed soon after the void. These specimens should not be used for culture. Other reliable ways for obtaining urine specimens in infants include percutaneous suprapubic aspiration or transurethral catheterization.

Specific Gravity

Specific gravity is measured using either refractometer or hydrometer; the former is convenient, requires less volume of urine and gives accurate values. The early morning urine specific gravity should exceed 1015.

pH

Urine is collected in a capped syringe if pH can be measured promptly. If measurement is likely to be delayed, urine should be collected under paraffin. Urine pH is lowest in the fasting, early morning specimen and increases following meals.

Protein

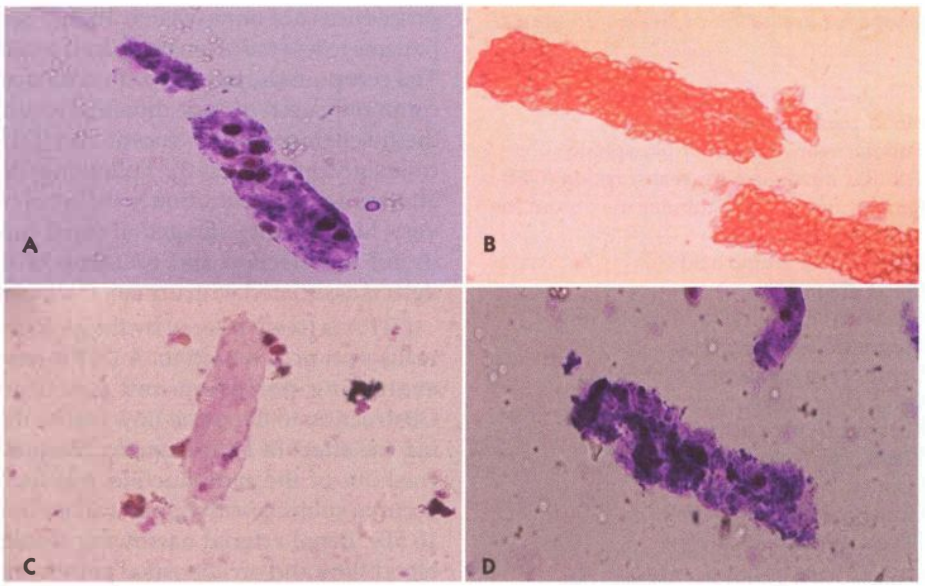
Proteinuria is an important marker of renal injury. Detection of 3–4+ albuminuria suggests glomerular disease. Low molecular weight proteinuria, including lysozyme, β2 microglobulin, neutrophil gelatinase associated lipocalin and retinol binding protein, suggest tubular injury. Dipstick methods (Uristix) for proteinuria are convenient and reliable. Composite strips for pH, glucose, hematuria, leukocyte esterase and nitrite are also available. Proteinuria can also be semiquantitatively tested using the boiling and the sulfosalicylic acid tests.

Reducing Substances

Reducing substances can be estimated by Benedict test or dipsticks based on the glucose oxidase method, both of which produce a graded color change.

Microscopic Examination

A fresh, well-mixed specimen is examined for cellular elements, crystals and casts. Alternatively, urine is centrifuged at 1500 rpm for 10 min; urine is decanted and the cell pellet resuspended in 0.3–0.5 ml urine. Evaluation for hematuria, defined as more than 5 red cells/hpf in a centrifuged specimen is abnormal. Red cell casts indicate glomerular inflammation. Leukocytes may occasionally be absent despite significant bacteriuria. On the other hand, isolated presence of leukocytes is not specific for UTI, and may be noted in interstitial nephritis, stones and high fever. The detection of bacteriuria in fresh, uncentrifuged urine is significant. Figure 16.4 shows common abnormalities picked up on urine microscopic examination.



Figs 16.4A to D: Appearance of casts on urine microscopic examination. (A) White blood cell casts; (B) red blood cells casts, (C) hyaline cast; (D) Granular cast

Blood Tests

Blood levels of creatinine and urea are used to assess renal function. The normal levels of serum creatinine are 0.2–0.5 mg/dl in children below 6 yr and 0.4–0.8 mg/dl in older children. Blood urea ranges between 20–35 mg/dl during childhood. However, it is important to realize the limitations of these investigations. Normal values of blood urea or creatinine do not increase even when glomerular filtration rate is reduced by 50%. The level of serum creatinine is dependent on muscle mass and is, therefore low in malnutrition. Bilirubin may interfere with creatinine measurements. Blood urea levels are low on a protein deficient diet and high with tissue breakdown, trauma, gastrointestinal bleeding and use of corticosteroids. Estimation of blood levels of cystatin C, which does not depend on the nutritional status, is considered a sensitive indicator of glomerular function.

Other specific investigations include albumin, cholesterol, antistreptococcal antibody titers, complement, immunoglobulins and autoantibodies. Estimation of blood pH, bicarbonate, electrolytes and osmolality are important in patients with tubular disorders and/or renal failure.

Glomerular Filtration Rate (GFR)

While clearance of inulin is regarded as the reference for estimating GFR, the test involves its accurate IV infusion followed by measurement of levels in timed urine and blood samples. Measurement of the creatinine clearance is adequate for assessing GFR in most cases.

Creatinine Clearance

Creatinine clearance depends on the body size; the values are normalized to surface area. The normal creatinine clearance is 80–120 ml/minute per 1.73 m^2. GFR can be estimated from serum creatinine (mg/dl) and patient height (cm). The value of the constant *k* ranges between 0.41–0.43.

$$\text{GFR (ml/minute per 1.73 m}^2) = \frac{k \times \text{height}}{\text{Serum creatinine}}$$

Radionuclide Clearance

Disappearance curves of the radionuclides, ^{125}I-iothalamate, ^{99m}Tc-DTPA or ^{51}Cr-EDTA following its IV injection can be used to accurately compute GFR.

Tests of Tubular Function

Table 16.1 lists some important evaluations useful in diagnosing disorders of tubular function.

Water Deprivation Test

Following a few hours of fluid deprivation, desamino-8-D-arginine vasopressin (DDAVP) is administered nasally (5–10 µg neonates and infants, 20 µg children) or by IM injection (0.4–1.0 µg infants and young children, 2 µg older children). Urine is collected every hr for the next 2–3 hr. Following administration of DDAVP, patients with nephrogenic diabetes insipidus fail to show a rise of urine osmolality that remains below 300 mOsm/kg (normal >800 mOsm/kg). Those with deficiency of the antidiuretic hormone concentrate urine appropriately following DDAVP administration.

Imaging of the Urinary Tract

Plain X-Ray

A plain film of abdomen provides information on renal size, shape and outline and radiopaque calculi. The length

Table 16.1: Investigations for evaluation of suspected tubular diseases

Substrate	*Test*
Phosphate	Blood parathormone
	Tubular reabsorption of phosphate
	Tubular maximum for reabsorption/GFR
Glucose	Renal threshold and tubular maximum for glucose reabsorption
Amino acids	Clearance of amino acid
Bicarbonate	Blood anion gap
	Fractional excretion of bicarbonate
H^+	Minimum urinary pH
	Urine anion gap; urine osmolal gap
	U-B CO_2 gradient
Water	Maximum urine osmolality
	Water deprivation test
	Plasma ADH
Sodium	Urinary sodium excretion
	Plasma renin, aldosterone

ADH antidiuretic hormone; GFR glomerular filtration rate

of normal kidney approximates the height of first four lumbar vertebrae. A small kidney may indicate hypoplasia or chronic damage. The opposite kidney, unless diseased, shows compensatory hypertrophy.

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Ultrasonography

Ultrasonography is the initial modality for imaging kidneys and urinary tract in renal diseases. This investigation is readily available, noninvasive and performed even in uncooperative patients, infants and those with renal failure. Anatomic details of the kidneys, ureters and bladder are examined. Doppler ultrasonography is useful for studying renal blood flow.

Intravenous Pyelogram (IVP)

The patient is prepared as for plain X-ray. The radiocontrast is injected and films taken at 2, 5, 10 and 30 min. IVP provides satisfactory details on renal size, shape, cortical outlines and calyceal pattern. The use of IVP has declined following the availability of radionuclide imaging.

Micturating Cystourethrogram (MCU)

MCU is necessary for studying the lower urinary tract. A sterile catheter is introduced into the bladder, which is filled with contrast medium; films are taken during and end-micturition. MCU provides precise details of the anatomy of the bladder and urethra, presence of vesicoureteric reflux and obstruction in the lower urinary tract (e.g. posterior urethral valves, urethral stenosis).

Radionuclide Imaging

Imaging of the kidney and urinary tract has been simplified by radionuclide methods, which have replaced conventional radiocontrast studies. Radionuclide procedures are noninvasive, highly sensitive and expose patients to less radiation compared to radiocontrast studies. The compounds, labeled with radioactive ^{99m}technetium, commonly used include dimercaptosuccinic acid (DMSA), diethylenetriaminepentaacetic acid (DTPA) and mercaptotriacylglycine (MAG-3). Following IV injection, DMSA attains high concentration in the renal cortex and provides very high quality images of renal morphology. This is useful in detection and followup of renal parenchymal defects associated with urinary tract infections (Fig. 16.5A).

DTPA is freely filtered by the glomeruli with no tubular reabsorption or excretion. A DTPA renogram is useful for evaluating perfusion and function of each kidney. Obstruction to the urine flow can be diagnosed by studying the effect of IV frusemide. Normally there is prompt washout of the radionuclide, but this clearing may not occur in subjects with upper urinary tract obstruction (Fig. 16.5B). Renal arterial narrowing results in reduced renal blood flow and an abnormal pattern on DTPA renogram. This effect is accentuated by administration of angiotensin converting enzyme inhibitors, thus increasing its sensitivity in diagnosis of renal artery stenosis. MAG-3 provides highly satisfactory information on renal structure and function.

^{99m}Tc-labeled radionuclide scan can be used instead of the radiocontrast MCU. Radionuclide cystography is sensitive for detecting vesicoureteric reflux with minimal radiation exposure. However, this procedure does not provide sufficient anatomic details of bladder and urethra to recommend its use for initial evaluation of patients with suspected urinary tract obstruction, nor grading of vesicoureteric reflux.

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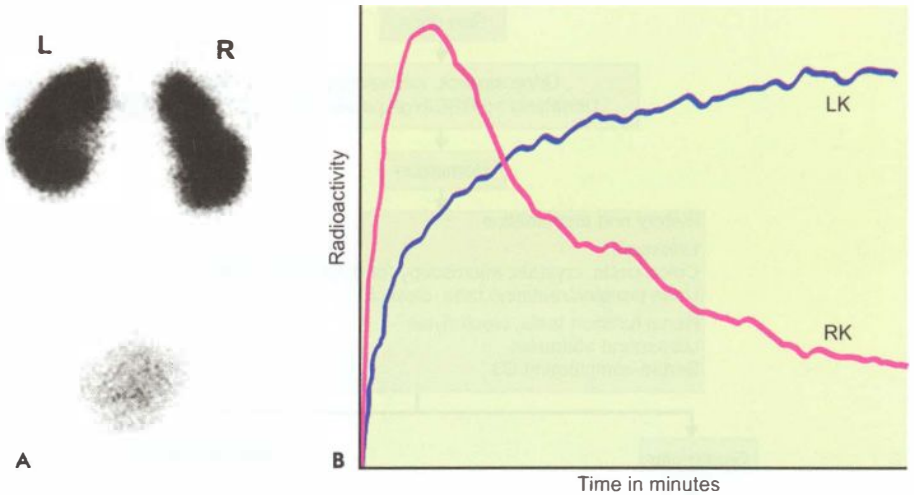
HEMATURIA

The presence of blood in urine imparts it a color, which includes various shades of deep red, smoky brown, cola-color and faint pink. Parents may mistake very concentrated urine for that containing blood. Microscopic examination of urine will show red blood cells. Reagent coated dipsticks detect free hemoglobin and myoglobin. Red urine may be present in porphyria and following beetroot ingestion. Urine appears orange-colored after administration of rifampicin or pyridium. Uric acid crystals may also impart a pink tinge to the nappy.



Figs 16.5A and B: (A) ^{99m}Tc-DMSA scintigraphy showing multiple scars and loss of volume in the right kidney. The left kidney is normal; (B) renal dynamic scan with diuretic was performed in a 6-wk-old newborn with isolated left hydronephrosis. The excretion of the tracer on the left side is sluggish and unchanged with administration of diuretic, suggesting an obstructive pattern of excretion, as seen with pelviureteric junction obstruction

In children, the commonest cause of gross hematuria is postinfectious GN. Urinary tract stones are not infrequent (Table 16.2). Gross hematuria is rare in acute pyelonephritis. Conditions that cause persistent microscopic hematuria include idiopathic hypercalciuria, benign familial hematuria, Alport syndrome, IgA nephropathy and membranoproliferative GN.

Diagnostic Evaluation

A history of pain in the flank or suprapubic region, dysuria and edema should be obtained. Physical examination includes assessment of growth and features of acute or chronic kidney disease such as edema, hypertension, unexplained pallor, bony abnormalities and abdominal mass. An audiogram and a detailed eye examination may be needed. Figure 16.6 shows an algorithm for evaluation of patients with hematuria.

A fresh specimen is examined for red cells, red cell casts and protein. Absence of large number of red cells in bloody urine suggests hemoglobinuria (intravascular hemolysis) or myoglobinuria. In glomerular disease, urine shows dysmorphic red cells, of different shapes, whereas in bleeding from renal pelvis or the lower urinary tract, the red cells maintain normal morphology (Fig. 16.7 and Table 16.3). Presence of significant proteinuria (2+ or more) and/or red cell casts suggests glomerular disease. Hypercalciuria should be excluded by determination of urinary calcium to creatinine ratio on one or more random samples.

A plain X-ray film of the abdomen and abdominal ultrasound is done to exclude major renal and urinary tract anomalies and calculi. Blood levels of creatinine are measured; other specialized blood tests depend on the likely clinical etiology. Surgical conditions that cause hematuria can be diagnosed by appropriate imaging. Invasive procedures such as cystoscopy are rarely indicated.

In a significant proportion, mild microscopic hematuria spontaneously disappears over a period of several years. Other family members may have similar urinary abnormalities. If there is no family history, a renal biopsy

Table 16.2: Causes of hematuria

Glomerular	*Non-glomerular*
Postinfectious glomerulonephritis (GN)	Hypercalciuria
IgA nephropathy	Renal calculi
Henoch-Schönlein nephritis	Urinary tract infection
Membranoproliferative GN	Hemorrhagic cystitis
Rapidly progressive GN	Trauma, exercise
	Cystic renal disease
	Interstitial nephritis
Uncommon	*Uncommon*
Lupus nephritis	Vascular malformations
Other vasculitides, e.g. microscopic polyangiitis	Coagulation disorders
Membranous nephropathy	Thrombocytopenia
Familial benign hematuria	Nutcracker syndrome
Alport syndrome	Renal or bladder malignancy

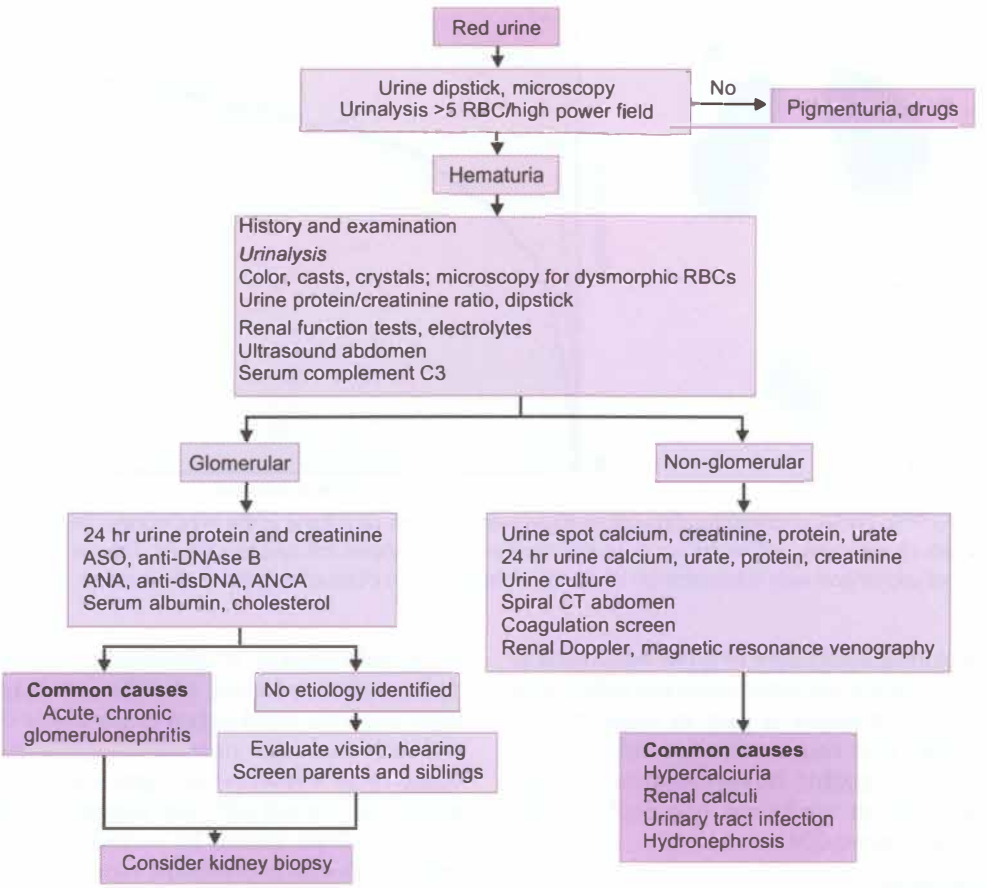


Fig. 16.6: Approach to evaluation of a patient with hematuria. The initial step in evaluation attempts to distinguish glomerular from nonglomerular causes of hematuria (*see* Table 16.3). Estimation of complement C3 is an important screening test for postinfectious glomerulonephritis. Patients with persistent glomerular hematuria might require kidney biopsy and/or screening for familial causes. ASO antistreptolysin O, ANA antinuclear antibody, anti dsDNA anti-double stranded DNA antibody, ANCA antineutrophil cytoplasmic antibody

Table 16.3: Features that distinguish glomerular from non-glomerular hematuria

Features	*Glomerular causes*	*Non-glomerular causes*
Dysuria	–	Suggests urethritis or cystitis
Systemic complaints	Edema, pharyngitis, rash, arthralgia (postinfectious glomerulonephritis, lupus, Henoch-Schönlein purpura)	Fever (UTI), loin pain (calculi)
Family history	Deafness, renal failure (Alport syndrome)	Calculi (hypercalciuria)
Hypertension, edema	Common	Rare
Abdominal mass	Absent	Wilms tumor, obstructive uropathy
Urine color	Brown, tea, cola	Bright red, clots
Proteinuria	2+ or more	Trace, 1+
Dysmorphic RBC	>20%	<15%
RBC casts	Common	Absent
Crystals	Absent	May suggest calculi

RBC red blood cells; UTI urinary tract infection

is not urgently indicated and the patient kept under observation.

Renal Biopsy

Renal biopsy should be done if hematuria is associated with persistent or heavy (3+ or more) proteinuria, history of renal disease in the family or evidence of chronic kidney disease in the patient, or if renal impairment or hypertension are seen on followup. A biopsy is also considered in children showing persistent microscopic hematuria for two or more years even in the absence of the above features. This procedure is necessary to diagnose IgA

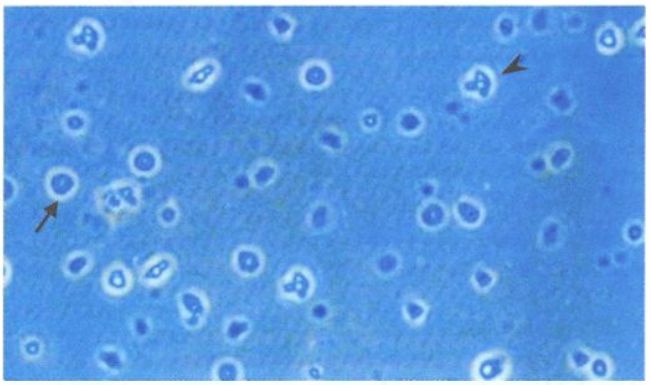


Fig. 16.7: Phase contrast microscopy showing dysmorphic red cells (arrowhead). Normal red cells are also seen (arrow)

nephropathy, Alport syndrome, thin basement membrane disease (typically presents as familial, benign hematuria) and chronic GN. The biopsy is evaluated by light, immunofluorescence and electron microscopy.

Alport Syndrome

This condition is inherited in an X-linked manner, although autosomal transmission is known. Mutations in the gene encoding alpha subunit of collagen IV *(COL4A5)* result in persistent microscopic hematuria, moderate proteinuria and progressive kidney failure. A significant proportion show high frequency sensorineural deafness; ocular defects (lenticonus, cataract, macular changes) are often associated. Ultrastructural examination of renal biopsy shows variable thickness of glomerular basement membrane with lengths of marked attenuation to areas of lamination. Therapy is supportive, including the use of angiotensin converting enzyme inhibitors. The majority of male patients show progression to end stage kidney disease.

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PROTEINURIA

The glomerular capillaries provide an effective barrier to filtration of proteins. Small amounts of protein are filtered but almost completely reabsorbed by the proximal tubule. Detection of more than trace amounts of protein in the urine is abnormal. However, the degree of proteinuria does not always reflect the severity of glomerular abnormality. Massive proteinuria occurs in minimal change nephrotic syndrome, in which glomeruli are normal or show mild changes. Persistent and heavy proteinuria, especially if associated with hematuria, should be promptly evaluated.

Quantitation of Proteinuria

Protein concentration of 100–1000 mg/m^2/day indicates mild to moderate proteinuria; more than that is heavy (nephrotic range) proteinuria. Accurate quantitative measurements of 24 hr urinary protein are not needed, if semiquantitative tests are done on a concentrated (first morning) specimen. Normally the protein to creatinine ratio, in the first morning urine specimen, is below 0.1 (mg/mg); a ratio of 0.1–2 indicates mild to moderate and >2 heavy proteinuria. The latter usually corresponds to 3+ or 4+ reaction on boiling or dipstick test.

Fever, dehydration and heavy exercise may cause transient and mild proteinuria. Mild proteinuria may occur in UTI, hydronephrosis and renal tuberculosis. Mild proteinuria in proximal tubular defects (e.g. Fanconi syndrome) is composed of low molecular weight proteins, while heavy proteinuria (predominantly albumin) indicates glomerular disease.

Important causes of asymptomatic proteinuria include orthostatic proteinuria, chronic glomerular diseases, reflux nephropathy, renal hypoplasia and rarely renal tubular disorders (Table 16.4). In orthostatic (postural) proteinuria, protein is absent in urine specimen collected after overnight recumbence. The pathogenesis of this condition is not clear but longterm outcome is good. Continued followup is necessary until proteinuria disappears. Chronic renal damage from vesicoureteric reflux and UTI may manifest with proteinuria. Several forms of glomerular diseases, especially focal segmental glomerulosclerosis, may cause persistent asymptomatic proteinuria; micro-

Table 16.4: Conditions presenting with proteinuria

Glomerular proteinuria
Nephrotic syndrome (minimal change disease, focal segmental glomerulosclerosis, congenital nephrotic syndrome)
Membranoproliferative glomerulonephritis, membranous nephropathy
Hepatitis B and C nephropathy, HIV nephropathy
Reflux nephropathy
Amyloidosis
Associated hematuria: Postinfectious glomerulonephritis, IgA nephropathy, Henoch-Schönlein nephritis, lupus nephritis, Alport syndrome
Tubular proteinuria
Drug induced nephropathy (analgesics)
Heavy metal nephropathy (e.g. gold, lead, cadmium)
Renal tubular acidosis
Interstitial nephritis, pyelonephritis
Intermittent or transient proteinuria
Postural (orthostatic)
Fever
Exercise

scopic hematuria is often associated. A renal biopsy is indicated in presence of persistent or heavy proteinuria. Longterm observation is necessary to monitor clinical course and renal function. Low salt diet and prolonged treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers are effective in reducing glomerular proteinuria.

Suggested Reading

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ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis (GN) is characterized by abrupt onset of hematuria, oliguria, edema and hypertension. The clinical severity varies, depending on histological involvement, salt and water retention and glomerular filtration rate. Mild disease may go undetected; severe cases have anuria, hypertensive encephalopathy and heart failure. The most common cause of acute GN is that following streptococcal infection (Table 16.5). Key investigations include renal function tests, urinalysis, serum complement C3 and titers of antistreptolysin. Renal biopsy is required if the presentation or course suggest a diagnosis other than poststreptococcal GN (Table 16.6).

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Poststreptococcal Glomerulonephritis

Acute GN following infection by group A beta-hemolytic streptococci is a common disorder. Streptococcal infection of the throat or skin precedes the onset of nephritis by 1 to 4 weeks. Only a few strains of streptococci are nephritogenic, e.g. types 4 and 12 causing pharyngitis and type 49 causing pyoderma.

Table 16.5: Etiology of the acute nephritic syndrome

Postinfectious
Streptococci, staphylococci, pneumococci, meningococci, *Treponema pallidum, Salmonella,* leptospira
Plasmodium malariae, P. falciparum, toxoplasma, filaria
Hepatitis B and C, cytomegalovirus, parvovirus, Epstein-Barr virus, coxsackievirus, echovirus, varicella
Associated with severe infections; infection of shunts, prostheses, bacterial endocarditis
Systemic vasculitis
Henoch-Schönlein purpura
Microscopic polyarteritis, Wegener granulomatosis
Others
Membranoproliferative glomerulonephritis
IgA nephropathy
Hereditary nephropathy
Systemic lupus erythematosus

Table 16.6: Indications for renal biopsy in acute glomerulonephritis

Systemic features. Fever, rash, joint pain, heart disease
Absence of serologic evidence of streptococcal infection; normal levels of C3 in the acute stage of illness
Mixed features of glomerulonephritis and nephrotic syndrome
High blood levels of urea or presence of anuria requiring dialysis (rapidly progressive GN)
Delayed resolution
Oliguria, hypertension and/or azotemia persisting past 7–10 days
Gross hematuria persisting past 3-4 weeks
Nephrotic range proteinuria beyond 2 weeks
Low C3 levels beyond 12 weeks
Persistent proteinuria beyond 6 months

Pathology

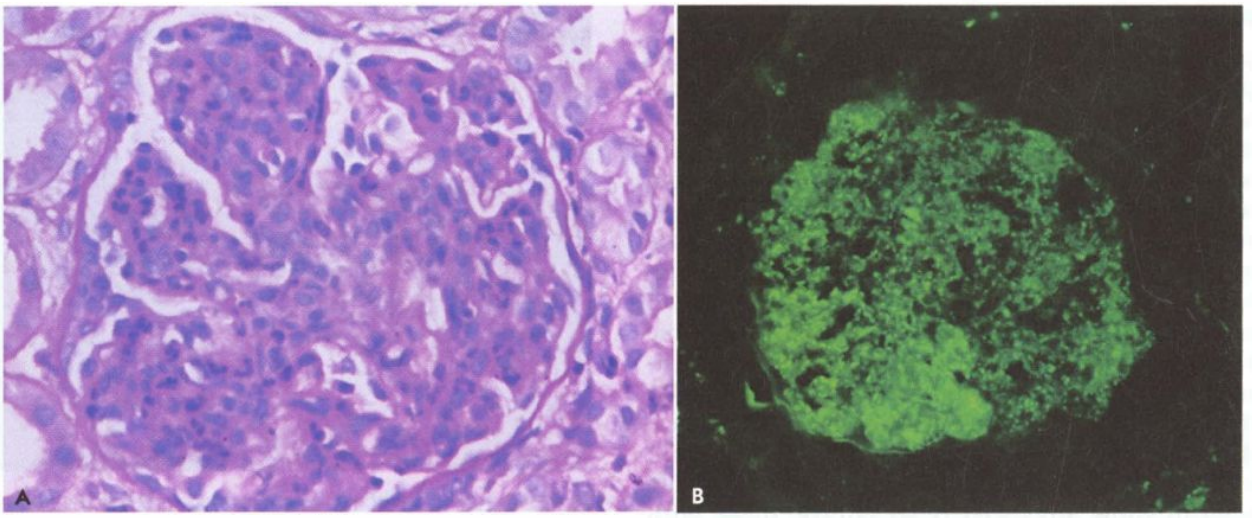
On light microscopy, glomeruli are enlarged and ischemic and capillary loops narrowed, making glomeruli appear bloodless (Fig. 16.8A); there is proliferation of mesangial cells and neutrophil infiltration. Immunofluorescence shows granular deposits of IgG and complement (C3) along capillary walls (Fig. 16.8B). Electron microscopy shows deposits (humps) on the subepithelial side of the glomerular basement membrane.

Clinical Features

Poststreptococcal GN involves school-age children, more commonly boys and is uncommon below 3 yr. Subclinical episodes are more common than overt disease, especially during epidemics. Patients may have mild proteinuria and microscopic hematuria. The onset is rapid, with puffiness around the eyes and pedal edema. Urine is cola-colored; hematuria is brief, often lasting only a few hours and does not persist beyond 1–2 weeks. While the degree of oliguria usually correlates with the disease severity, anuria is uncommon. Hypertension, present in over half the patients, resolves with loss of edema. Atypical presentations include (i) convulsions due to hypertensive encephalopathy; (ii) left ventricular failure and pulmonary edema, due to malignant hypertension and hypervolemia; (iii) acute kidney injury; and (iv) nephrotic syndrome.

Laboratory Findings

Urine shows 1–2+ protein with red cells, and red cell and granular casts. White cells indicate glomerular inflammation and should not be regarded as evidence of UTI. Hemodilution may result in normocytic anemia; ESR is raised. Blood levels of urea and creatinine are elevated reflecting renal impairment; hyponatremia and hyperkalemia occur with continuing oliguria. Chest X-ray may show prominent vascular markings suggesting hypervolemia. Serologic evidence for streptococcal infection is present in most patients with pharyngitis, though antibiotic therapy may blunt this response. ASO titer is increased in more than 80% patients; anti-DNase B is



Figs 16.8A and B: (A) Poststreptococcal GN. Moderately severe proliferation and exudative changes with infiltration of neutrophils. Few open capillary lumina are seen; (B) Immunofluorescence examination showing extensive fine granular deposition of IgG along the capillary wall and in mesangium with a starry sky appearance

elevated in cases of streptococcal skin infection. The titers decrease to low levels within 4–6 weeks. The level of serum C3 is low in 90% patients but normalizes by 8–12 weeks. Persistent low C3 levels indicate other forms of GN.

Management

Patients with mild oliguria and normal blood pressure can be managed at home. Close attention to blood pressure and dietary intake is essential. Once acute GN has occurred, treatment with penicillin has no effect on the course of the disease, but may be given if active pharyngitis or pyoderma is present. The principles of management of patients with severe oliguria and acute kidney injury are discussed later.

Diet. The intake of sodium, potassium and fluids should be restricted until blood levels of urea reduce and urine output increases. Overhydration is a dangerous complication as it may increase hypertension and precipitate left ventricular failure. Patients with azotemia require accurate measurement of urine output and daily weight, and restriction of fluid intake to an amount equal to insensible losses and 24 hr urine output.

Diuretics. Patients showing modest edema are treated with oral frusemide at a dose of 1–3 mg/kg; the edema disappears with the return of renal function. Therapy with IV frusemide (2–4 mg/kg) is necessary in subjects with pulmonary edema.

Hypertension. Mild hypertension may be controlled by restriction of salt and water intake. Effective antihypertensive agents include amlodepine, nifedipine or diuretics. Beta-blockers and angiotensin converting enzyme inhibitors carry risk of hyperkalemia. Patients with hypertensive emergencies need prompt treatment with IV nitroprusside or labetalol.

Left ventricular failure. Hypertension should be controlled and IV frusemide given to induce diuresis, leading to improvement in heart failure. If diuresis is not noted, dialysis is initiated. Respiratory support with positive end-expiratory pressure may be needed.

Prolonged oliguria. Treatment, as outlined above, should be continued and levels of blood urea and electrolytes monitored. *Dialysis is required in children with severe renal failure and prolonged oligoanuria, fluid overload and life-threatening electrolyte disturbances.* Occurrence of secondary infections should be avoided.

Outcome and Prognosis

Acute poststreptococcal GN has an excellent prognosis in childhood. The symptoms begin to resolve in the first week with loss of edema and fall in blood pressure. Gross hematuria and significant proteinuria disappear within 2-weeks, although microscopic hematuria and slight proteinuria may persist for several months. Hypertension subsides within 2–3 weeks, but rarely may persist for several weeks. Patients with acute GN of nonstreptococcal etiology have variable and unpredictable outcome. These cases need close followup over several years with periodic urinalyses and measurements of blood pressure.

Renal biopsy. A biopsy is rarely indicated in those suspected to have poststreptococcal GN except when renal function is severely impaired beyond 7–10 days or serum C3 remains depressed beyond 6–8 weeks. Patients with unresolving acute GN (persistent oliguria or azotemia past 7–10 days, hypertension or gross hematuria past 2–3 weeks) or those with features of a systemic illness (e.g. systemic lupus) require a kidney biopsy (Table 16.6).

Crescentic Glomerulonephritis

Rapidly progressive GN (RPGN) is defined as an acute nephritic illness accompanied by rapid loss of renal function over days to weeks. The histopathological correlate is the presence of crescents (crescentic GN) involving 50% or more glomeruli (Fig. 16.9) suggesting severe glomerular injury. The chief forms of RPGN are: (i) immune complex crescentic GN (immunofluorescence showing immunoglobulin and C3 deposits; normal or low C3), (ii) pauci-immune crescentic GN (related to small vessel vasculitis; positive antineutrophil cytoplasmic antibodies; scant immune deposits) and (iii) anti-glomerular basement membrane GN (with anti-GBM antibodies; linear IgG deposits). The severity of clinical and histological features often correlates. Patients with circumferential crescents involving more than 80% glomeruli show advanced renal failure; those with noncircumferential crescents in fewer glomeruli have an indolent course. Renal biopsy should be performed in all patients with severe nephritic features, which do not resolve within 1–2 weeks.

The outcome is related to histological severity and prompt institution of therapy. Without appropriate treatment, patients are at risk for progressive renal failure. Satisfactory results have been obtained with initial administration of IV and oral corticosteroids and IV cyclophosphamide, followed by maintenance immunosuppression. Plasmapheresis is recommended in patients with pauci-immune crescentic GN and Goodpasture syndrome.

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Nephritis in Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is the most common vasculitis in children (Fig. 16.10). Mild renal involvement indicated by microscopic hematuria and mild proteinuria is common. Serum IgA levels may be elevated. Renal biopsy shows mesangial proliferation with mesangial deposition of IgA. Most patients recover without any specific treatment. However, longterm observation is necessary to detect insidious renal damage. Rarely a patient may present with nephritic or nephrotic syndrome, hypertension, azotemia and crescentic GN. Therapy with a combination of oral/IV corticosteroids and cyclophosphamide initially, followed by maintenance steroids and azathioprine is recommended. Longterm outcome depends on the severity of renal manifestations.

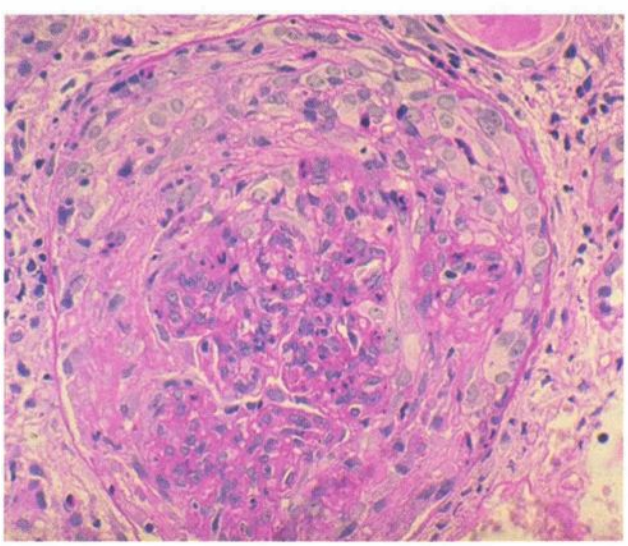

Fig. 16.9: Large cellular crescent with compression of glomerular tuft (Masson trichome X 200)

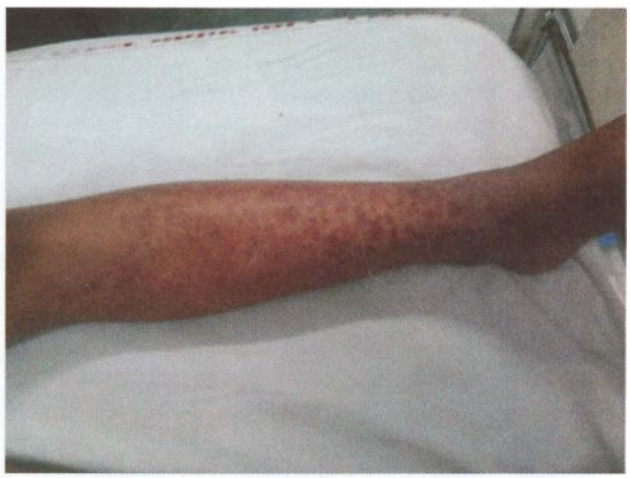

Fig. 16.10: Henoch-Schönlein purpura in a 6-yr-old girl admitted with severe abdominal pain. Note purpuric rash over the lower limbs

Immunoglobulin A Nephropathy

Predominant deposition of IgA in the glomeruli, chiefly in the mesangium and occasionally in capillary walls is characteristic. The usual clinical manifestation is recurrent episodes of gross hematuria following upper respiratory infections; each episode lasts for 2–5 days. In between these episodes, microscopic hematuria and mild proteinuria may persist. An acute nephritic or nephrotic syndrome is rarely the initial manifestation. Renal histology shows mesangial proliferation of varying severity. Patients with hematuria and non-nephrotic proteinuria are treated using angiotensin converting enzyme inhibitors. Therapy with corticosteroids and alkylating agents is indicated in patients with nephrotic range proteinuria or deranged renal function.

Lupus Nephritis

Variable clinical and renal histological patterns are observed in patients with systemic lupus erythematosus. Asymptomatic proteinuria and/or hematuria, acute nephritic syndrome and nephrotic syndrome are most common. Rarely renal involvement may be manifested as rapidly progressive GN. Renal biopsy may show almost normal glomeruli, focal or diffuse proliferative GN or membranous nephropathy. Immunofluorescence studies show mesangial and capillary wall deposits of IgG and

C3 and usually C1q and IgA. Antinuclear and double-stranded DNA autoantibodies are present in most cases with lupus nephritis; C3 levels are reduced.

Remissions and relapses and progressive renal damage are characteristic. Infections and end stage renal disease are the chief cause of mortality. Judicious use of corticosteroids, cytotoxic agents (cyclophosphamide, mycophenolate mofetil and azathioprine), calcineurin inhibitors (cyclosporine, tacrolimus) and monoclonal antibodies and prompt treatment of infections has improved outcomes.

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NEPHROTIC SYNDROME

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia and edema; hyperlipidemia is often associated. Some patients show hematuria and hypertension. Heavy proteinuria (more than 1 g/m^2 per day) is the underlying abnormality, leading to hypoalbuminemia (serum albumin below 2.5 g/dl). The resultant fall in plasma oncotic pressure leads to interstitial edema and hypovolemia. This stimulates the renin-angiotensin-aldosterone axis and antidiuretic hormone secretion that enhances sodium and water retention. The pathogenesis of edema may however be different in patients with significant glomerular lesions, who show primary sodium retention and expanded intravascular volume. Hypoalbuminemia also induces hepatic synthesis of β-lipoproteins resulting in hypercholesterolemia.

More than 90% of childhood nephrotic syndrome is primary (or idiopathic). Other causes such as amyloidosis, vasculitis, systemic lupus erythematosus, postinfectious GN and hepatitis B nephropathy are infrequent. Nephrotic syndrome in children can be divided into two groups based on renal histological characteristics: (i) minimal change nephrotic syndrome (MCNS); and (ii) nephrotic syndrome with significant lesions (Table 16.7).

Steroid sensitive nephrotic syndrome (which is usually MCNS) has a satisfactory longterm outcome. In contrast, the steroid resistant form (usually associated with significant glomerular lesions) has less satisfactory course and a significant proportion progress to chronic renal failure.

STEROID SENSITIVE NEPHROTIC SYNDROME

MCNS accounts for 80% cases of nephrotic syndrome in children. Renal biopsy does not show significant abnormalities on light microscopy (Fig. 16.11A). Electron microscopy shows nonspecific obliteration of epithelial foot processes. Immunofluorescence studies do not demonstrate deposition of immune reactants except occasional mesangial IgM. On the other hand, patients with focal segmental glomerulosclerosis (FSGS) show evidence of sclerosis involving a segment of the glomerular tuft (Fig. 16.11B). The pathogenesis of MCNS is obscure. There is evidence to suggest perturbation of cell mediated immunity, which through yet undefined mechanisms alters the permselectivity of the glomerular filter, resulting in massive proteinuria. A proportion of patients have a primary abnormality of the epithelial foot processes (podocytes).

Table 16.7: Features of idiopathic nephrotic syndrome

Features	*Minimal lesion*	*Significant lesions*
Age at onset	2–6 yr	Older children
Sex incidence	Higher in boys	Equal
Hematuria	Rare	Usual
Blood pressure	Normal	Normal or increased
GFR	Normal	Normal or decreased
Renal biopsy	Normal glomeruli; mild mesangial proliferation; often IgM deposits	Changes of varying severity; C3, immunoglobulin deposits
Serum C3	Normal	Low in MPGN
Selectivity of proteinuria	High	Low
Response to steroids	Remission in >95%	Unsatisfactory
Prognosis	Good; relapses stop by second decade	Variable progression of renal damage

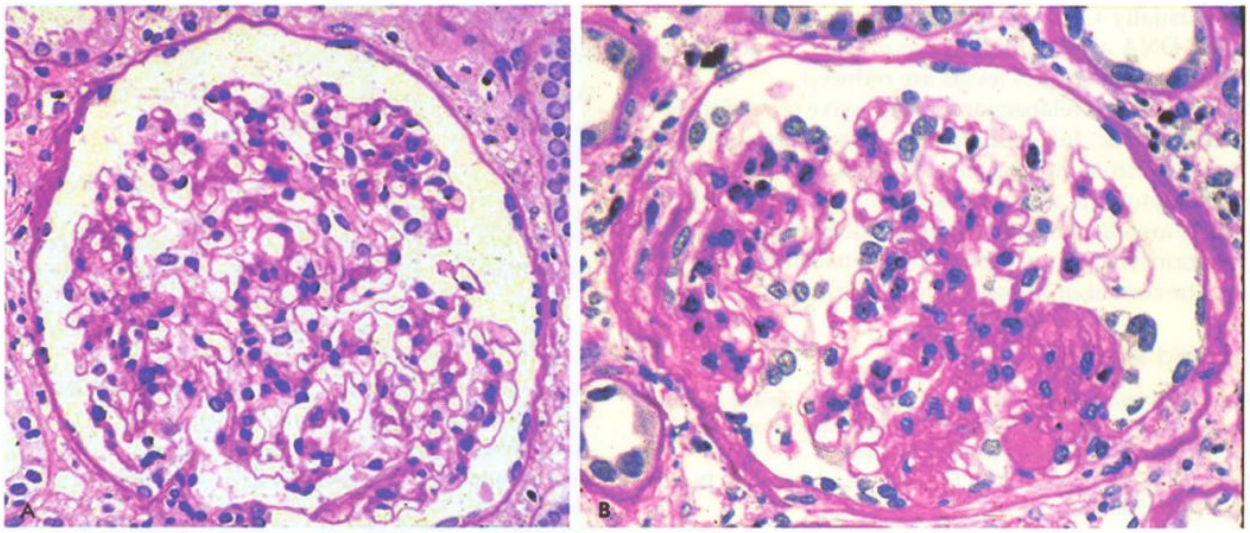
MPGN membranoproliferative glomerulonephritis

Clinical Features

The onset is insidious with edema first noticed around the eyes and subsequently on legs. It is soft and pits easily on pressure. Gradually edema becomes generalized, with ascites, hydrothorax and hydrocele (Fig. 16.12). With increasing edema, urine output may fall. The blood pressure is usually normal; sustained elevation suggests the possibility of significant glomerular lesions. The bloated appearance and relative well-being of the child is misleading and after the loss of edema, severe muscle wasting is revealed. Infections may be present at the onset and during relapses.

Laboratory Findings

Urine examination shows heavy (3 – 4+) proteinuria. Gross hematuria or persistent microscopic hematuria suggests the likelihood of significant glomerular lesions; hyaline and granular casts are present. Serum albumin is low and values below 1 g/dl are often obtained. Hypercholesterolemia may impart a milky appearance to the plasma. Blood



Figs 16.11A and B: (A) Renal histology in a 4-yr-old boy with steroid dependent nephrotic syndrome. There is normal morphology of glomerular capillary loops, mesangial matrix and cells suggestive of minimal change disease; (B) histological features in a 6-yr-old girl with steroid resistant nephrotic syndrome secondary to focal segmental glomerulosclerosis. Note the hilar sclerosis involving large areas of the glomerulus and adhesions to the Bowman's capsule

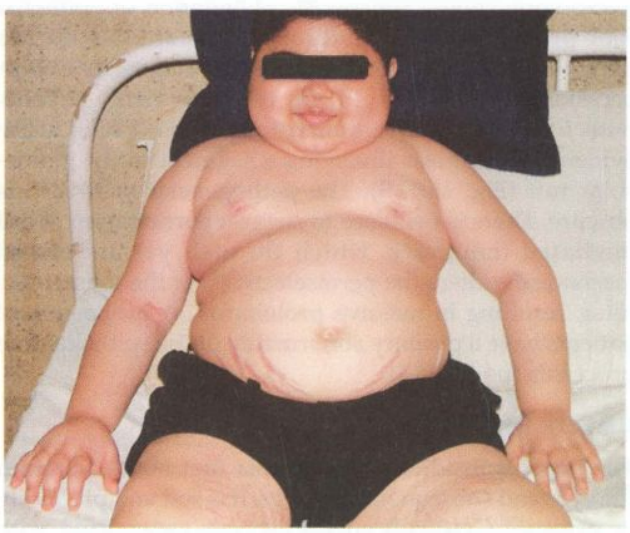


Fig. 16.12: An 8-yr-old boy with steroid dependent nephrotic syndrome. Anasarca is seen affecting upper limbs (including dorsa of hands), trunk and ascites. Note the cushingoid features and striae on lower abdominal wall and upper legs

urea and creatinine values are within the normal range except when there is hypovolemia and fall in renal perfusion.

Blood levels of IgG are low and those of IgM elevated; C3 level is normal. The severity of glomerular damage is reflected in the passage of proteins of large molecular weight, chiefly globulin. Protein selectivity is the ratio of clearance of high molecular weight (e.g. IgG) to low molecular weight proteins (e.g. transferrin, albumin). A low ratio indicates highly selective proteinuria, as in MCNS. However, this information does not offer diagnostic help.

Evaluations considered at onset of nephrotic syndrome include: (i) urinalysis for proteinuria, red cells, casts; (ii) blood levels of urea, creatinine, albumin, cholesterol; (iii) complete blood counts and (iv) tuberculin test. Depending on clinical and laboratory findings, the following additional tests may be required: (i) C3 and antistreptolysin O (gross or persistent microscopic hematuria); (ii) chest X-ray (positive tuberculin test; history of contact with tuberculosis); (iii) hepatitis B surface antigen (recent jaundice, raised levels of transaminases); (iv) antinuclear antibodies (suspected systemic lupus erythematosus); and (v) urine culture (suspected urinary tract infection). A renal biopsy is not required to confirm the diagnosis of MCNS prior to starting treatment. A biopsy is recommended in children with atypical features at the onset (age below 12 months, gross or persistent microscopic hematuria, low blood C3, hypertension or impaired renal function). Patients who continue to show nephrotic range proteinuria despite appropriate steroid therapy require a biopsy to determine the underlying disorder.

Management of Initial Episode

The child should receive a high protein diet. Salt is restricted to the amount in usual cooking with no extra salt given. Any associated infection is treated. The presence of tuberculosis should be looked for. Diuretics are administered only if edema is significant. Frusemide (1–4 mg/kg/day in 2 divided doses) alone or with an aldosterone antagonist, spironolactone (2–3 mg/kg/day in 2 divided doses) is adequate. Diuretics should be used cautiously and overzealous fluid loss avoided. Therapy with corticosteroids results in abolition of proteinuria (remission) usually by 10–14 days, diuresis and loss of edema.

The first episode of nephrotic syndrome should be treated adequately, both in terms of dose and duration of corticosteroids, since this is considered an important determinant of longterm course. Only prednisolone and prednisone are of proven benefit in the treatment of proteinuria. Either of these agents is given at a dose of 2 mg/kg per day (maximum 60 mg) in single or divided doses for 6 weeks, followed by 1.5 mg/kg (maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks. Therapy with corticosteroids is then stopped. While some experts propose that therapy with corticosteroids should not be stopped abruptly and tapered over the next 8–12 weeks, the benefits of prolonged therapy need to be balanced by the risk of steroid adverse effects.

Parent Education

The parents should be explained about the disease and the usual outcome and their cooperation ensured. They are taught how to examine urine for protein, which should be done periodically to detect a relapse early. During the periods of remission, no dietary restrictions are imposed.

Subsequent Course

A small proportion of patients have only a single episode of the illness, while the majority shows relapses. Some patients have three or less relapses in a year (infrequent relapsers), while others have four or more relapses (frequent relapsers) (Table 16.8). About 15% remain in remission while on prednisolone therapy and relapse whenever the dose is reduced or within 2 weeks of its discontinuation (steroid dependent). About 10–15% patients either do not respond to the initial treatment with prednisolone, or do so transiently and later cease to respond (steroid resistant).

Management of Relapse

Relapses are often triggered by minor infections. Symptomatic therapy of infectious illness might result in remission of low grade (1–2+) proteinuria. However, persistence of 3–4+ proteinuria requires treatment for relapse. Prednisolone is given at a dose of 2 mg/kg/day until protein is negative/trace for three consecutive days, and then on alternate days at a dose of 1.5 mg/kg for 4 weeks. Thus, treatment for a relapse usually lasts for 5–6 weeks and there is no evidence that its prolongation affects the outcome.

The first 2–3 relapses are treated in the manner described above. Once the pattern of relapses is known, therapy is individualized. Patients with infrequent relapses continue to receive treatment for individual relapses as outlined above.

Table 16.8: Important definitions to clarify course of nephrotic syndrome

Remission: Urine albumin nil or trace (or proteinuria <4 mg/m^2/hr) for 3 consecutive early morning specimens

Relapse: Urine albumin 3+ or 4+ (or proteinuria >40 mg/m^2/hr) for 3 consecutive early morning specimens, having been in remission previously

Frequent relapses: Two or more relapses in initial six months or four or more relapses in any twelve months

Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation

Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks and alternate day for next 4 weeks.

Frequent Relapses and Steroid Dependence

Patients with frequent relapses or steroid dependence require prolonged treatment in order to maintain disease remission.

Longterm Alternate Day Prednisolone

Following treatment of a relapse, the dose of prednisolone is tapered to maintain the patient in remission; usually a small dose is given on alternate days for 9–18 months. This strategy is effective in maintaining remission in many patients. Since infections precipitate relapses, administering the same small dose daily for 5–7 days starting at onset of infections may prevent relapses. However, relapses, while on this therapy, are treated with daily prednisolone at 2 mg/kg/day until remission, after which alternate day therapy is resumed at 1.5 mg/kg. Patients with repeated relapses, while on longterm therapy, should be considered for treatment with a steroid sparing agent.

Steroid Sparing Agents

The additional use of an alternative agent should be considered in patients with: (i) prednisolone threshold (for maintaining remission) higher than 0.5–0.7 mg/kg on alternate days, or (ii) features of corticosteroid toxicity (growth failure, hypertension and cataract). The agents used, usually in successive order, are listed below and in Table 16.9.

Levamisole. This immunomodulator is effective in reducing relapses in a proportion of patients with frequent relapsing or steroid dependent nephrotic syndrome. After inducing remission, levamisole is administered at a dose of 2–2.5 mg/kg on alternate days. Alternate day prednisolone is given in decreasing doses, until a dose of 0.3–0.5 mg/kg is reached, for 3–6 months; it is occasionally possible to discontinue steroids altogether. Treatment with levamisole is given for 1–2 yr or longer. The chief side effect is leukopenia, which should be monitored every 2 months; others include flu like symptoms and rash.

Cyclophosphamide. Treatment with alkylating agents and alternate day prednisolone is effective in many patients with frequent relapsing or steroid dependent nephrotic syndrome. A 12-week course of treatment may induce long-lasting remission in 30–40% cases. Side effects include

Table 16.9: Therapy for steroid sensitive nephrotic syndrome

Agent	*Dose*	*Duration*	*Adverse effects*
Prednisolone	Maintain on 0.3–0.7 mg/kg on alternate days	9–18 mo	Cushingoid body habitus, hypertension, short stature, cataract, hirsutism
Levamisole	2–2.5 mg/kg on alternate days	1–2 yr	Leukopenia, rash, flu-like symptoms
Cyclophosphamide*	2–2.5 mg/kg/day	12 weeks	Leukopenia; alopecia; gonadal toxicity; nail discoloration (hemorrhagic cystitis; nausea and vomiting are more common with IV administration)
Mycophenolate mofetil	600–1000 mg/m^2/day or 20–25 mg/kg/day	1–3 yr	Gastrointestinal discomfort, diarrhea; leukopenia
Cyclosporine (CyA)* or Tacrolimus (Tac)*	CyA: 4–5 mg/kg/day Tac: 0.1–0.2 mg/kg/day	12–36 mo	Acute and chronic nephrotoxicity, elevated transaminases (both agents); hirsutism, gum hyperplasia, hypertension or hyperlipidemia (CsA > Tac); hyperglycemia, neurotoxicity with headache and seizures (Tac > CsA)
Rituximab*	375 mg/m^2 IV once a week	2–3 doses	Infusion reactions (fever, rash, bronchospasm); hypogammaglobulinemia, neutropenia

* Preferred earlier if relapses are life threatening (associated with peritonitis, other serious infections or thrombosis) or in presence of significant steroid toxicity

leukopenia, nausea and vomiting; a high fluid intake is ensured to prevent hemorrhagic cystitis. Alkylating agents are associated with a risk of gonadal toxicity and malignancies, although at the doses and duration used these risks are minimal. Another alkylating agent, chlorambucil has significant additional toxicities and a low margin of safety, and is not recommended.

Mycophenolate mofetil. Prolonged treatment with this agent is useful in reducing relapse rates and corticosteroid sparing. The lack of renal, hemodynamic and metabolic toxicity makes it an alternative to calcineurin inhibitors. Chief side effects include gastrointestinal discomfort, diarrhea and leukopenia. The dose of the medication is 600–1000 mg/m^2/day or 20–25 mg/kg/day in two divided doses for 12–36 months. Tapering doses of prednisolone are given for 6–12 months.

Cyclosporine and tacrolimus. Therapy with either of these agents is indicated in patients that fail to benefit with levamisole, cyclophosphamide and/or mycophenolate mofetil. Treatment may be associated with significant adverse effects. Cyclosporine A (4–5 mg/kg/day) or tacrolimus (0.1–0.2 mg/kg/day) are administered, in two divided doses, for 12–24 months aiming for respective trough levels of 80–120 ng/ml and 3–7 ng/ml. Both agents have strong steroid sparing potential, with steroid discontinuation achieved in most patients over 6–9 months.

Adverse effects are common and include acute and chronic nephrotoxicity. A renal biopsy is done after 2–3 yr of continuous therapy. Patients receiving cyclosporine have cosmetic side effects (hirsutism, gum hyperplasia), hypertension and hypercholesterolemia. Treatment with tacrolimus is associated with risk of hyperglycemia, elevated transaminases, diarrhea, tremors, headache and seizures.

Rituximab. This monoclonal anti-CD20 antibody has been used with success in patients with steroid dependent nephrotic syndrome, with remission lasting 6–18 months. This agent appears to be useful in patients who fail to respond or show toxicity with other therapies.

Complications in Nephrotic Syndrome

The patient should be maintained in remission, as far as possible. Relapses should be promptly treated so that the child does not develop more than minimal edema. Several complications that are associated with massive edema and ascites.

Edema

Edema is controlled with salt restriction and oral hydrochlorothiazide or frusemide for a few days. Salt must not be totally stopped and the usual amounts used in cooking should be allowed. For massive edema, higher doses of frusemide along with spironolactone are needed. Infusion of albumin may be necessary in intractable cases where serum albumin levels are extremely low causing poor renal perfusion and oliguria.

Infections

Nephrotic syndrome and steroid therapy render children susceptible to infections. Infection with *S. pneumoniae*, gram-negative organisms and varicella are common. Children present with serious infections, e.g. peritonitis, cellulitis, pneumonia and meningitis. Peritonitis may manifest with low grade fever, diarrhea and abdominal discomfort. Patients with varicella should receive oral acyclovir for 7 days; severe illness requires administration of IV acyclovir. Immunization with pneumococcal and varicella vaccines is advised once the patient is off steroids for 4 weeks.

Thrombotic Complications

Patients with nephrotic syndrome are at risk for thrombosis involving renal, pulmonary and cerebral veins. Aggressive use of diuretics, venepuncture of deep veins and hypovolemia increase the risk of this complication. Treatment with low molecular weight heparin followed by oral anticoagulants is recommended.

Hypovolemia and Acute Renal Failure

Hypovolemia may occur during a severe disease relapse or following administration of diuretics, particularly in children with poor oral intake, diarrhea and vomiting. Features include abdominal pain, lethargy, dizziness and leg cramps, tachycardia, hypotension, delayed capillary refill, low volume pulses and clammy distal extremities. Elevated ratio of blood urea to creatinine, high hematocrit, urine sodium <20 mEq/l, fractional excretion of sodium 0.2–0.4% and urinary potassium index [urine K^+/(urine K^+ + urine Na^+)] >0.6 suggest the presence of hypovolemia. Therapy with diuretics should be discontinued. Patients require admission and rapid infusion of normal saline (10–20 ml/kg) over 20–30 min. Those who do not respond to two boluses of saline should receive infusion of 5% albumin (10–15 ml/kg) or 20% albumin (0.5–1 g/kg).

Steroid Toxicity

Repeated and prolonged courses of steroids often result in significant toxicity, characterized by cushingoid features, short stature, hypertension, osteoporosis and subcapsular cataract. Timely use of steroid sparing agents (levamisole, alkylating agents, cyclosporin) are recommended.

Longterm Outcome

Children with MCNS usually have an excellent prognosis. The frequency of relapses decreases with time and a majority of patients outgrow the condition by adulthood. It is unfortunately not possible to predict when a particular patient will stop getting relapses. The mortality rate of 1–4% is associated with infections and hypovolemia that should be preventable.

STEROID RESISTANT NEPHROTIC SYNDROME

The management of patients with steroid resistant nephrotic syndrome is difficult, with patients showing a variable response to immunosuppression, adverse effects of prolonged therapy and risk of progressive renal damage. Steroid resistance is diagnosed if there is lack of remission despite treatment with prednisolone, at a dose of 2 mg/kg/day (60 mg/m^2/day) for 4 weeks. Care is taken to exclude systemic infections (e.g. peritonitis, cellulitis, respiratory tract infections), which might result in persistent proteinuria.

Baseline assessment of renal function, blood levels of albumin and cholesterol, and estimation of proteinuria (24 hr quantitation) guides evaluation. Patients should be evaluated for secondary causes. Children with steroid resistance should undergo renal biopsy before instituting specific treatment. While patients with minimal change disease show satisfactory response to therapy, the presence of FSGS with chronic tubulointerstitial changes is associated with less satisfactory outcomes. Before start of immunosuppressive therapy, patients with steroid resistant nephrotic syndrome should undergo testing for hepatitis B surface antigen, anti-HCV IgG and HIV.

About 10–20% patients with familial and sporadic steroid resistant nephrotic syndrome have homozygous or compound heterozygous mutations in genes encoding podocyte proteins, including podocin (*NPHS2*), nephrin (*NPHS1*) and Wilm's tumor (*WT1*) genes. These patients are unresponsive to immunosuppressive medications, progresses rapidly to end stage renal disease and unlike nongenetic FSGS (which recurs after transplantation in 30%), does not recur. Where facilities exist, mutational analysis should be offered to patients with (i) congenital nephrotic syndrome (onset below 3 months of age), (ii) family history of SRNS, (iii) sporadic initial steroid resistance that does not respond to therapy with cyclophosphamide or calcineurin inhibitors, and (iv) girls with steroid resistant FSGS.

Management

Patients with steroid resistant nephrotic syndrome secondary to minimal change disease, FSGS or mesangioproliferative GN are treated similarly. *The chief factor predicting renal outcome is the response of proteinuria to therapy, rather than the renal histology.* The aim of therapy in patients is thus to induce and maintain remission of proteinuria, while avoiding medication related adverse effects. Most regimens use a combination of an immunosuppressive agent with prednisolone (given on alternate days) and an angiotensin converting enzyme inhibitor (Table 16.10). The best results are obtained with regimens combining calcineurin inhibitors (cyclosporine or tacrolimus) and tapering doses of corticosteroids. The aim of treatment is the achievement of complete remission, but occurrence of partial remission is also satisfactory. Patients who respond to treatment do so within 3–6 months; those that fail therapy with one regimen may show response to different agents.

Adjunctive therapy with angiotensin converting enzyme inhibitors (e.g. enalapril 0.3–0.6 mg/kg/day, ramipril 6 mg/m^2/day) is associated with decrease in proteinuria and control of hypertension. Adverse effects include dry cough, hyperkalemia and decline in renal function. Angiotensin receptor blockers (e.g. losartan, valsartan) may be used in case of persistent dry cough with ACE inhibitors, or as add-on therapy for better antiproteinuric effect. Therapy with HMG coenzyme-A reductase inhibitors is useful in lowering blood levels of cholesterol in subjects with persistent hypercholesterolemia.

Table 16.10: Agents for management of steroid resistant nephrotic syndrome

Agent	*Dose*	*Duration*	*Efficacy*	*Adverse effects*
Calcineurin inhibitors				
Cyclosporine (CsA)	4–5 mg/kg/day	12–36 months	50–80%	Acute and chronic nephrotoxicity (both agents); hirsutism and gum hyperplasia (CsA > Tac); hypertension, high cholesterol (CsA > Tac); hyperglycemia (Tac); elevated transaminases, neurotoxicity, headache and seizures (Tac > CsA)
Tacrolimus (Tac)	0.1–0.2 mg/kg/day	12–36 months	70–85%	
Cyclophosphamide				
Intravenous	500–750 mg/m^2	6 pulses	40–50%	Leukopenia; alopecia; nausea and vomiting; gonadal toxicity; hemorrhagic cystitis
Oral	2–2.5 mg/kg/day	12 weeks	20–25%	
High dose corticosteroids with cyclophosphamide				
Methylprednisolone	20–30 mg/kg IV	'Pulses' on alternate days × 6; once weekly × 8; fortnightly × 4	30–50%	Hypertension, hypokalemia, hyperglycemia, steroid psychosis, systemic infections
Prednisolone	Tapering doses*	18 mo		
Cyclophosphamide	2–2.5 mg/kg/day**	12 weeks		Side effects of cyclophosphamide therapy and prolonged steroid therapy

*Prednisolone 1.5 mg/kg on alternate days × 4 weeks; 1.25 mg/kg × 4 weeks; 1 mg/kg × 4 mo; 0.5–0.75 mg/kg × 12–18 mo
**Cyclophosphamide is administered during 3–15 weeks

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Hypertension must be controlled and infections managed appropriately. Edema is minimized with judicious use of diuretics. The use of intravenous albumin should be limited to cases with (i) symptomatic hypovolemia, (ii) symptomatic edema or (iii) marked ascites that is causing respiratory compromise. In cases with hypovolemia, 10–20 ml/kg of 4.5–5% albumin should be infused. Severe symptomatic edema or ascites may be treated with 0.75–1 g/kg of 20% albumin, infused over 2 hr, to expand the circulating volume followed by frusemide 1 mg/kg. Close monitoring is essential to avoid fluid overload and pulmonary edema. Albumin infusion augments diuresis when co-administered with frusemide in severely hypoalbuminemic patients with refractory edema.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome present in the first 3 months of life with anasarca, hypoalbuminemia and oliguria. The etiology of congenital nephrotic syndrome is heterogeneous. The 'Finnish' form of the disease is inherited in an autosomal recessive manner, with mutations in the gene encoding nephrin *(NPHS1)*. The characteristic renal histology with microcystic dilation of proximal tubules is seen after a few months of life, although ultrastructural abnormalities of the glomerular basement membrane are present at birth. Elevated levels of alpha-fetoprotein (AFP) in maternal serum and amniotic fluid enable antenatal screening. The clinical course is complicated by failure to thrive, recurrent infections, hypothyroidism and progression to renal failure by 2–3 yr.

Patients with Denys Drash syndrome show mutations in the *WT1* gene, congenital nephrotic syndrome, male pseudohermaphroditism and high risk of bilateral Wilms' tumor. Renal histology is characterized by diffuse mesangial sclerosis and there is progressive renal failure.

Other causes of congenital nephrotic syndrome include infections (congenital syphilis, cytomegalovirus disease, toxoplasmosis) and mutations in *PLCE1* or *NPHS2* genes; rarely renal histology may be normal (minimal change nephrotic syndrome) or show focal segmental glomerulosclerosis. Therapy of patients with congenital nephrotic syndrome is supportive with appropriate nutrition, control of edema, thyroxin supplements and reduction of proteinuria through ACE inhibitors and/or indomethacin.

Suggested Reading

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CHRONIC GLOMERULONEPHRITIS

Chronic GN is not a single disease entity, but comprises advanced stages of several forms of GN. In most cases, the glomerular disease is primary and not part of a systemic disorder. However, chronic GN may occur in systemic lupus erythematosus, microscopic polyarteritis, familial nephropathies and nephropathies due to drugs and toxins. Variable glomerular deposition of immunoglobulin, complement and fibrin is found on immunofluorescence studies. Renal biopsy examination in early stages shows several patterns, while later the histologic changes are nonspecific. Most glomeruli are sclerosed with corresponding tubular, interstitial and vascular changes. Poststreptococcal GN seldom leads to chronic GN.

Clinical Features

The patient may be asymptomatic and the disease detected on routine urine examination. Others may show failure to thrive, persistent anemia, moderate to severe hypertension, edema, nocturia, microscopic or gross hematuria, bone pains and deformities.

Differential Diagnosis

It might be difficult to distinguish chronic from acute GN. The presence of anemia, growth retardation, evidence of long-standing hypertension (hypertensive retinopathy, left ventricular hypertrophy) and radiological skeletal changes indicate impaired renal function of long duration. Examination of the renal biopsy is valuable in confirming the diagnosis.

Urinalysis shows proteinuria, hematuria, white cells and casts. Urine specific gravity is fixed and low (around 1010). Blood urea and creatinine levels are raised and the glomerular filtration rate less than 30 ml/min/1.73 m^2. Ultrasonography shows small kidneys with regular outline.

Management

There is no specific treatment for chronic GN. Treatment with steroids and immunosuppressive drugs does not offer any benefit. The blood pressure should be controlled and infections treated. If renal function is compromised, the treatment is that of advanced chronic kidney disease.

INTERSTITIAL NEPHRITIS

This is focal or diffuse inflammatory reaction of renal interstitium with secondary involvement of tubules and rarely, glomeruli. Acute interstitial nephritis is usually due to infections or drugs (e.g. ampicillin, cephalosporins). Common causes of chronic interstitial nephritis include urinary tract obstruction and vesicoureteric reflux. Interstitial nephritis may be a feature of a systemic disorder (e.g. systemic lupus, vasculitis, associated with uveitis); autoantibodies to tubular basement membrane are found in some cases. In many instances, no cause is determined.

The clinical features are nonspecific and include abdominal pain, anorexia, pallor, headache and edema. Hypertension is absent. The presence of progressive renal insufficiency associated with satisfactory urine output, and urinary abnormalities such as hyposthenuria and mild proteinuria suggest the diagnosis. Leukocytes and eosinophils are frequently seen in the urine, the latter a feature of drug-associated disease.

A renal biopsy establishes the diagnosis and helps assess severity. Drug-related interstitial nephritis is treated with stoppage of the offending drug; treatment with corticosteroids is beneficial. Systemic illness, if any, should be appropriately managed. The treatment of chronic interstitial nephritis is symptomatic.

Suggested Reading

Ulinski T, Sellier-Leclerc AL, Tudorache E, et al. Acute tubulointerstitial nephritis. Pediatr Nephrol 2012;27:1051–7

URINARY TRACT INFECTIONS

Urinary tract infection (UTI) is a common medical problem in children, affecting 3–10% girls and 1–3% boys. They are an important cause of morbidity and might result in renal damage, often in association with vesicoureteric reflux (VUR). Beyond infancy, the incidence of UTI is higher in girls. During infancy, UTI are equally common in boys and girls because the route of infection is often hematogenous and boys have a higher incidence of urinary tract anomalies.

Microbiology

In most cases, UTI are caused by *E. coli* that forms the predominant periurethral flora, and uncommonly by *Klebsiella, Enterobacter* and *Staphylococci epidermidis. Proteus* and *Pseudomonas* infections occur following obstruction or instrumentation, while *Candida* infection occurs in immunocompromised children or after prolonged antimicrobial therapy.

Predisposing Factors

Recurrent UTI are observed in 30–50% children, usually within 3 months of the first episode. Predisposing factors for recurrent UTI include female sex, age below 6 months, obstructive uropathy, severe vesicoureteric reflux (VUR), habitual postponement of voiding (voiding dysfunction), constipation and repeated catheterization, e.g. for neurogenic bladder. Children with malnutrition and those receiving immunosuppressive therapy are also susceptible.

Clinical Features

The clinical features depend upon the age and the severity of UTI. Neonates show features of sepsis with fever, vomiting, diarrhea, jaundice, poor weight gain and lethargy. The older infant has unexplained fever, frequent micturition and occasionally convulsions. Gross hematuria

is uncommon. The presence of crying or straining during voiding, dribbling, weak or abnormal urine stream and palpable bladder suggest urinary obstruction.

It is difficult to distinguish between infection localized to the bladder (cystitis) and upper tracts (pyelonephritis). The distinction is not necessary since radionuclide studies show that most UTI in children below 5 yr of age involve the upper tracts. Hence, all children should be managed as if they have pyelonephritis. Patients with high fever (>39°C), systemic toxicity, persistent vomiting, dehydration, renal angle tenderness or raised creatinine are considered as having *complicated UTI*. Patients with low grade fever, dysuria, frequency and urgency and absence of symptoms of complicated UTI are considered to have *simple UTI*. This distinction is important for purposes of therapy.

Important features on evaluation include history of straining at micturition, incontinence or poor urinary stream, voiding postponement and surgery for meningomyelocele or anorectal malformation. Finding of palpable kidney(s), distended bladder, tight phimosis or vulval synechiae and neurological deficit in lower limbs suggest a predisposing cause.

Diagnosis

The diagnosis of UTI is based on growth of significant number of organisms of a single species in the urine. Significant bacteriuria is defined as a colony count of $>10^5$/ml of a single species in a clean catch sample. Urine is obtained by suprapubic bladder aspiration or urethral catheterization in children below 2 yr. Any colonies on suprapubic aspiration and >50,000/ml on urethral catheterization are considered significant. The occurrence of significant bacteriuria in absence of symptoms is termed *asymptomatic bacteriuria*.

The presence of >10 leukocytes per mm^3 in fresh uncentrifuged sample, or >5 leukocytes per high power field in centrifuged sample is useful for screening. Dipstick examination, combining leukocyte esterase and nitrite, has moderate sensitivity and specificity for detecting UTI.

Treatment

Once UTI is suspected, a urine specimen is sent for culture and treatment started. *Infants below 3 months of age and children with complicated UTI should initially receive parenteral antibiotics.* The initial choice of antibiotics is empiric and is modified once culture result is available. While a third generation cephalosporin is preferred, therapy with a single daily dose of aminoglycoside is also safe and effective (Table 16.11). Once oral intake improves and symptoms abate, usually after 48–72 hr, therapy is switched to an oral antibiotic. The duration of treatment for complicated UTI should be 10–14 days. Older infants and patients with simple UTI should receive treatment with an oral antibiotic for 7–10 days. Adolescents with cystitis may receive shorter duration of antibiotics, lasting 72 hr. Patients with asymptomatic bacteriuria do not require treatment.

Table 16.11: Antimicrobials for treatment of UTI

Medication	*Dose (mg/kg/day)*
Parenteral	
Ceftriaxone	75–100, in 1–2 divided doses IV
Cefotaxime	100–150, in 2–3 divided doses IV
Amikacin	10–15, single dose IV or IM
Gentamicin	5–6, single dose IV or IM
Coamoxiclav	30–35 of amoxicillin, in 2 divided doses IV
Oral	
Cefixime	8–10, in 2 divided doses
Coamoxiclav	30–35 of amoxicillin, in 2 divided doses
Ciprofloxacin	10–20, in 2 divided doses
Ofloxacin	15–20, in 2 divided doses
Cephalexin	50–70, in 2–3 divided doses

All children with UTI are encouraged to take enough fluids and empty the bladder frequently to prevent stasis of urine. Routine alkalization of the urine is not necessary. With appropriate therapy, fever and systemic toxicity reduce and urine culture is sterile within 24–36 hr. Failure to obtain such a result suggests either lack of bacterial sensitivity to the medication or presence of an underlying anomaly of the urinary tract. A repeat urine culture is not required during or following treatment, unless symptoms fail to resolve despite 72 hr of therapy; symptoms recur, suggesting recurrent UTI, or contamination of the initial urine culture is suspected.

Imaging Studies

Following treatment of the first episode of UTI, plans are made for evaluation of the urinary tract. The aim of imaging studies is to identify urologic anomalies that predispose to pyelonephritis, such as obstruction or vesicoureteric reflux, and detect evidence of renal scarring. Renal ultrasonography is useful in detecting hydronephrosis or anomalies of the urinary bladder and may be performed even during therapy for UTI. Micturating cystourethrogram is necessary for the diagnosis and grading of VUR (Fig. 16.13) and defines urethral and bladder anatomy. This procedure may be performed 2–4 weeks after treatment of the UTI. DMSA scintigraphy detects cortical scars, which are regions of decreased uptake with loss of renal contours or presence of cortical thinning with decreased volume (Fig. 16.5A). In order to differentiate between scars and reversible changes of pyelonephritis, this procedure is done 3–4 months after therapy for UTI.

These investigations should be performed judiciously, such that sufficient evaluation is done but at minimum risks of complications, such as radiation exposure and iatrogenic infections. The recommendations of the Indian Society of Pediatric Nephrology on evaluation following the first UTI are summarized in Table 16.12. All infants (<1 yr) require evaluation using ultrasonography, MCU and DMSA scan, since they are at the highest risk of UTI

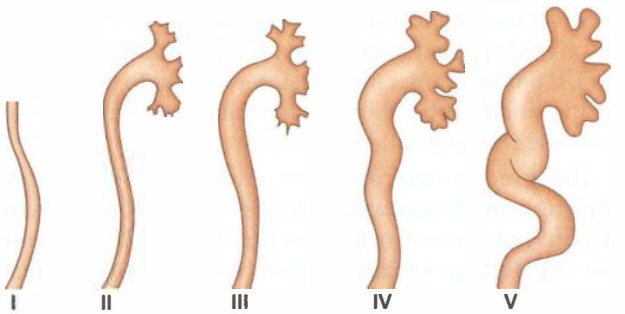

Fig. 16.13: Grading of vesicoureteric reflux (VUR) on micturating cystourethrogram. *Grade I*: VUR does not reach the renal pelvis; *Grade II*: VUR extending up to the renal pelvis without dilatation of pelvis or calyceal fornices; *Grade III*: VUR extending up to the kidney, with mild dilatation or tortuosity of the ureter and renal pelvis, and no or minor blunting of the calyceal fornices; *Grade IV*: Moderate dilatation or tortuosity of the ureter, renal pelvis and fornices, with complete obliteration of the sharp angles of the calyceal fornices, but normal appearance of the papillary impressions; *Grade V*: Gross dilatation and tortuosity of the ureter, renal pelvis and calyces, with loss of papillary impressions on calyces

recurrence and scarring. Early detection of high grade VUR or obstructive uropathy allows interventions to prevent progressive kidney damage. Imaging is less aggressive in older children, but patients with recurrent UTI require complete evaluation for anomalies.

Preventing Recurrent UTI

Prophylactic antibiotics are administered to young infants until results of imaging are available. The medication used should be effective, nontoxic with few side effects and not alter the gut flora or induce bacterial resistance (Table 16.13). The medication is given as a single bedtime dose. Longterm antibiotic prophylaxis is also recommended in patients with VUR and in those with frequent febrile UTI (3 or more episodes in a year) even if the urinary tract is normal.

Circumcision reduces the risk of recurrent UTI in infant boys, and might have benefits in patients with high grade VUR. Children with recurrent UTI and/or VUR might have dysfunctional voiding and require appropriate advice. Constipation should be managed with dietary modifications and medications as required. Some patients may require bladder retraining, anticholinergic medications and/or clean intermittent catheterization.

Table 16.12: Evaluation following the first episode of urinary tract infection

Age	*Evaluation**
Below 1 yr	Ultrasound Micturating cystourethrogram (MCU) Dimercaptosuccinic acid (DMSA) renal scan
1–5 yr	Ultrasound DMSA scan MCU, if ultrasound or DMSA scan is abnormal
Above 5 yr	Ultrasound If ultrasound abnormal: MCU and DMSA scan

*Patients with recurrent UTI need detailed evaluation with ultrasonography, DMSA scan and MCU

Table 16.13: Antimicrobials for prophylaxis of urinary tract infections

Medication	*Dose (mg/kg/day)*	*Remarks*
Cotrimoxazole	1–2 of trimethoprim	Avoid in infants <3-mo-old, glucose-6-phosphate dehydrogenase (G6PD) deficiency
Nitrofurantoin	1–2	May cause vomiting and nausea; avoid in infants <3-mo-old, G6PD deficiency, renal insufficiency
Cephalexin	10	Drug of choice in first 3–6 months of life
Cefadroxil	5	An alternative agent in early infancy

Usually given as single bedtime dose

Suggested Reading

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VESICOURETERIC REFLUX

Vesicoureteric reflux (VUR) refers to the retrograde flow of urine from bladder to ureters and pelvis at rest or during micturition. Pathogenic organisms that might be present in the bladder can gain access to the renal parenchyma, initiate inflammation and renal scarring (*reflux nephropathy*). VUR may be an isolated anomaly (primary) or associated with other anomalies of the urinary tract (secondary).

VUR is present in 30–35% of children with febrile UTI and is a major risk factor for acute pyelonephritis and reflux nephropathy. The latter may result in hypertension, renal insufficiency and cause morbidity during pregnancy.

Two techniques are commonly used to detect VUR. The radiocontrast MCU is commonly used since in addition to showing VUR it provides excellent anatomical details (Fig. 16.14). The severity of VUR is graded from I to V (Fig. 16.13). Isotope radionuclide cystography is more sensitive for detecting VUR and causes less radiation exposure but provides less anatomical details.

Management

The proposed guidelines for management of VUR are outlined in Fig. 16.15. It is recommended that patients

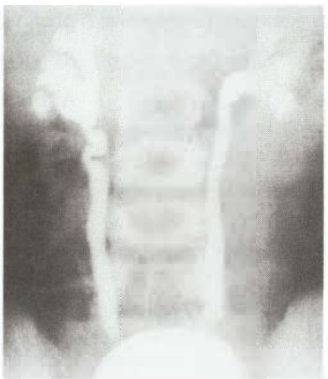

Fig. 16.14: Bilateral grade V vesicoureteric reflux in a girl with recurrent UTI. Note the dilatation, tortuosity of ureters and cupping of the calyces

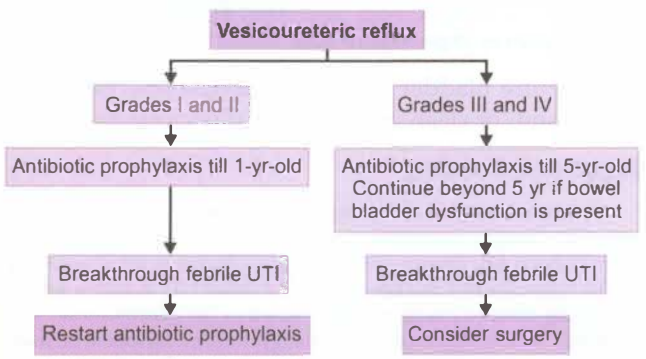

Fig. 16.15: Management of vesicoureteric reflux. Medical therapy of VUR is based on the principle that VUR resolves over time, and prophylactic antibiotics maintain urine sterility and prevent infections while awaiting spontaneous resolution. Reflux takes longer to resolve if associated with bowel bladder dysfunction or if high grade reflux is present; such patients require prolonged prophylaxis. Surgical correction of VUR is indicated if breakthrough infections occur, since significant parenchymal injury may occur with pyelonephritis

should initially receive antibiotic prophylaxis while awaiting spontaneous resolution of VUR. Continuous antibiotic prophylaxis is recommended as the initial treatment for all children with VUR since it reduces periurethral colonization and, thereby, the risk of recurrent UTI in patients with VUR. Cotrimoxazole or nitrofurantoin is given as a bedtime dose. Since the risk of recurrent UTI and renal scarring is low after 4–5 yr of age, prophylaxis may be discontinued in children older than 5 yr with normal bowel and voiding habits, even if mild to moderate reflux persists. While evidence from a few studies suggests that the strategy of prompt diagnosis and treatment of UTI might be as effective as antibiotic prophylaxis, this approach requires validation.

Other measures to be instituted include a liberal fluid intake, regular and complete bladder emptying and local toilet. Constipation should be avoided. A close followup is required for occurrence of breakthrough UTI.

The indications for surgical correction of primary VUR are limited and include poor compliance or intolerance to medical treatment. Patients with grade III to V reflux may be offered surgical repair if they have breakthrough febrile UTI, if parents prefer surgical intervention to prophylaxis, or in patients who show deterioration of renal function. Ureteric reimplantation has cure rates of 95–97%.

The precise indication for endoscopic submucosal injection of dextranomer/hyaluronic acid copolymer (Deflux) at ureteric orifices is not defined. While results are satisfactory in centers with expertise, a significant proportion of patients, particularly those with bowel bladder dysfunction, may show persistence and/or recurrence of reflux and progressive renal damage.

Followup

Repeat imaging is required after 18–36 months in patients with grade III-V VUR. Radionuclide cystogram, with lower radiation exposure and higher sensitivity, is preferred for followup evaluation. Urinalysis and measurement of height, weight and blood pressure are done annually. Urine cultures are obtained if patient has symptoms of UTI.

Screening of Siblings and Offspring

VUR is inherited in an autosomal dominant manner with incomplete penetrance; almost one-third siblings and offspring of patients show VUR. Ultrasonography is recommended to screen for presence of reflux; further imaging is performed if ultrasonography is abnormal.

Outcome

Primary VUR tends to resolve by 6–10 yr of age. Factors favoring resolution are younger age and low grade and unilateral VUR. The rate of resolution is 70–90% for grades I–III and 10–35% for higher grades.

Reflux Nephropathy

This is characterized by renal cortical scarring, predominantly at the poles. The underlying calyces lose their normal concave shape and show clubbing. Such scarring occurs early in life when the kidneys are still growing. Reflux nephropathy is an important cause of hypertension and end stage renal disease in children.

Suggested Reading

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ACUTE KIDNEY INJURY

Acute kidney injury (AKI) or acute renal failure (ARF) denotes an acute impairment of renal function resulting in retention of nitrogenous wastes and other metabolic derangements. Oliguria or anuria is a prominent feature, though rarely urine output may be normal.

Definition and Classification

In the absence of a standard definition of ARF, the term **acute kidney injury** (AKI) is proposed to reflect the entire spectrum of the disorder. Patients are diagnosed to have AKI if there is abrupt (within 48 hr) reduction in kidney function, defined as either (i) absolute increase in serum creatinine of more than or equal to 0.3 mg/dl, or a percentage increase of more than or equal to 50% from baseline, or (ii) reduction in urine output (less than 0.5 ml/kg/hr for >6 hr). The inclusion of both an absolute and a percentage change in creatinine allows for variations related to age, gender and body mass index. Table 16.14 shows a proposed method for classifying the severity of AKI.

Incidence and Etiology

The etiology of AKI is classified as prerenal, intrinsic renal or postrenal (Table 16.15). The chief causes of AKI include acute tubular necrosis (ATN) secondary to hypovolemia, sepsis and nephrotoxic agents, acute glomerulonephritis and hemolytic uremic syndrome (HUS). Postrenal failure is consequent to mechanical obstruction in the collecting system. In developing countries, common causes include septicemia with multiorgan failure, HUS, gastroenteritis with dehydration, postinfectious and crescentic GN and intravascular hemolysis. In developed countries, AKI follows major surgical procedures, HUS and severe systemic infections.

Pathophysiology

Prerenal failure is secondary to systemic hypovolemia or renal hypoperfusion, where renal tubular injury leads to marked decline in glomerular filtration and renal blood flow, often by 50 to 75%. Leakage of glomerular filtrate back into the circulation across the damaged tubular epithelium and tubular obstruction from impaction of casts and cellular debris results in oliguria. While early stages are rapidly reversible by infusion of fluids, prolonged or severe ischemia may lead to acute tubular necrosis. Nephrotoxic agents cause uniform epithelial damage, especially in the proximal tubules, without disruption of tubular basement membrane.

Table 16.15: Important causes of acute kidney injury

Prerenal failure

Hypovolemia (dehydration, blood loss, diabetic ketoacidosis)
Third space losses (septicemia, nephrotic syndrome)
Congestive heart failure
Perinatal asphyxia
Drugs (ACE inhibitors, diuretics)

Intrinsic renal failure

Acute tubular necrosis
Prolonged prerenal insult (*see* above)
Medications: aminoglycosides, radiocontrast, NSAIDs
Exogenous toxins: diethylene glycol, methanol
Intravascular hemolysis, hemoglobinuria
Tumor lysis syndrome
Hemolytic uremic syndrome: diarrhea associated (D+) and atypical (D-) forms
Glomerulonephritis (GN)
  Postinfectious GN
  Systemic disorders: SLE, Henoch-Schönlein syndrome, microscopic polyangiitis
  Membranoproliferative GN
Interstitial nephritis (drug-induced, idiopathic)
Bilateral renal vessel occlusion (arterial, venous)

Postrenal failure

Posterior urethral valves, urethral stricture
Bilateral pelviureteric junction obstruction
Ureteral obstruction (stenosis, stone, ureterocele)
Neurogenic bladder

NSAIDs nonsteroidal anti-inflammatory drugs; SLE systemic lupus erythematosus

Clinical Features

In acute tubular necrosis, examination may be normal except for dehydration. The oliguric phase lasts about 3–10 days, during which period the biochemical and clinical abnormalities gradually worsen, more rapidly if infection, trauma and bleeding are associated. Subse-

Table 16.14: Staging of acute kidney Injury (AKI), based on criteria proposed by the AKI network (AKIN)*

AKIN Stage	*Serum creatinine criteria*	*Urine output criteria*
1	Increase in serum creatinine of ≥0.3 mg/dl or ≥150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for >6 hr
2	Increase in serum creatinine to more than 200% to 300% (>2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for >12 hr
3**	Increase in serum creatinine to more than 300% (>3-fold) from baseline (or serum creatinine ≥4.0 mg/dl with acute increase of ≥0.5 mg/dl)	Less than 0.3 ml/kg per hour for 24 hr, or anuria for 12 hr

*Only one criterion (creatinine or urine output) should be fulfilled to qualify for a stage
**Patients receiving renal replacement therapy (RRT) are considered in stage 3 or F

quently urine output increases steadily. A diuretic phase may be observed, usually lasting for a week, during which large amounts of water and electrolytes, particularly potassium may be lost.

Approach to Evaluation

History provides clues to the underlying cause of AKI. It is important to examine for prerenal factors that lead to renal hypoperfusion. A history of diarrhea, vomiting, fluid or blood loss is taken and assessment of fluid intake in the previous 24 hr made. In patients with nephrotoxicity or intravascular hemolysis, urine output is often not diminished (nonoliguric renal failure).

Laboratory evaluation (Table 16.16) includes complete blood counts and estimation of blood levels of urea, creatinine, electrolytes, pH and bicarbonate and urinalysis. In prerenal azotemia, the renal tubular function is intact and reabsorption of water and sodium is increased. The urine is concentrated with low sodium content. Impaired tubular function in intrinsic renal failure results in increased sodium excretion and failure to concentrate urine. Determination of urine sodium and osmolality and fractional excretion of sodium help in differentiating functional oliguria (prerenal) from established (intrinsic) renal failure. Ultrasonography is a useful imaging tool in renal failure since it allows visualization of the pelvicalyceal system and assessment of the renal size, structural anomalies and calculi, does not depend on renal function.

Most patients with AKI do not require a renal biopsy. Indications for biopsy are: (i) rapidly progressive or nonresolving glomerulonephritis; (ii) AKI associated with underlying systemic disorder, e.g. lupus erythematosus, Henoch-Schönlein purpura; (iii) suspected interstitial nephritis; (iv) clinical diagnosis of acute tubular necrosis or HUS, if significant dysfunction persists beyond 2–3 weeks; (v) underlying cause of AKI not apparent on clinical features and investigations. Patients with severe azotemia might require dialysis prior to biopsy to reduce the risk of bleeding.

Occasionally a patient with undetected chronic kidney disease may present for the first time with acute onset of oliguria. History of previous renal disease may be present. The presence of the following suggests the possibility of chronic kidney disease: (i) retarded physical growth, (ii) severe anemia, (iii) hypertensive retinopathy, (iv) hypocalcemia, hyperphosphatemia and high parathormone, (v) radiologic features of mineral bone disease and (vi) small kidneys on imaging.

Table 16.16: Investigations in patients with acute kidney injury

Blood
Complete blood counts
Urea, creatinine, sodium, potassium, calcium, phosphate, pH, bicarbonate
Urine
Urinalysis; culture
Sodium, osmolality, fractional excretion of sodium
Chest X-ray (for fluid overload, cardiomegaly)
Abdominal ultrasonography
Investigations to determine cause
Peripheral smear examination, platelet and reticulocyte count, complement (C3), LDH levels; stool shigatoxin (suspected hemolytic uremic syndrome)
Blood ASO, C3, antinuclear antibody, antineutrophil cytoplasmic antibody (suspected acute or rapidly progressive GN)
Doppler ultrasonography (suspected arterial or venous thrombosis)
Renal biopsy (specific diagnosis feasible)

Management

Prompt clinical and laboratory evaluation is necessary. Management includes treatment of life-threatening complications, maintenance of fluid and electrolyte balance and nutritional support. Evaluation for complications includes measurement of blood pressure, search for signs of congestive heart failure, fluid overload, acidosis and anemia. Complications such as dehydration or fluid overload, hypertension, heart failure, severe anemia, hyperkalemia and acidosis require urgent treatment.

Fluid Repletion

Prerenal ARF responds to fluid replacement with improved renal perfusion and increased urine output. Dehydration is corrected by infusion of 20–30 ml/kg of normal saline or Ringer's lactate over 45–60 min. If hemorrhage accounts for vascular collapse, blood transfusion should be given. Potassium should not be administered until urine flow is established; care is taken to avoid overhydration. Patients with renal hypoperfusion, in whom the only reason for oliguria is intravascular volume depletion, respond to fluids with increase in urine output (2–4 ml/kg over 2–3 hr). Appropriate fluid therapy should be continued. However, if no diuresis occurs despite *correction of dehydration*, frusemide (2–3 mg/kg IV) may be given. If these measures fail to induce diuresis, a diagnosis of AKI is made.

Fluid Restriction

In patients with established AKI, fluid retention may result from excessive oral or parenteral fluids, and leads to edema, hypertension and heart failure. The daily fluid requirement is restricted to insensible water losses (300–400 ml/m^2), urinary output and extrarenal fluid losses. This is usually given orally; intravenous fluids are not required.

Intake-output monitoring, daily weight, physical examination and serum sodium guide fluid management. Hyponatremia usually reflects overhydration. If fluid in an appropriate volume and composition is given, the patient

should lose 0.5–1% of weight every day because of tissue breakdown. The serum sodium concentration should stay within normal range. A rapid weight loss and rising sodium suggest inadequate fluid replacement, while absence of weight loss and low serum sodium indicate fluid excess.

Diet

Patients with AKI have increased metabolic needs and are usually catabolic. Adequate nutritional support with maximization of caloric intake should be achieved as early as possible. A diet containing 1.0–1.2 g/kg of protein in infants and 0.8–1.2 g/kg in older children and a minimum of 60–80 Cal/kg is recommended. Energy requirements are met by addition of carbohydrates and fat in the diet. Vitamin and micronutrient supplements are provided. In patients with oligoanuria and fluid overload, daily caloric requirement cannot be met due to fluid restriction. Once dialysis is initiated, dietary protein, fluid and electrolyte intake should be increased.

General Measures

Patients with ARF are managed under intensive care conditions. Accurate records of intake and output and daily weight should be maintained. Urine should be collected by condom drainage; bladder should preferably not be catheterized. The risk of infection is high and appropriate preventive measures are necessary. Prophylactic antibiotics are not recommended, but infections should be promptly managed.

Drugs that increase severity of renal damage, delay recovery of renal function or reduce renal perfusion, e.g. aminoglycosides, radiocontrast media, NSAIDs, amphotericin B, ACE inhibitors and indomethacin should be avoided. Standard charts are used for modifying the dose and dosing interval of antibiotics, depending on the severity of renal injury. While diuretics may transiently improve urine output, they do not affect renal function. Their utility is limited to settings where high urine flow is required to prevent intratubular precipitation, such as with intravascular hemolysis, hyperuricemia and myoglobinuria.

Dopamine at low doses causes renal vasodilatation and may induce a modest natriuresis and diuresis. However, it has no beneficial effect on the outcome of AKI, and may be associated with transient tachyarrhythmia or tissue ischemia. Hence, its use for prevention or treatment of acute tubular necrosis is not recommended. The role of other medications, including fenoldopam, atrial natriuretic peptide, calcium channel blockers and other medications is investigational. Mannitol is not recommended for children.

Treatment of Complications

In a child with ARF, immediate attention is directed towards detection and management of life-threatening complications. Table 16.17 lists important complications and measures for their management. Children with pulmonary edema and congestive cardiac failure may

Table 16.17: Management of complications

Complication	*Treatment*	*Remarks*
Fluid overload	*Fluid restriction.* Insensible losses (400 ml/m²/day); add urine output and other losses; 5% dextrose for insensible losses; N/5 saline for urine output	Monitor other losses and replace as appropriate, consider dialysis
Pulmonary edema	Oxygen; frusemide 2–4 mg/kg IV	Monitor using CVP; consider dialysis
Hypertension	*Symptomatic.* Sodium nitroprusside 0.5–8 µg/kg/minute infusion; frusemide 2–4 mg/kg iv; nifedipine 0.3–0.5 mg/kg oral/sublingual	In emergency, reduce blood pressure by one-third of the desired reduction during first 6-8 hr, one-third over next 12–24 hr and the final one-third slowly over 2–3 days
	Asymptomatic. Nifedipine, amlodepine, prazosin, labetalol, clonidine	
Metabolic acidosis	Sodium bicarbonate (IV or oral) if bicarbonate levels <18 mEq/l	Watch for fluid overload, hypernatremia, hypocalcemia; consider dialysis
Hyperkalemia	Calcium gluconate (10%) 0.5–1 ml/kg over 5–10 minutes IV	Stabilizes cell membranes; prevents arrhythmias
	Salbutamol 5–10 mg nebulized	Shifts potassium into cells
	Sodium bicarbonate (7.5%) 1–2 ml/kg over 15 min	Shifts potassium into cells
	Dextrose (10%) 0.5–1 g/kg and insulin 0.1–0.2 U/kg IV	Requires monitoring of blood glucose
	Calcium or sodium resonium (Kayexalate) 1 g/kg per day	Given orally or rectally, can be repeated every 4 hr
Hyponatremia	Fluid restriction; if sensorial alteration or seizures 3% saline 6–12 ml/kg over 30–90 min	Hyponatremia is usually dilutional; 12 ml/kg of 3% saline raises sodium by 10 mEq/l
Severe anemia	Packed red cells 3–5 ml/kg; consider exchange transfusion	Monitor blood pressure, fluid overload
Hyper-phosphatemia	Phosphate binders (calcium carbonate, acetate; aluminum hydroxide)	Avoid high phosphate products: milk products, high protein diets

require endotracheal intubation and assisted ventilation. Severe acidosis is treated by administration of sodium bicarbonate, and, if persistent, dialysis. Patients should be monitored for fluid retention and hypertension; correction of acidosis may precipitate hypocalcemic seizures.

Factors that aggravate hyperkalemia are acidosis, which causes potassium to shift from the intracellular compartment, infection, hemolysis and tissue damage. Urgent treatment is instituted, depending on blood potassium levels and EKG changes. The benefit following medical therapy is transient and most patients with hyperkalemia secondary to ARF require dialysis.

Severe hypertension may occur with acute GN and HUS, leading to encephalopathy and heart failure. Symptoms of hypertensive encephalopathy are related to the rapidity of rise rather than the absolute value of blood pressure. Infusion of nitroprusside causes a predictable reduction in blood pressure; the rate of infusion is titrated depending on the response. Since the half-life of this drug is in minutes, it may be stopped if there is a precipitous fall in blood pressure. Frusemide is given if there are features of fluid excess. IV infusion of labetalol is as effective as sodium nitroprusside. Maintenance oral therapy is instituted using a calcium channel blocker (nifedipine, amlodepine), beta-adrenergic blocker (atenolol), or vasodilator (prazosin) alone or in combination.

Hyponatremia (sodium <130 mEq/l) usually is the result of excessive fluid administration rather than salt loss. Plasma sodium concentration >125 mEq/l is rarely symptomatic. Sodium concentration between 120–125 mEq/l may be associated with encephalopathy, lethargy and seizures. Fluid restriction is the primary mode of therapy. Treatment with hypertonic saline is reserved for those with symptomatic hyponatremia or level <115–120 mEq/l. A dose of 6 ml/kg of 3% saline (given over 30–60 min) raises serum sodium by 5 mEq/l. Hypertonic saline must be used cautiously because of complications of fluid overload and hypertension.

Infections, including respiratory and urinary tract, peritonitis and septicemia, are important causes of death. Procedures should be performed with aseptic techniques, IV lines carefully watched, skin puncture sites cleaned, and longterm catheterization of the bladder avoided.

Dialysis

AKI requiring dialysis can be managed with multiple modalities, including peritoneal dialysis, intermittent hemodialysis and continuous hemofiltration or hemodiafiltration. The purpose of dialysis is to remove endogenous and exogenous toxins and maintain fluid, electrolyte and acid base balance until renal function recovers. Indications for dialysis include persistent hyperkalemia (>6.5 mEq/l), fluid overload (pulmonary edema, severe hypertension), uremic encephalopathy, severe metabolic acidosis (total CO_2 <10–12 mEq/l) and hyponatremia (<120 mEq/l) or hypernatremia. The decision to institute dialysis should be based on assessment of the patient keeping in view the likely course of ARF. *Dialysis should begin early to prevent these complications, especially in hypercatabolic states* (e.g. extensive trauma, infections).

The choice of dialysis modality is influenced by several factors, including goals of dialysis, the advantages and disadvantages of each modality and institutional resources. It is important to assess the clinical situation and anticipate the course of ARF, depending on type and severity of renal injury.

Peritoneal dialysis. Peritoneal dialysis does not require vascular access and sophisticated equipment and is easy to perform even in neonates. It is often the initial renal replacement therapy of choice in sick and unstable infants. Peritoneal access is obtained using a stiff catheter and trocar, or a soft silastic catheter. The abdominal skin is prepared as for a surgical procedure. Dialysis fluid is infused 30–50 ml/kg, left in the peritoneal cavity for 30–60 min and then drained using siphon effect. Initially 30–40 cycles are carried out. Commercially available dialysates are lactate based and with a dextrose concentration of 1.7%. In patients with fluid overload, the concentration of dextrose is increased to 2.5–3% to facilitate ultrafiltration. The initial dialysis cycles are of short duration (20–30 min). Potassium is not added in the first 5–10 cycles, to enable correction of hyperkalemia. Later, 3–4 mEq/l potassium chloride is added to the dialysate. Patients who are sick and have severe lactic acidosis are dialyzed using a bicarbonate dialysate. The results of peritoneal dialysis are gratifying. In acute tubular necrosis, often a single dialysis is adequate. The procedure can be repeated if necessary.

The most important complication is peritonitis. Meticulous aseptic precautions will minimize its incidence. The dialysate should be examined for white cells and bacteria and cultured. Stiff catheters should be removed after 48–72 hr, beyond which the risk of infection is very high. The risk of injury to viscera and infections is considerably less with soft silastic (Tenckhoff or Cook) catheters, which therefore can be used for prolonged periods. While the standard (double-cuff) Tenckhoff catheter needs to be placed surgically, a temporary (peel away) catheter is inserted bedside. The use of an automated cycler is preferred to manual peritoneal dialysis.

Hemodialysis. Hemodialysis is efficient for correction of fluid and electrolyte abnormalities. It is expensive to institute, and requires expertise and skilled nursing. The procedure might not be suited for patients with hemodynamic instability, bleeding tendency and in young children with difficult vascular access.

The equipment required is the hemodialysis machine, pediatric dialyzer with tubings and dialysate fluid. These dialyzers are available in different sizes (0.5–1.5 m^2) and selection depends upon patient size and ultrafiltrate

properties. Vascular access is necessary for removing and returning large quantities of blood required for the procedure. This is usually achieved using a double lumen catheter inserted into the internal jugular, femoral vein or subclavian vein. Most children are maintained on a hemodialysis regimen of 3–4 hr, three times a week. Sick patients with fluid overload benefit from daily dialysis initially.

Continuous renal replacement therapies (CRRT). CRRT is any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for, or aimed at being applied for, 24 hr a day. Continuous hemofiltration provides smoother control of ultrafiltered volume and gradual correction of metabolic abnormalities in unstable patients. Special equipment and trained staff is necessary to provide CRRT in children. Various modalities include CAVH (continuous arteriovenous hemofiltration), CVVH (continuous venovenous hemofiltration), continuous venovenous hemodiafiltration (CVVHD) and slow continuous ultrafiltration (SCUF). These therapies are useful when large amount of fluids have to be removed in sick and unstable patients. CVVH is preferred modality in AKI secondary to major surgical procedures, burns, heart failure and septic shock, especially when conventional hemodialysis or intermittent peritoneal dialysis is not possible. Hemodialysis is less expensive than CRRT and is often preferred in limited resources.

Slow long extended daily dialysis (SLEDD). Sick patients often benefit from hybrid treatments that combine the advantages of CRRT and feasibility of hemodialysis. SLEDD is done daily for an extended but limited period (8–10 hr) using low dialysate flow rates and at the same time minimizing the cost and technical complexities of CRRT.

Specific Therapy

Patients with atypical HUS benefit from plasma exchanges. Immunosuppressive medications and plasma exchange are useful in dialysis dependent patients with vasculitis, crescentic GN or systemic lupus erythematosus. If interstitial nephritis is suspected, the offending agent should be withdrawn and oral corticosteroids given.

Outcome

ARF carries a mortality of 20–40%, chiefly related to the underlying etiology and duration of renal failure. Patients with septicemia and HUS with prolonged anuria are associated with poor prognosis. The outcome in crescentic GN and vasculitis depends on the severity of the renal injury and promptness in initiation of specific therapy. The outlook is satisfactory in acute tubular necrosis without complicating factors. Other factors associated with poor outcome include delayed referral, presence of complicating infections and cardiac, hepatic or respiratory failure. Maintenance of nutrition and prevention of infections is extremely crucial in improving outcome.

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Acute Renal Failure in the Newborn

Newborns are at high risk of AKI. Important causes of renal failure include: (i) perinatal hypoxemia, associated with birth asphyxia or respiratory distress syndrome; (ii) hypovolemia secondary to dehydration, intraventricular hemorrhage, heart disease and postoperatively, (iii) sepsis with hypoperfusion; (iv) delayed initiation and inadequacy of feeding in early neonatal period; (v) increased insensible losses (due to phototherapy, radiant warmers, summer heat), twin-to-twin transfusions and placental hemorrhage; (vi) nephrotoxic medications, e.g. aminoglycosides, indomethacin; maternal intake of ACE inhibitors, nimesulide; and (vii) renal vein thrombosis, e.g. in infants of diabetic mothers, severe birth asphyxia, dehydration, polycythemia and catheterization of umbilical veins. Renal failure may occasionally be the first manifestation of a congenital anomaly of the urinary tract.

Symptoms of renal failure may be insidious, including lethargy, puffiness and some decline in urine output. Oliguria may not be present. Renal vein thormobosis is suspected in at-risk neonates with hematuria, enlarging flank mass, thrombocytopenia and azotemia. Features suggestive of urinary tract obstruction include an abdominal mass, hypertension and oligoanuria.

Levels of serum creatinine and urea should be monitored in sick neonates. Renal failure is suspected in the presence of oliguria (urine output <0.5 ml/kg/hr) or blood creatinine >1.2 mg/dl. Serum creatinine levels are high at birth (reflecting maternal levels) and decrease to below 0.5 mg/dl by 5–7 days of age. Failure of reduction or rise of serum creatinine indicates impaired renal function. Urinary indices should be interpreted with caution (Table 16.18).

The principles of management are similar to that for older children. Fluid should be limited to insensible (30 ml/kg per day for full-term, 50–100 ml/kg per day for preterm neonates), gastrointestinal and renal losses. Extremely premature neonates nursed in radiant warmers require extra fluids. Systolic blood pressure more than 95–100 mm Hg may need treatment. Extra care should be taken while dialyzing these children; peritoneal dialysis is technically easier and preferred. Sudden distention of peritoneal cavity may cause respiratory embarrassment or apnea. Hypothermia should be avoided by carefully

Table 16.18: Indices to differentiate pre-renal azotemia from intrinsic renal failure

	Pre-renal azotemia	*Intrinsic renal failure*
Urinary sodium (mEq/l)	<20	>40
Urinary osmolality (mOsm/kg)	>500	<300
Blood urea-creatinine ratio	>20	<20
Urine-plasma osmolality ratio	>1.5	<1.0
Fractional excretion of sodium* (%)	<1	>3

$$*\text{FeNa (\%)} = \frac{\text{urine sodium} \times \text{serum creatinine}}{\text{serum sodium} \times \text{urine creatinine}} \times 100$$

warming the dialysis fluid. A number of drugs are dialyzable and appropriate amounts should be added to supplement for their losses.

Mortality rates for oliguric renal failure are approximately 40–50%; nonoliguric patients have a better prognosis. The outcome is related to the underlying condition unless the renal failure is prolonged beyond a few days. Infants with tubular necrosis usually show complete recovery; those with cortical or medullary necrosis regain partial function and show chronic kidney disease.

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16

HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome is a heterogeneous group of disorders that are a common cause of acute renal failure in children. They are characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency. Two broad subgroups are recognized; the first is more common, occurs in young children and is associated with shigatoxin producing enteropathogens (shigatoxin-associated HUS), whereas the second is uncommon, affects children of all ages and is associated with abnormalities of the alternative complement pathway (complement associated or atypical HUS). Atypical HUS might also be associated with pregnancy, lupus erythematosus, use of oral contraceptives and some chemotherapeutic medications, deficiency of ADAMTS13, and disorders of cobalamin metabolism.

Shigatoxin Associated HUS

Verotoxin-producing *E. coli* (in North America and Europe; most commonly with the strain O157: H7; O104:H4 in a recent epidemic) and *Shigella dysenteriae 1* (in south Asia) cause the diarrheal prodrome preceding HUS. Cytotoxin mediated injury to endothelium in the renal microvasculature leads to localized coagulation and fibrin deposition. As red cells and platelets traverse these damaged vessels, they are injured and sequestered. Though the brunt of the microvascular injury is on the kidney, other organs especially the brain may be affected. Since chiefly shigatoxins 1 and 2 are implicated, the illness is also called shigatoxin *E. coli*-related hemolytic uremic syndrome (STEC-HUS).

Atypical HUS

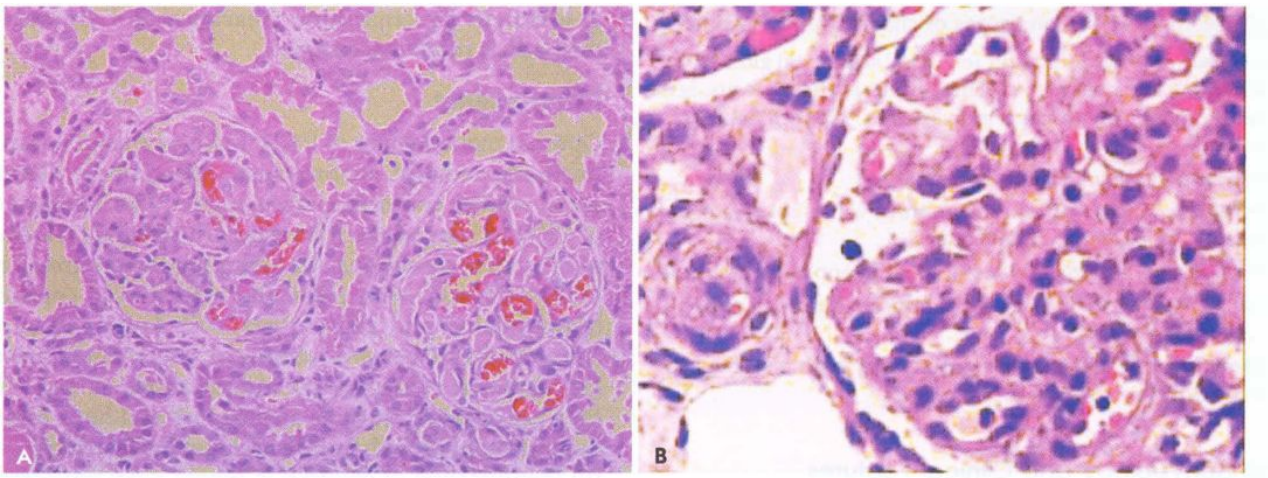
This condition, seen at any age, often lacks the prodromal history of diarrhea or dysentery, but may be triggered by minor infections. The onset may be insidious or present with a rapidly progressive illness. The microangiopathic lesions chiefly affect interlobular arteries and result in severe hypertension and progressive renal insufficiency. Predisposing factors include mutations in regulators of the complement pathway (factors H, I and B, C3, membrane cofactor protein and thrombomodulin), antibodies against complement factor H, infection with neuraminidase-producing organisms (pneumococci) or HIV, cobalamin deficiency, systemic lupus and medications (e.g. cyclosporin, mitomycin). A proportion of children with atypical HUS show presence of antibodies to factor H. Defective cobalamin metabolism leads to a severe form presenting in early infancy. Patients with thrombotic thrombocytopenic purpura (TTP) may have an inherited or acquired deficiency of a metalloproteinase with thrombospondin motifs-13 (ADAMTS13) which leads to massive platelet thrombi.

Clinical and Laboratory Features

Children less than 2–3 yr are usually affected. Following a prodrome of acute diarrhea or dysentery, patients show sudden onset of pallor and oliguria. Blood pressure may be high. Focal or generalized seizures and alteration of consciousness are common.

The blood film shows broken and distorted red cells, increased reticulocyte count and high blood levels of LDH. Coombs' test is usually negative except in *S. pneumoniae* associated HUS where the direct Coombs' test is positive. Thrombocytopenia is usually present; neutrophilic leukocytosis is seen in patients with shigellosis. Urine shows microscopic hematuria and mild proteinuria. Blood levels of urea and creatinine reflect the severity of renal failure. In patients with STEC-HUS, establishing etiology requires either stool culture or PCR for STEC or ELISA for shigatoxin. Serum complement C3 levels are low in some patients with atypical HUS and abnormalities of the complement system. Detailed analysis of components of the alternative complement pathway and its regulators is recommended in all patients with atypical HUS.

On renal biopsy, the endothelial cells are swollen and separated from the basement membrane with accumulation of foamy material in the subendothelial space (Figs 16.16A and B). The capillary lumen is narrowed by swollen endothelial cells, blood cells and fibrin thrombi. Arterioles may show similar changes. Patchy or extensive renal cortical necrosis may be present. HUS is diagnosed



Figs 16.16A and B: Features of thrombotic microangiopathy showing (A) Glomeruli showing marked endothelial swelling and capillary lumina occluded with fibrin thrombi, resulting in mesangiolysis; (B) glomerulus showing endothelial swelling and detachment, widened subendothelial space with narrowing of capillary lumina. Arteriole shows endothelial swelling and intimal hyperplasia, and platelet thrombi resulting in occlusion of the lumen

on clinical and laboratory features, and a renal biopsy is rarely required.

Treatment

Treatment includes management of complications of renal failure, treatment of hypertension and correction of anemia. Proper nutrition must be ensured. Peritoneal or hemodialysis may be necessary to prevent complications of renal insufficiency. Repeated plasma exchange with infusion of fresh frozen plasma is recommended for patients with atypical HUS. Plasma exchanges are initiated as early as possible, performed daily until hematological remission, and then less frequently. Patients with anti-factor H antibodies benefit from immunosuppression with agents that reduce antibody production. The use of eculizumab, a high affinity monoclonal antibody targeted against C5, is reported to benefit patients with HUS associated with activation of the complement cascade.

Outcome

Mortality during the acute episode of shigatoxin associated HUS is low. On followup, 20–30% patients show varying degree of residual renal damage. Factors suggestive of poor outcome include oligoanuria for more than 2 weeks, severe neurological involvement and presence of cortical necrosis. The acute and longterm outcome in atypical HUS is unsatisfactory, though the prognosis has improved with supportive measures. Recurrent episodes of HUS may occur, including in the allograft after renal transplantation.

Suggested Reading

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CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is defined as kidney damage lasting for at least 3 months, as characterized by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR). Abnormalities may include structural malformations (e.g. hydronephrosis, single kidney), pathological conditions (e.g. focal segmental glomerulosclerosis) and markers of kidney damage such as abnormal urinalysis (hematuria, proteinuria) or biochemistry (persistently increased serum creatinine). CKD is divided into 5 stages, based on level of GFR estimated from level of serum creatinine and height using the modified Schwartz formula (Table 16.19). Since renal maturation increases from infancy to reach adult values at the age of 2 yr, CKD stages apply only to children beyond >2-yr-old. Terms such as chronic renal failure and end stage renal disease are avoided. Important conditions resulting in CKD are listed in Table 16.20.

Table 16.19: Stages of chronic kidney disease (CKD)

Stage	*GFR, ml/min/1.73 m²*	*Description*
1	90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild reduction of GFR
3	30–59	Moderate reduction of GFR
4	15–29	Severe reduction of GFR
5	<15, or dialysis*	Kidney failure

* Patients on dialysis are denoted as CKD stage 5D; GFR glomerular filtration rate

Table 16.20: Common causes of chronic kidney disease

Glomerulonephritis: Idiopathic (e.g. focal segmental glomerulosclerosis); secondary (to systemic lupus erythematosus, IgA nephropathy, microscopic polyarteritis, Henoch-Schönlein purpura)
Reflux nephropathy: Primary, secondary
Obstructive uropathy: Posterior urethral valves, pelviureteric junction obstruction, renal stones
Developmental anomalies: Bilateral renal hypoplasia, dysplasia
Familial nephropathy: Nephronophthisis, Alport syndrome, polycystic kidneys
Others: Hemolytic uremic syndrome, amyloidosis, renal vein thrombosis, renal cortical necrosis

Pathophysiology and Clinical Features

The term CKD implies permanent decrease in renal function. Most children with CKD stage 1–3 (GFR more than 30 ml/min/1.73 m^2) are asymptomatic; reduction of GFR below this level is associated with symptoms. Regardless of the etiology, once there is a critical loss of nephron mass, the renal failure is progressive and manifests with similar symptoms. Loss of urinary concentrating ability results in frequent passage of urine, nocturia and increased thirst. Anemia that is usually normocytic and normochromic is chiefly due to reduced renal erythropoietin production. Mild hemolysis and blood loss from gastrointestinal tract may also contribute.

Resistance to the action of growth hormone, the levels of which are increased, is considered to be responsible for growth failure. Anorexia, malnutrition and skeletal deformities contribute to growth retardation. Abnormalities in metabolism of calcium and phosphate and bone disease results from hyperphosphatemia, lack of renal formation of 1, 25-dihydroxyvitamin D3, deficiency of calcium, chronic acidosis and secondary hyperparathyroidism.

The blood pressure may be increased and optic fundi show hypertensive retinopathy. Severe proximal muscle weakness, peripheral neuropathy, itching, purpura and pericarditis are late features. Infections are common and may acutely worsen renal function. Failure to thrive, growth retardation, anemia, hypertension and bony deformities may be the presenting features of CKD, without a previous history of renal disease.

Investigations

The patient should be investigated to find the cause of renal failure and detect reversible factors (e.g. urinary tract obstruction, UTI, severe hypertension, drug toxicity and dehydration). Appropriate imaging studies are done. Blood counts and levels of urea, creatinine, electrolytes, pH, bicarbonate, calcium, phosphate, alkaline phosphatase, parathormone, protein and albumin are obtained. Blood levels of ferritin and transferrin saturation are obtained in patients with anemia. GFR can be estimated based on serum creatinine and height; its accurate assessment by creatinine clearance or radionuclide methods is rarely necessary.

Management

Optimal management of CKD involves a team approach involving pediatric nephrologist, trained nurse, dietitian, social worker and orthopedic surgeon. The management of CKD focuses on the following principles:(i) Treatment of reversible conditions; (ii) Retarding the progression of kidney disease, with particular attention to control of hypertension and proteinuria; (iii) Anticipation and prevention of complications of CKD; (iv) Optimal management of significant complications as and when they are detected, such as anemia, mineral bone disease, malnutrition, growth failure and metabolic acidosis; and (v) Identification of children in whom renal replacement therapy (RRT) is anticipated; adequate counseling and preparation of the family for RRT.

At the initial stages, management aims at maintaining nutrition and retarding progression of the renal failure. Later, treatment of complications and renal replacement therapy in the form of dialysis or transplantation is required.

Treatment of Reversible Renal Dysfunction

Common conditions with potentially recoverable kidney function include an obstruction in the drainage, recurrent urinary tract infections with vesicoureteric reflux and decreased renal perfusion due to renal arterial stenosis. In addition, care should be taken to avoid AKI that may potentially follow the administration of nephrotoxic drugs, herbal medications and radiocontrast agents, and occur with hypoxic injury due to inadequate hydration during or following surgery.

Retarding Progression of Renal Failure

Hypertension and proteinuria lead to increased intraglomerular perfusion, adaptive hyperfiltration and progressive renal injury. Hypertension should be adequately controlled. Longterm therapy with angiotensin converting enzyme inhibitors has been shown to reduce proteinuria and may retard progression of renal failure. Recent evidence emphasizes that strict control of blood pressure to 50th to 75th centile for age, gender and height, is useful in delaying CKD progression. Children with proteinuria should be treated with an ACE inhibitor or an angiotension receptor blocker (ARB) because of their antiproteinuric effect. Therapy with lipid lowering agents and correction of anemia, shown to be useful in retarding progression of CKD in adults, may have utility in children, as well.

Diet

Careful attention to diet is essential. Recommended daily amounts of calories should be ensured. A diet high in polyunsaturated fats, such as corn oil and medium chain triglycerides and complex carbohydrates is preferred.

Water restriction is usually not necessary, except in ESRD or presence of fluid overload. Excessive use of diuretics, overzealous restriction of salt and gastroenteritis may lead to dehydration that should be corrected.

Proteins The protein intake should be 1–2 g/kg/day; proteins consumed should be of high biologic value. Restriction of protein intake is not required.

Sodium Since renal regulation of sodium reabsorption is impaired, its dietary intake needs to be individualized. Some infants are polyuric and lose large amounts of sodium requiring salt supplementation. Children with chronic glomerulonephritis retain sodium and water, which contributes to hypertension. These patients require salt and water restriction and may benefit from diuretics.

Potassium Renal regulation of potassium balance is maintained until very late, but the capacity to rapidly excrete a potassium load is reduced. Dietary items with large potassium content should be avoided.

Calcium and phosphorus Calcium supplements are given as calcium carbonate or acetate. Excessive consumption of dairy products should be avoided to restrict phosphate intake.

Vitamins Vitamins B1, B2, folic acid, pyridoxine and B12 are supplemented.

Hypertension

Hypertension in patients with proteinuria and glomerular filtration rate >30 ml/min/1.73 m^2 should preferably be treated with angiotensin converting enzyme inhibitors (e.g. enalapril). Beta-adrenergic blockers (atenolol) and calcium channel antagonists (nifedipine, amlodipine) are also effective agents; the latter are the preferred initial choice in CKD stage 4–5. Additional treatment with loop diuretics is beneficial in those with fluid overload. Patients with severe hypertension, uncontrolled with the above medications, may require additional treatment with clonidine or prazosin.

Anemia

Anemia due to reduced erythropoietin production generally develops when the GFR falls below 30 ml/min/1.73 m^2. Iron deficiency, indicated by low transferrin saturation (<20%) and elevated serum ferritin (above 100 ng/dl), is the most common underlying contributing factor. Therapy with iron (elemental iron 4–6 mg/kg per day) should be initiated if iron deficiency is detected. Subcutaneous administration of recombinant human erythropoietin allows satisfactory increase in levels of hemoglobin. The dose of erythropoietin should be adjusted to achieve target hemoglobin of 11–12 g/dl. Patients should receive iron and micronutrient supplements concomitantly. Patients on hemodialysis should receive intravenous iron supplementation. Inadequate response to erythropoietin may occur due to iron, folate or vitamin B12 deficiency, chronic infection, aluminum toxicity and severe hyperparathyroidism. Patients with hemoglobin level below 6 g/dl should receive leukocyte-poor, packed red cell transfusions. Blood should be transfused slowly, since it may aggravate hypertension and heart failure.

Infections

Urinary tract and other infections should be promptly treated with effective and least toxic drugs. The dosage of most drugs requires modification (reduction of dosage and/or increase in dosing interval), depending on the severity of renal failure.

Growth

Optimization of caloric and protein intake and treatment of mineral bone disease is important. Administration of recombinant human growth hormone improves growth velocity in children with chronic renal failure. Early recognition and management of malnutrition, mineral bone disease, metabolic acidosis and electrolyte disturbances should take precedence over the institution of therapy with growth hormone. The goal of therapy is to achieve the patient's genetic height potential. The high cost of this treatment, however, limits its use.

Mineral Bone Disease

Mineral bone disease is a serious problem in children as it occurs during the period of active growth (Fig. 16.17). Its prevention and adequate treatment is crucial. The proximal nephron is the chief site of synthesis of 1,25-dihydroxyvitamin D3 (calcitriol), the most potent

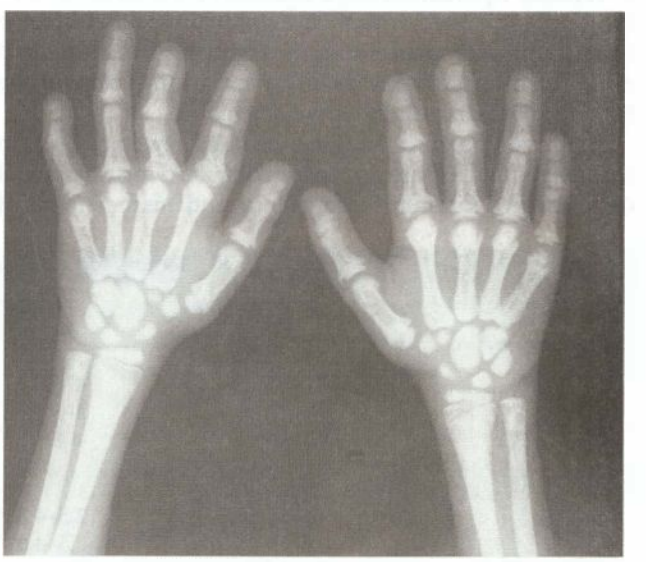

Fig. 16.17: Mineral bone disease associated with hyperphosphatemia and secondary hyperparathyroidism in a 12-yr-old girl on chronic hemodialysis. Note the osteopenia and bone resorption in terminal phalanges of the fingers

metabolite of vitamin D. Its decreased production is an important factor in the pathogenesis of secondary hyperparathyroidism in CKD. Recent studies have also shown a high incidence of vitamin D deficiency among children with CKD. With reduction of renal function, phosphate balance is initially maintained by its increased excretion from the normal nephrons. However, when the GFR falls below 25%, blood phosphate levels rise.

The symptoms are vague and nonspecific. Bone pain, muscle weakness, growth retardation and skeletal deformities are prominent. Blood examination shows hypocalcemia, hyperphosphatemia and raised levels of alkaline phosphatase and parathyroid hormone. X-rays reveal metaphyseal changes suggestive of rickets. Radiologic features of secondary hyperparathyroidism are initially seen in the phalanges and clavicles.

The goals of early intervention are to maintain normal bone mineralization and growth, avoid hyperphosphatemia and hypocalcemia, and prevent or reverse increased PTH secretion. Treatment is based on dietary restriction of phosphate, and administration of phosphate binders and vitamin D. Recommended values targeted in different stages of CKD are provided in Table 16.21. When serum phosphate exceeds the target range, phosphate containing dietary articles (e.g. dairy products) are restricted. Blood phosphate levels should be maintained in the normal range using oral phosphate binders. Calcium carbonate or acetate, 0.5–1 g/day with meals, reduces intestinal absorption of phosphate. The renal excretion of aluminum, in children with renal failure, is poor; its accumulation may increase the risk of bone disease and aluminum-related encephalopathy. Prolonged administration of aluminum hydroxide as a phosphate binder is therefore avoided. Sevelamer hydrochloride, a calcium and aluminum free ion-exchange resin which binds phosphorus within the intestinal lumen preventing its absorption, is a safe and effective alternative to calcium containing phosphate binders, with no risk of hypercalcemia.

The first steps in managing elevated levels of PTH in children with CKD are correction of underlying nutritional deficiency of vitamin D deficiency and management of hyperphosphatemia. If the PTH still remains elevated after these measures, therapy with activated vitamin D should be started. Vitamin D analogs with short half-life are preferred. Medications that may be used include calcitriol (20–50 ng/kg/day) or 1α-hydroxy D3 (25–50 ng/kg/day). Excessive vitamin D intake may cause hypercalcemia, hypercalciuria and elevation of calcium phosphorus product, which should be monitored.

Osteotomy may be required to correct bony deformities.

Immunization

Children with CKD have relatively poor immunity and hence it should be ensured that these children receive all routine immunizations. Apart from the regular immunization, children with CKD should also receive vaccines against pneumococcal, chicken pox and hepatitis A and B infections, especially if prepared for transplantation. Immunization is scheduled so as to complete live vaccinations prior to transplantation. Primary as well as booster doses of inactivated vaccines can be given 6 months after transplant.

Longterm Care

The rate of progression of chronic renal injury is variable. In some disorders (e.g. hemolytic uremic syndrome, crescentic GN), stage V CKD is present within few weeks or months. In others (e.g. reflux nephropathy and some forms of chronic GN), the decline in renal function is slow. Patients showing a rapid deterioration of renal function should be evaluated for potentially reversible complications (infection, urinary outflow obstruction, fluid loss, hypertension and use of nephrotoxic drugs).

Suggested Reading

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Table 16.21: Targets for laboratory markers of mineral bone disease

	*Calcium, mg/dl**	*Phosphorus, mg/dl*	*Ca × P product*	*SAP, IU/dl*	*PTH, pg/ml*
Age 1–12 yr					
CKD 2–3	9.0–10.2	4–6	100–450	<65	35–70
CKD 4	9.0–10.2	4–6	100–450	<65	70–110
CKD 5, 5D	8.8–9.7**	4–6	100–450	<65	200–300
Age >12 yr					
CKD 2–3	8.8–10.2	2.5–4.5	40–180	<55	35–70
CKD 4	8.8–10.2	2.5–4.5	40–180	<55	70–110
CKD 5, 5D	8.8–9.7**	3.5–5.5	40–180	<55	200–300

SAP serum alkaline phosphatase; PTH parathormone; CKD chronic kidney disease

*In patients with hypoalbuminemia, corrected calcium (mg/dl) = observed calcium + 0.8 × [4 – albumin g/dl]

** Hypercalcemia is defined as blood level >10.2 mg/dl

RENAL REPLACEMENT THERAPY

Preparation of a child for end stage care should be discussed in advance with the family members. The financial resources and the family support available should be addressed. Initiation of dialysis should be considered when the glomerular filtration rate (GFR) falls below 12 ml/min/1.73 m^2 body surface area and is strongly recommended when the GFR is <8 ml/min/1.73 m^2. The well-being of the patient is more important than the estimated GFR for deciding when dialysis should be started. The presence of fluid overload, hypertension, gastrointestinal symptoms, growth retardation and neurological consequences of uremia influence the decision to initiate RRT.

The different forms of renal replacement therapy are chronic peritoneal dialysis, hemodialysis and renal transplantation. In children with stage V CKD (ESRD), transplantation is the desired form of therapy. While chronic dialysis is life sustaining, it is inferior to renal transplantation in providing adequate renal replacement. Transplantation is associated with significant survival advantage, decreased risks of hospitalization and improved quality of life.

Chronic Peritoneal Dialysis (PD)

Chronic PD is done through a Tenckhoff catheter tunneled through the abdominal wall into the peritoneum. Chronic PD can be done manually (ambulatory PD) or with the help of an automatic cycler (cyclic PD). The duration of dialysis is usually 10–12 hr a day during which 4–6 cycles are performed. Chronic PD is preferred to chronic hemodialysis since it is done at home, without the need for hospital visits. Patients on chronic PD have less restriction on fluid and caloric intake; control of hypertension is better and hematocrit is maintained. The success of chronic PD, however, relies upon the motivation of families to carry out the procedure.

Chronic Hemodialysis (HD)

HD is mostly carried out in the hospital setting. These children require vascular access either an arteriovenous fistula or graft, or a double lumen indwelling catheter in a central vein (e.g. internal jugular, femoral or subclavian vein). Dialysis is done for 3–4 hr/session, with a frequency of 3 sessions/week. During a hemodialysis session, blood is circulated through an extracorporeal circuit that includes a hollow fiber dialyzer (artificial kidney) (Fig. 16.18). Anticoagulation of the circuit is achieved by systemic heparinization. The procedure requires technical expertise and need for continuous monitoring.

Renal Transplantation

The feasibility and efficacy of renal transplantation as standard therapy for ESRD in children is well established. Advances in surgical skills, availability of better immunosuppressive medications and ability to prevent and treat infections, has improved the short- and longterm outcome. The usual immunosuppressive therapy is a combination of a calcineurin inhibitor (cyclosporin or tacrolimus), purine synthesis inhibitor (azathioprine or mycophenolate mofetil) and prednisolone. Longterm allograft survival is better with live compared to deceased donors. Following successful renal transplantation the child can lead a normal life and resume physical activity and schooling. The allograft survival varies between 10 and 17 yr.

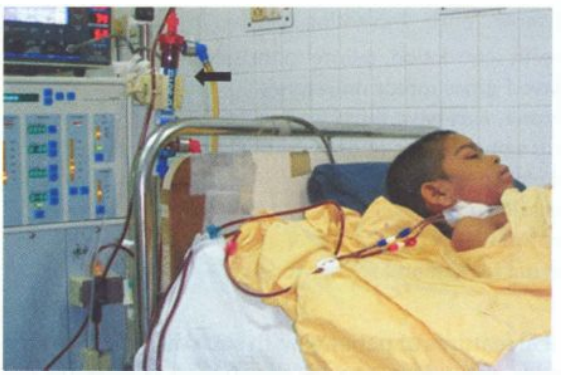

Fig. 16.18: Hemodialysis in a patient with end-stage renal disease. Note the vascular access through a catheter in the internal jugular vein, hemodialysis machine and the dialyzer (solid arrow)

Suggested Reading

Auron A, Brophy PD. Pediatric renal supportive therapies: the changing face of pediatric renal replacement approaches. Curr Opin Pediatr 2010;22:183–8

Certain conditions have a high risk of recurrence in the renal allograft, such as membranoproliferative glomerulonephritis type II, focal segmental glomerulosclerosis and atypical hemolytic uremic syndrome

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Transplantation offens survival advantage and improved quality of life

DISORDERS OF RENAL TUBULAR TRANSPORT

In comparison to glomerular diseases, tubular disorders are less common. Early and correct diagnosis is essential since specific management is possible in many cases. The diagnosis of a *primary* tubular disorder implies that there is no significant impairment of glomerular function or tubulointerstitial inflammation. A tubular disorder may be congenital or acquired and involve a single function of a tubule (renal glucosuria, nephrogenic diabetes insipidus) or multiple functions (Fanconi syndrome).

Initial Evaluation

Children with primary defects in tubular function usually present during infancy. Table 16.22. shows important

Table 16.22: Presenting features in tubular disorders

Growth retardation, failure to thrive
Delayed gross motor milestones
Polyuria, excessive thirst
Recurrent episodes of dehydration, vomiting, fever
Rickets, bone pains
Episodic weakness
Constipation
Craving for salt and savory foods

clinical features of patients with such disorders. Most renal tubular disorders can be diagnosed following careful interpretation of urine and plasma biochemistry, and tests useful in arriving at a diagnosis are listed in Table 16.1.

Renal Tubular Acidosis (RTA)

RTA encompasses conditions characterized by a defect of renal acidification, which result in hyperchloremic metabolic acidosis and inappropriately high urine pH. Defects in tubular transport result in reduced proximal tubular reabsorption of bicarbonate (HCO_3^-), the distal secretion of protons (hydrogen ion, H^+) or both, leading to impaired capacity for net acid excretion and persistent hyperchloremic metabolic acidosis. The plasma anion gap [$Na^+ - (Cl^- + HCO_3^-)$] is in the normal range (8–12 mEq/l). The renal function is normal or only mildly impaired. Two main forms are recognized: distal RTA (type 1) and proximal RTA (type 2). Another variety (type 4) distinguished by the presence of hypoaldosteronism and hyperkalemia is less common in children. The above conditions are either secondary to other causes or primary, with or without known genetic defects.

Distal RTA

Distal (type 1) RTA is due to defective secretion of H^+ in the distal tubule, in the absence of significant decrease in glomerular filtration rate. Patients with distal RTA are unable to excrete ammonium (NH_4^+) ions adequately, and the urine pH cannot reach maximal acidity (i.e. remains >5.5) despite acidemia, indicating low H^+ concentration in the collecting duct. Hypokalemia is caused by increased urinary losses of potassium and aldosterone stimulation by urinary Na^+ loss and volume contraction, leading to further increase in tubular K^+ secretion.

The condition is often sporadic, but may be inherited (dominant, recessive or X-linked). Important forms are listed in Table 16.23. The disease may be associated with systemic diseases (systemic lupus erythematosus, Wilson disease) or secondary to renal disease (obstructive uropathy, reflux nephropathy) or drug toxicity (lithium, analgesics, amphotericin B).

Presenting features. Children present with failure to thrive, polyuria, polydipsia, hypokalemic muscle weakness and rickets. Ultrasonography may show nephrocalcinosis (Fig. 16.19). Patients with incomplete forms of distal RTA may present with nephrolithiasis or incidentally detected nephrocalcinosis.

Diagnosis. Biochemical abnormalities include hyperchloremic metabolic acidosis, hypokalemia, increased urinary excretion of calcium and decreased urinary citrate. Urinary net acid excretion (titratable acid and ammonium) is markedly reduced. Despite moderate to severe acidosis, patients cannot lower urine pH below 5.3. Measurement of the difference between urinary and blood CO_2, during

Table 16.23: Inherited forms of renal tubular acidosis (RTA)

Type of RTA	*Associated disorders*
Type 1 (distal)	Hemolytic anemia Early hearing loss Normal hearing; delayed hearing loss
Type 2 (proximal), isolated	Ocular abnormalities (band keratopathy, cataracts, glaucoma); defective dental enamel; intellectual impairment; basal ganglia calcification
Type 2, Fanconi syndrome	Dent disease Cystinosis Tyrosinemia type 1 Fanconi Bickel Wilson disease Galactosemia Hereditary fructose intolerance Lowe syndrome Glycogen storage disease type I Mitochondrial disorders
Type 3 (combined)	Osteopetrosis; blindness, deafness
Type 4 (hyperkalemic)	Congenital adrenal hyperplasia Pseudohypoaldosteronism (PHA) PHA type 2, Gordon syndrome

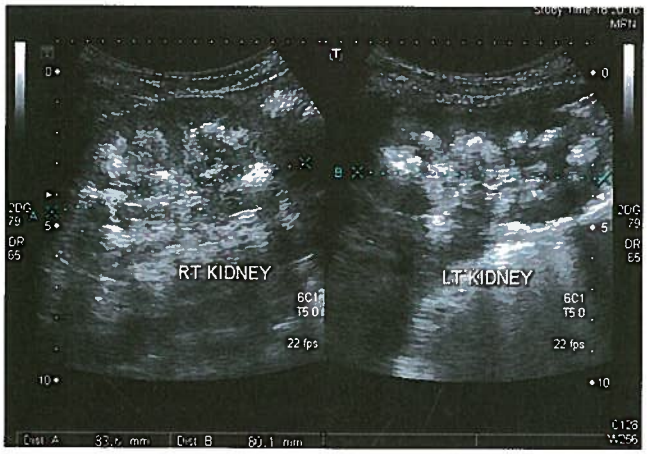

Fig. 16.19: Medullary nephrocalcinosis. Ultrasonography in a 3-yr-old boy with distal renal tubular acidosis shows hyperechoic medulla

the passage of alkaline urine, is a reliable indicator of distal tubular acidification. Normally the difference is more than 20 mm Hg, provided the urine pH is >7.5. In children with distal RTA, the urine to blood CO_2 gradient is reduced below 10 mm Hg. Table 16.24 shows useful tests for the evaluation of patients with RTA. Hearing evaluation should be performed in all patients with idiopathic distal RTA.

Patients with incomplete forms of distal RTA show normal levels of serum pH and bicarbonate. The defect in distal acidification can be demonstrated by the fludrocortisone frusemide test. Hypercalciuria and hypocitraturia are associated.

Treatment. Hypokalemia should be treated before correction of acidosis. Acidosis is treated by administration of sodium bicarbonate (initially 2–3 mEq/kg in divided doses); the dose of alkali can be increased until the blood bicarbonate level is normal. Alkali requirements decrease beyond 5 yr of age. Treatment of acidosis reduces potassium losses and promotes growth and healing of rickets. Some patients require prolonged potassium replacement. Vitamin D supplements are not required. If hypercalciuria persists, administration of thiazides is necessary.

Proximal (Type 2) RTA and Fanconi Syndrome

Proximal RTA is due to reduced proximal tubular reabsorption of bicarbonate, so that marked bicarbonaturia is found at normal levels of plasma bicarbonate. Once the plasma bicarbonate falls below 16 mEq/l, it is mostly reabsorbed. At steady state, daily acid loads are excreted successfully and the distal acidification mechanism is intact. Thus, children with proximal RTA have less severe acidosis than distal RTA.

Pathophysiology. The primary defect in proximal RTA is reduced renal threshold for bicarbonate, resulting in bicarbonaturia. Proximal RTA may represent isolated or generalized proximal tubular dysfunction (Table 16.23). The latter, termed Fanconi syndrome, is characterized by tubular proteinuria and aminoaciduria and variable degrees of bicarbonaturia, phosphaturia, electrolyte wasting and glucosuria. Fanconi syndrome may be (i) idiopathic, or secondary to (ii) a metabolic disorder (cystinosis, galactosemia, tyrosinemia, Lowe syndrome, fructosemia, some forms of glycogen storage disease, Wilson disease and mitochondrial disorders), (iii) drugs (ifosfamide, aminoglycosides, cisplatin), (iv) toxins (cadmium, lead, mercury) and (v) tubulointerstitial nephritis.

Clinical features. Failure to thrive and physical retardation are the chief clinical features. Irritability, anorexia and listlessness may be present. Rickets is rare in isolated proximal RTA but common in Fanconi syndrome. Those with secondary Fanconi syndrome may have features of the underlying disorder. Nephrocalcinosis and urolithiasis are not seen. Symptoms related to hypokalemia (weakness, paralysis) are uncommon.

Diagnosis. Table 16.24 shows the features that allow proximal RTA to be distinguished from other forms of RTA. The blood pH and HCO_3^- levels are low and urine

Table 16.24: Investigations to differentiate types of renal tubular acidosis (RTA)

	Proximal RTA	*Classic distal RTA*	*Type 4 RTA*
Plasma potassium	Normal or low	Normal or low	High
Urine pH	<5.5	>5.5	<5.5
Urine anion gap	Positive	Positive	Positive
Urine ammonium	Low	Low	Low
Fractional bicarbonate excretion	>10–15%	<5%	>5–10%
U-B PCO_2 mm Hg	>20	<20	>20
Urine calcium	Normal	High	Normal or low
Other tubular defects	Often present	Absent	Absent
Nephrocalcinosis	Absent	Present	Absent
Bone disease	Common	Often present	Absent

U-B PCO_2 urine to blood PCO_2 gradient

pH relatively alkaline. However if the blood HCO_3^- falls below 14–16 mEq/l, urine pH falls to <5.5. Urinary calcium and citrate excretion is normal. Demonstration of its high fractional excretion of bicarbonate (>15%), following bicarbonate infusion to raise the plasma bicarbonate level above 22 mEq/l, is confirmatory.

Evaluation of other proximal tubular functions is essential. This includes an assessment of phosphate excretion and evaluation for aminoaciduria, glucosuria and low molecular weight proteinuria. Estimation of calcium excretion and examination for rickets is important. Disorders that are associated with Fanconi syndrome should be screened for, including cystinosis, Lowe syndrome, galactosemia and Wilson disease.

Treatment. The correction of acidosis requires administration of 5–20 mEq/kg of alkali daily. Part of the alkali is replaced as potassium citrate. Since administration of large amounts of alkali result in bicarbonate wasting, it is prudent to give a modest amount of sodium bicarbonate (5–8 mEq/kg/day in divided doses) along with restriction of dietary sodium. The latter causes contraction of extracellular fluid volume and increased proximal bicarbonate reabsorption. Administration of hydrochlorothiazide has a similar effect. Children with Fanconi syndrome also need supplements of phosphate (neutral phosphate, Joulie solution). Treatment with vitamin D is necessary in children with rickets.

16

Cystinosis

This autosomal recessive disorder presents in infancy with features of severe Fanconi syndrome. The underlying defect is in the lysosomal membrane protein (cystinosin) that transports cystine from lysosomes into the cytosol. This leads to very high levels of free lysosomal cystine, which is deposited as crystals in the cornea, conjunctiva, bone marrow, leukocytes and lymph nodes. Tubular handling of cystine is normal. The most common form of cystinosis is the infantile nephropathic form in which patients present in early infancy. Later, patients may be noted to have photophobia and enlarged liver and spleen; some have blond hair.

In most patients, diagnosis is indicated by the presence of cystine crystals in cornea on slit lamp microscopy (Fig. 16.20). Confirmation depends on demonstration of elevated levels of cystine in polymorphonuclear leukocytes or cultured fibroblasts. Prenatal diagnosis is possible, and requires measurement of cystine level in chorionic villi or cultured amniotic fluid cells.

Correction of metabolic acidosis and replacement of electrolytes is an essential part of management. Early initiation of treatment with oral cysteamine may retard progression of systemic disease. Topical therapy is essential to prevent corneal deposits, since oral treatment is ineffective. Longterm complications include hypothyroidism and diabetes mellitus. If untreated, most patients show progression to end stage renal failure by late childhood.

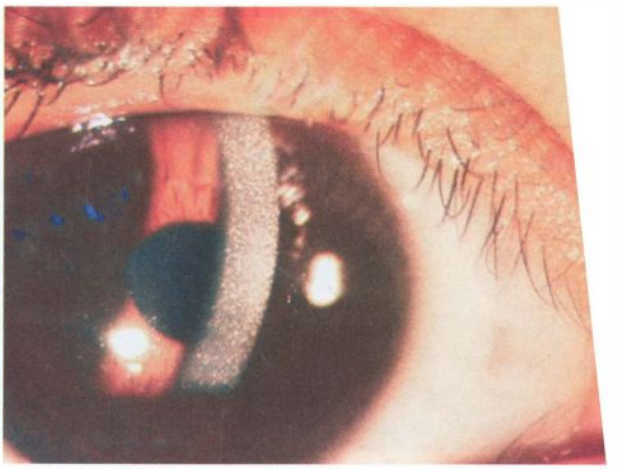

Fig. 16.20: Slit lamp examination of the cornea in a 4-yr-old girl wi cystinosis; diffuse crystal deposition is noted

Lowe Syndrome

This X-linked condition presents within the first few months of life with Fanconi syndrome, severe rickets, ocular defects (congenital cataracts, buphthalmos, corneal degeneration, strabismus), neonatal or infantile hypotonia, rickets, seizures, developmental delay and mental impairment. Hypercalciuria may be prominent. Diagnosis is confirmed by either mutational analysis of the affected gene (*OCRL*) or measurement of the activity of the enzyme (phosphatidylinositol bisphosphate 5-phosphatase) in cultured fibroblasts. Chronic tubular injury leads to glomerulosclerosis and slowly progressive chronic renal insufficiency. Most children die in early childhood.

Hyperkalemic (Type 4) RTA

Hyperkalemia with distal RTA occurring due to aldosterone resistance or deficiency is termed type 4 RTA. Aldosterone directly stimulates the proton pump, increases Na^+ absorption resulting in negative intratubular potential and increases urinary K^+ losses, and stimulates basolateral Na^+/K^+ ATPase. Hence, aldosterone deficiency or resistance is expected to cause hyperkalemia and acidosis. Maximally acidic urine (<5.5) can be formed, indicating the ability to establish a maximal H^+ gradient. However, the rate of ammonium excretion is low. Aldosterone deficiency without renal disease may occur with Addison disease, or following adrenal necrosis or tuberculosis. Aldosterone resistance may occur with chronic renal insufficiency such as obstructive uropathy or interstitial nephritis or with use of certain drugs (e.g. amiloride, spironolactone, ACE inhibitors, heparin, NSAIDs, calcineurin inhibitors).

Clinical features are not distinctive. Nephrocalcinosis and urolithiasis are absent and bone lesions are rare. In

children, aldosterone unresponsiveness is more common than aldosterone deficiency and is commonly associated with obstructive uropathy. The autosomal recessive form of pseudohypoaldosteronism (PHA type 1) should be considered in infants presenting with salt loss, hypotension, hyperkalemia and metabolic acidosis. Patients with PHA type 2 have hypertension, acidosis and hyperkalemia with hyporeninemic hypoaldosteronism.

Diagnostic workup should include ultrasound to identify structural abnormalities and renal function tests for parenchymal dysfunction. Measurement of plasma renin activity and aldosterone levels are necessary. The transtubular potassium gradient (TTKG) is useful in diagnosing type 4 RTA. It is calculated as follows:

$$\text{TTKG} = \frac{\text{urine } K^+ \times \text{plasma osmolality}}{\text{plasma } K^+ \times \text{urine osmolality}}$$

In patients with hyperkalemia, inappropriately low TTKG (<8) suggests hypoaldosteronism or tubular resistance to aldosterone. Following administration of fludrocortisone, TTKG rises to above 7 in patients with hypoaldosteronism, but not in those with aldosterone resistance.

Nephrogenic Diabetes Insipidus

Congenital nephrogenic diabetes insipidus is an inherited disorder of water reabsorption, caused by resistance to the action of ADH on its receptor. Absorption of water in the distal tubules and collecting ducts is significantly impaired. The defect usually involves the arginine vasopressin V2 receptor (*AVPR2*) gene on the X chromosome. Less commonly, the disease is inherited in an autosomal recessive manner due to mutations in genes encoding the aquaporin 2 channels.

The usual history is of a boy who, within a few weeks of life, shows failure to thrive, excessive thirst, recurrent episodes of dehydration and unexplained fever. The infant continues to have increased or normal urine output even when dehydrated. Constipation is common. Polyuria, polydipsia and nocturnal enuresis are striking in older children. Recurrent episodes of dehydration and rapid rehydration may lead to neurological injury with intracranial calcification, seizures and psychomotor dehydration.

Hypernatremia (serum sodium often more than 170 mEq/l), with low urine sodium is characteristic. Correspondingly, serum chloride and osmolality are high. The urine osmolality is inappropriately low (usually below 150–200 mOsm/kg) for the elevated plasma osmolality. Further, urine osmolality does not increase despite administration of DDAVP. This allows nephrogenic diabetes insipidus to be differentiated from deficiency of the ADH (central diabetes insipidus). The latter show normal response to DDAVP with increase in urine osmolality to more than 600–800 mOsm/kg. Tubular unresponsiveness to ADH may also occur as part of chronic pyelonephritis, obstructive uropathy, sickle cell disease, lithium toxicity, hypercalcemia, hypokalemia and tubulointerstitial disease. A DMSA scan may be useful in detecting subtle renal scars.

Treatment consists of increased fluid intake and sodium restriction to reduce the osmolar load. Administration of hydrochlorothiazide (2–3 mg/kg/day), alone or in combination with amiloride (20 mg/1.73 m^2/day), reduces polyuria and leads to clinical improvement. Indomethacin may also reduce urine volume, but its use is limited beyond infancy.

Renal Glucosuria

Renal glucosuria is an autosomal recessively transmitted, isolated defect of tubular glucose transport. It is recognized by the presence of glucose in the urine, despite normal blood glucose levels. Glucose metabolism and other renal tubular transport mechanisms are normal. Several members of a family may be affected. The disorder is asymptomatic and benign, and does not require treatment.

Type A defects are characterized by generalized decrease in capacity of tubules to reabsorb glucose, and a low tubular maximum for glucose. In type B defects, the tubular maximum for glucose is normal, but the capacity of individual nephrons to reabsorb glucose is affected variably. In type O defects, there is no tubular reabsorption of glucose.

Bartter Syndrome

Bartter syndrome is an autosomal recessive disorder characterized by hypokalemia and metabolic alkalosis, resulting from excessive chloride, potassium and sodium wasting in the thick ascending limb of the loop of Henle. Clinical features include failure to thrive, polyuria, polydipsia and recurrent episodes of dehydration. Vomiting, constipation, muscle weakness and cramps are other manifestations. Patients show marked hypokalemia with high urinary potassium and hypochloremic metabolic alkalosis. Volume contraction leads to increase in levels of plasma renin and aldosterone. Elevated urinary levels of chloride (>20–30 mEq/l) are characteristic.

Several subtypes of Bartter syndrome are recognized, differing in their molecular basis and clinical severity. The condition may occasionally present in the neonatal period with history of maternal polyhydramnios and postnatal polyuria, dehydration and nephrocalcinosis; some have sensorineural deafness.

Bartter syndrome should be differentiated from other conditions with persistent hypokalemic metabolic alkalosis (e.g. cystic fibrosis, recurrent vomiting, inherited forms of hypertension and Gitelman syndrome) by the presence of normal blood pressure and high urinary chloride and calcium excretion.

Therapy is directed towards replacement of urinary losses of fluid, sodium, potassium and chloride. Most

patients require supplements of potassium chloride (1–3 mEq/kg/day). Despite supplementation, serum potassium rarely returns to normal range. Use of prostaglandin synthase inhibitors (indomethacin 2–3 mg/kg/day or ibuprofen 20–30 mg/kg/day) is beneficial. Potassium sparing diuretics and ACE inhibitors have been used with modest benefit in correcting hypokalemia.

Gitelman Syndrome

Hypokalemia, hypomagnesemia and metabolic alkalosis may be caused by Gitelman syndrome, an autosomal recessive condition characterized by a defect in the apical thiazide sensitive sodium chloride cotransporter (NCCT) in the distal tubules. Clinical and laboratory features are milder than in Bartter syndrome. Patients present in adolescence or adulthood, with episodes of muscle weakness, cramps, tetany, vomiting or fatigue. Polyuria and failure to thrive are less pronounced.

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NEPHROLITHIASIS AND NEPHROCALCINOSIS

Renal calculi are uncommon in children and occur usually in the setting of an underlying metabolic abnormality. Symptoms include dysuria, hypogastric pain, hematuria and occasionally urinary infections. Nephrocalcinosis refers to formation of crystalline deposits within the renal parenchyma, presenting as enhanced renal echogenicity, which may be cortical, medullary or diffuse. Table 16.25 lists common underlying metabolic causes. Urinary tract infection, particularly with urease producing organisms like *Proteus, Staphylococcus* and *Pseudomonas* spp. favor precipitation of magnesium ammonium phosphate and calcium phosphate (struvite stones). Progressive renal impairment may occur in patients with nephrocalcinosis, untreated obstruction or recurrent UTI.

Evaluation

Ultrasonography detects most radiopaque and radiolucent calculi and nephrocalcinosis. High resolution computerized tomography detects even minute calculi. Plain radiographs and intravenous pyelography are rarely required; the latter is useful only if suspecting radiolucent or low density stones (uric acid, xathine), duplex system or obstruction, particularly in a young child where performing CT would necessitate sedation. However, high resolution ultrasonography may overdiagnose nephrocalcinosis, particularly in newborns where physiologically increased echogenicity or deposition of Tamm-Horsfall protein is mistaken for medullary nephrocalcinosis.

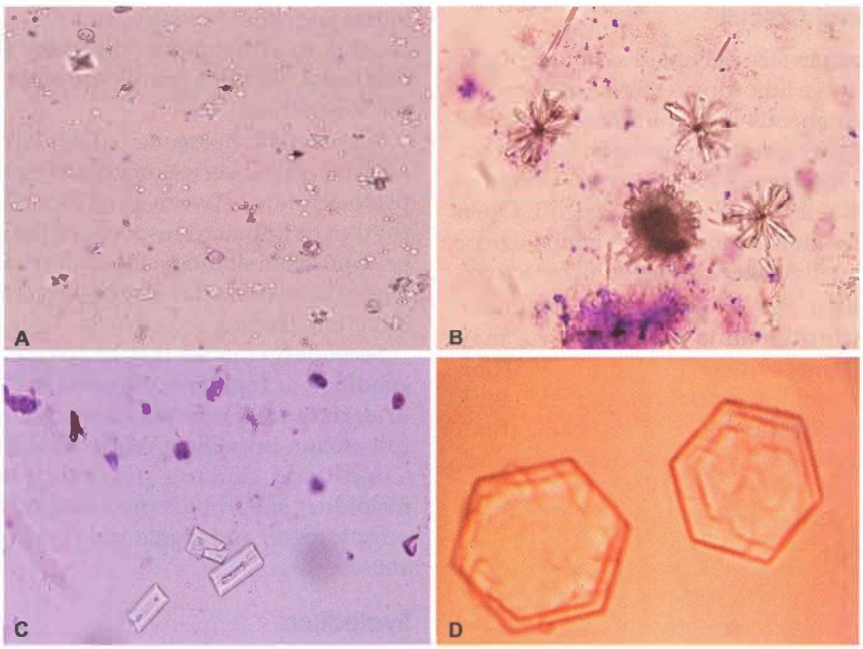
Table 16.25: Underlying metabolic abnormalities in children with nephrolithiasis or nephrocalcinosis

Hypercalciuria with hypercalcemia
Vitamin D overdose
Primary hyperparathyroidism
Production of PTH related peptide (malignancy, sarcoidosis)
Hypercalciuria with normal serum calcium
Idiopathic hypercalciuria
Familial hypophosphatemia with hypercalciuria
Dent's disease
Bartter syndrome with/without sensorineural deafness
Autosomal dominant hypocalcemic with hypercalciuria
Familial hypomagnesemia, hypercalciuria and nephrocalcinosis
Lowe syndrome
Frusemide use
Miscellaneous causes
Distal renal tubular acidosis (hypocitric aciduria and hypercalciuria)
Primary hyperoxaluria, type I, type II
Cystinuria
Abnormal purine, pyrimidine metabolism: Lesch-Nyhan syndrome, glycogenosis type 1, xanthinuria
Melamine toxicity

Investigations aiming at detecting abnormalities show a metabolic cause in 50–75% patients. Initial investigations should include renal functions tests, blood levels of calcium, phosphorus, uric acid, pH and bicarbonate. Detection of specific crystals in the urine may suggest an etiology (Figs 16.21A to D). High (>5.5) urine pH in first morning sample suggests defective tubular acidification. Quanti-fication of calcium, oxalate and uric acid in timed urine collections evaluates excretion of solutes as compared to normal inidividuals. Alternatively, solute excretion is expressed as a ratio to urinary creatinine in spot samples. Patients with hypercalciuria require evaluation for hypercalcemia (intact PTH, 25-hydroxyvitamin D) and for association with partial form of distal renal tubular acidosis, hypomagnesemia, hypophosphatemic rickets and abnormalities of the thyroid hormone. Where available, stone analysis is performed using X-ray diffraction or near red spectroscopy.

Idiopathic Hypercalciuria

This is the most common underlying cause in patients with nephrolithiasis, but may alternatively present with microscopic and gross hematuria. A family history of hematuria or nephrolithiasis is often present. Urinary calcium to creatinine ratio in the early morning 'spot' urine serves as a screening test. The upper limit of normal in children over 2 yr is 0.2 (mg/mg); higher values suggest



Figs 16.21A to D: Morphology of urine crystals may suggest etiology of renal stones. (A) Envelope shaped oxalate dihydrate crystals; (B) florets of calcium phosphate; (C) coffin lid shaped triple phosphate; (D) hexagonal cystine crystals

hypercalciuria. The diagnosis is confirmed by an accurate measurement of 24 hr urinary calcium; values greater than 4 mg/kg/day are abnormal. *Blood levels of calcium and magnesium are normal.* Idiopathic hypercalciuria should be distinguished from hypercalciuria secondary to persistent hypercalcemia (e.g. hyperparathyroidism, vitamin D toxicity) or associated with renal tubular acidosis. A high fluid intake and diet low in animal protein and salt is advised. Therapy with thiazide diuretics, which reduces urinary calcium excretion, may be required.

Endemic Vesical Calculi

Vesical calculi are usually single stones, detected in young boys (<5-yr-old) in some regions of the country, e.g. Rajasthan, Andhra Pradesh and North-Eastern states, and in neighboring countries, e.g. Pakistan and Afghanistan. These stones are composed of ammonium acid urate and calcium oxalate. Risk factors for formation include consumption of a predominantly cereal (wheat or jowar) based diet, which has low amounts of calcium and phosphate and high oxalate content. Recurrent diarrheal episodes contribute by causing dehydration and an acidic, concentrated urine. A high intake of dairy products and animal proteins has led to a decline in the prevalence of these stones. Treatment requires suprapubic cystolithotomy; these stones rarely recur.

Primary Hyperoxaluria

Primary hyperoxaluria type 1 is an autosomal recessive disorder of glyoxylate metabolism with deficient activity of the liver specific enzyme, alanine glyoxylate aminotransferase causing overproduction of endogenous oxalate, manifest as renal stones and/or nephrocalcinosis. Precipitation of oxalate also affects the eyes, heart, bones and bone marrow. The diagnosis is suggested by elevated oxalate in plasma and/or urine, and confirmed by deficient activity of affected enzyme on liver biopsy and sequencing of the affected gene, *AGXT*. Treatment is supportive; some patients with partial deficiency benefit from pyridoxine supplementation. Patients presenting in childhood progress to end-stage renal disease by adolescence and require combined liver kidney transplantation.

Cystinuria

This autosomal recessive disorder is characterized by impaired proximal tubular reabsorption of cystine and dibasic amino acids (ornithine, lysine and arginine). Supersaturation of urine with cystine crystals may lead to formation of recurrent radiopaque calculi and account for 10% of cases presenting in childhood. The diagnosis is suggested by presence of hexagonal crystals in urine, urinary excretion of specific amino acids (as above) and positive urine nitroprusside cyanide test. Confirmation requires quantification of urinary cystine excretion (24 hr or cystine:creatinine ratio), stone analysis or genetic testing. A high fluid intake and urinary alkalization help, since cystine is poorly soluble at normal urinary pH but dissolves well at pH >8.0. Agents such as penicillamine and tiopronin prevent formation of calculi by cleaving disulfide bonds of cystine to form the more soluble homodimer cysteine.

Management of Renal Calculi

Stones less than 5–7 mm in size may pass spontaneously. Extracorporeal shock wave lithotripsy (ESWL) may suffice for small stones. Percutaneous nephrolithotomy may be appropriate in patients with relative contraindication for ESWL or with stones too large for lithotripsy. Ureteroscopy is useful for distal and mid ureteric calculi. Open surgery is necessary for stones more than 3 cm in size or those with associated pelviureteric junction obstruction.

UTI should be treated and an adequate fluid intake ensured. Patients with idiopathic hypercalciuria may benefit from a low salt intake; dietary calcium restriction is not necessary. Persistent hypercalciuria is treated with oral potassium citrate, an inhibitor of crystallization. Thiazide diuretics reduce urine calcium excretion, reducing the risk of stone formation; their longterm use is, however, restricted due to side effects. Prolonged alkali supplementation is necessary in patients with distal RTA.

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16

ENURESIS

Enuresis is defined as normal, nearly complete evacuation of the bladder at a wrong place and time at least twice a month after 5 yr of age. Enuresis should be differentiated from continuous or intermittent incontinence or dribbling. The bed is usually soaking wet in enuresis, compared to incontinence in which there is loss of urine without normal emptying of the bladder. Enuresis is usually functional while continuous or daytime incontinence is often organic.

More than 85% children attain complete diurnal and nocturnal control of the bladder by five years of age. The remaining 15% gain continence at approximately 15% per year, such that by adolescence only 0.5–1% children have enuresis. Up to the eleventh year, enuresis is twice as common in boys as it is in girls; thereafter, the incidence is similar or slightly higher in girls.

Enuresis is called primary when the child has never been dry and secondary when bed wetting starts after a minimum period of six months of dryness at night. It is termed monosymptomatic if it is not accompanied by any lower urinary tract symptoms and nocturnal if it occurs only during sleep. Children with *monosymptomatic nocturnal enuresis* require no further evaluation.

Etiology

Maturational delay is the most likely cause of nocturnal enuresis, suggested by high spontaneous cure rates with increasing age. Anxiety producing episodes during the second to fifth years, the time for development of nocturnal bladder control, are associated with increased risk of enuresis.

Antidiuretic hormone (ADH) has a circadian rhythm, with increased secretion occurring during the night and peak secretion between 4 and 8 am. A lack of this circadian rhythm or impaired response of the kidneys to ADH may be a possible etiology for nocturnal enuresis. A lack of inadequate arousal is also believed to impair vasopressin secretion, leading to polyuria.

Secondary enuresis may be precipitated by acute stressful condition or traumatic experience. Bladder irritability due to urinary tract infection or severe constipation with the full rectum impinging on the bladder can cause enuresis. Conditions causing polyuria (diabetes mellitus or insipidus), spina bifida (neurological bladder dysfunction), ectopic ureter and giggle and stress incontinence are other causes.

Evaluation

Less than 5% of cases with nocturnal enuresis have an organic basis. A careful history helps determine whether the enuresis is primary or secondary, whether any daytime symptoms are present and whether any voiding difficulty is present. In cases of secondary enuresis, history should be taken to rule out acute stressful conditions, polyuria and features of bladder irritability such as frequency and urgency. Physical examination should focus on spinal anomalies.

If the child has a normal urinary stream with no daytime symptoms suggestive of a voiding disorder and normal physical examination, the child does not require extensive evaluation. Clinical and neurological examination excludes an anatomical or neurological cause for incontinence.

A voiding diary with frequency and volume charting of urine output and fluid intake for at least 2 days, with a record of daytime accidents, bladder symptoms and bowel habits for at least 7 days is useful. It helps detect children with non-monosymptomatic enuresis or polydipsia, provides information on nocturnal polyuria (such children benefit from desmopressin) and helps monitor compliance to instructions and response to therapy. A urinalysis rules out infection, proteinuria and glucosuria. Additional diagnostic and invasive procedures, ultrasonography and MCU are limited to patients with suspected neurological or urological dysfunction.

Treatment

The decision about when to start treatment should be guided by the degree of concern and motivation on the part of the child rather than the parents. General advice should be given to all enuretic children, but active treatment need not begin before the age of 6 yr. Caffeinated drinks like tea, coffee and sodas should be avoided in the evening. Adequate fluid intake during the day as 40% in

the morning, 40% in the afternoon and 20% in the evening is recommended.

The first line of treatment is usually non-pharmacological, comprising motivational therapy and use of alarm devices. *Motivational therapy* alone is successful in curing enuresis in 25% patients. The child is reassured and provided emotional support. Every attempt is made to remove any feeling of guilt. The benign nature of the disorder is explained to the child and parents using diagrams, if required, to explain the probable basis of the disorder. The child is encouraged to assume active responsibility, including keeping a dry night diary, voiding urine before going to bed and changing wet clothes and bedding. Dry nights should be credited with praise and encouraging words from the parents. Punishments and angry parental responses should be avoided.

Behavioral modification is encouraged to achieve good bladder and bowel habits. The child is encouraged both to void frequently enough to avoid urgency and daytime incontinence and to have a daily bowel movement. A stool softener such as polyethylene glycol helps children with constipation. Bladder training exercises have not been shown to be useful in improving the functional bladder capacity.

Alarm therapy involves the use of a device to elicit a conditioned response of awakening to the sensation of a full bladder. Gradually, the association with bladder distention evokes micturition. The alarm device consists of a small sensor attached to the child's underwear, or a mat under the bed-sheet and an alarm attached to the child's collar or placed at the bedside. When the child starts wetting the bed, the sensors are activated causing the alarm to ring. The child should awaken to the alarm, void in the toilet and reattach the alarm; a parent should attend the child each time to ensure the child does not merely wake to switch off the alarm. The alarm is best used after seven years of age and is successful in about two-thirds of children; a third of children may relapse afterwards. Alarm systems are now available in India; however, the ordinary alarm clock may be used to wake the child up, to void in the toilet at a critical time when the bladder is full and the child is still dry. The combination of motivational and alarm therapy is successful in up to 60–70% of children.

Pharmacotherapy is considered if enuresis persists despite institution of alarm, regular voiding habits, exclusion or treatment of constipation and exclusion of postvoid residual urine, dysfunctional voiding or low voiding frequency. Imipramine works by altering the arousal-sleep mechanism. It gives a satisfactory initial response at a dose of 1–2.5 mg/kg/day, but relapse rate after discontinuation of therapy is high. Cardiac arrhythmias are a serious adverse event effect. Anticholinergic drugs reduce uninhibited bladder contractions and are useful in children who have significant daytime urge incontinence besides nocturnal enuresis. The usual dose is 5 mg for oxybutynin, 2 mg for tolterodine or 0.4 mg/kg for propiverine at bedtime, given above 6 yr of age. Desmopressin (DDAVP, 10 µg orally or intranasally) works by reducing the volume of urine. However, its the relapse rate is high after stopping the medication. Its rapid onset of action makes it a satisfactory choice for special occasions like staying out for the night.

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CONGENITAL ABNORMALITIES OF KIDNEY AND URINARY TRACT

Congenital abnormalities of kidney and urinary tract (CAKUT) are common and account for about 25% cases of CKD in children.

Single Kidney

Unilateral renal agenesis is present when one kidney fails to form while the other kidney is normal in size, position and function. Agenesis may occur due to primary failure of formation of the ureteric bud or its inability to engage with the renal mesenchyme. The condition may occur sporadically or as part of syndromes such as branchio-otorenal, Di George, Fanconi anemia, Fraser or nail-patella syndromes. Renal agenesis is asymptomatic, usually detected incidentally on ultrasonography. Ultrasound also confirms compensatory hypertrophy of the normal single kidney. A DMSA scan helps in ruling out scarring due to associated vesicoureteric reflux or an ectopic kidney. Children with single kidney should avoid contact sports. While affected patients are expected to maintain glomerular function, they require annual monitoring for hypertension and proteinuria.

Fetuses with bilateral renal agenesis or hypoplasia rarely survive to term. Lack of fetal urine production leads to oligohydramnios and limb anomalies. Neonates show low set ears, flat nose, prominent epicanthic folds and small chin (Potter facies). Pulmonary hypoplasia is the usual cause of death.

Renal Dysplasia

Renal dysplasia implies abnormal development of renal parenchyma. Primitive ducts surrounded by connective tissue, metaplastic cartilage, poorly differentiated glomeruli and dilated tubules are present. Bilateral total renal dysplasia is fatal in the neonatal period.

Multicystic dysplastic kidney. A multicystic dysplastic kidney (MCDK) is an enlarged nonfunctioning kidney with cysts of varying sizes resulting from abnormal differentiation of the metanephros. Affecting 1 in 2400 to 4300 live births, it is the most common cystic renal malformation in children. Ultrasonography shows

characteristic findings, including multiple thin-walled noncommunicating cysts of varying size, in an enlarged kidney without identifiable parenchyma or renal pelvis (Fig. 16.22).

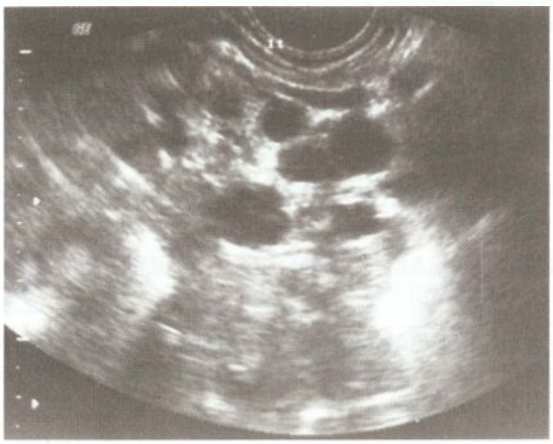

Fig. 16.22: Multicystic dysplastic kidney. Multiple, thin-walled and noncommunicating cysts are seen to involve the left kidney on postnatal ultrasound at one month age

Most patients with MCDK have a normal contralateral kidney showing compensatory hypertrophy. However, 20–40% cases may show associated abnormalities of the contralateral genitourinary tract, such as vesicoureteric reflux or pelviureteric junction obstruction. A DMSA scan confirms that the affected kidney is nonfunctional and rules out reflux-associated scarring of the contralateral kidney. Children with MCDK require regular monitoring by ultrasound to ensure compensatory hypertrophy of the normal kidney and progressive involution of the affected kidney, which is undetectable by 5–7 yr of age in most cases. Progressive renal impairment is seen only if other abnormalities are associated. The risk of malignant transformation (Wilms' tumor) and hypertension are negligible. Nephrectomy is not indicated except in presence of severe hypertension, suspected malignancy, or a large kidney that fails to involute.

Obstructive Uropathy

Obstructive anomalies of the urinary tract are an important cause of irreversible renal damage in childhood. The common lesions include pelviureteric junction obstruction, vesicoureteric junction obstruction and posterior urethral valves. Diagnosis is suspected on antenatal ultrasonography or following presentations with dribbling of urine, poor urinary stream, fever and/or urinary tract infections. Chronic obstruction results in dysfunction of distal tubules with impaired urinary concentration and acidification, leading to polyuria, polydipsia, failure to thrive, refractory rickets and systemic acidosis.

Pelviureteric junction (PUJ) obstruction Stenosis of the PUJ may be unilateral or bilateral. Obstruction is more common in boys and in presence of ectopic, malrotated or horseshoe kidney. It may present as an asymptomatic flank mass, or with upper abdominal pain, UTI or hematuria. Ultrasonography shows a dilated renal pelvis without ureteric dilatation. Radionuclide (DTPA) renal scan shows impaired drainage of the affected kidney which does not improve despite administration of a diuretic. Where scintigraphy is not available, intravenous pyelography is performed, which shows renal pelvis dilatation with an abrupt cut-off at the PUJ. Mild cases are followed up with ultrasound. Surgical treatment by pyeloplasty is indicated if the relative function of the affected kidney is impaired. Nephrectomy may be required for a kidney in which extremely poor function does not improve despite temporary nephrostomy and severe hypertension or recurrent urinary infections are present.

Posterior urethral valves These constitute an important cause of distal urinary tract obstruction in boys. The usual presenting features are dribbling, abnormal urinary stream, palpable bladder and recurrent UTI. The presence of severe obstruction in the urinary tract in utero may lead to renal dysplasia, with mild to moderate renal dysfunction at birth. Antenatal ultrasound shows bilateral hydroureteronephrosis with or without a thick-walled bladder and oligohydramnios. The diagnosis is confirmed on MCU, which shows dilated posterior urethra and valves at its junction with the anterior urethra. The bladder is enlarged and may show diverticuli and trabeculations; secondary vesicoureteric reflux is common.

Endoscopic fulguration of the valves is performed as early as possible. Alternatively, temporary urinary diversion by vesicostomy or bilateral ureterostomies is necessary. Longterm followup after surgery is necessary since a significant proportion of patients may show progressive kidney disease. Additionally, bladder dysfunction is common, with delayed continence or incontinence, poor bladder sensation and a poorly compliant low capacity bladder. If pharmacotherapy fails, patients may require clean intermittent catheterization and occasionally bladder augmentation.

Meatal stenosis Significant narrowing of urethral meatus is rarely a cause of urinary tract obstruction. The treatment consists of meatal dilatation, failing which meatoplasty may be needed.

Phimosis Phimosis may predispose to recurrent UTI in infants. However, up to the age of 2 yr, the prepuce cannot be fully retracted because of its congenital adhesions with the glans. Therefore, the diagnosis of phimosis should be made with caution in young children.

VUJ obstruction This condition is caused by an aperistaltic segment of the ureter near VU junction. Primary VUJ obstruction is more common in males and on the left side, and may be associated with ureterocele or VUR.

Ureterocele This is a congenital condition in which the terminal part of the ureter distends within the bladder to form a sac, due to an abnormality of the submucosal part of the ureter and stenosis of the ureteric orifice. Ureteroceles are commonly associated with duplex systems, particularly in girls. Endoscopic deroofing is the treatment of choice.

Miscellaneous

Renal ectopia, renal fusion An ectopic kidney may lie in the pelvis or the iliac fossa. It may be structurally normal or hypoplastic. The patient may be asymptomatic, or have abdominal discomfort or dysuria. A horseshoe kidney results from fusion of identical poles of both kidneys. Patients with horseshoe kidney show vesicoureteric reflux in 30% cases.

Renal duplication A duplex (duplicated) system is a kidney with two pyelocalyceal systems. In patients with partial or incomplete duplication, either a single or bifid ureter is present; in those with complete duplication, two ureters from the affected side empty separately into the bladder. Evaluation consists of imaging of the upper tract (ultrasonography, DTPA renal scan, intravenous pyelography) to evaluate for obstruction and lower tract (MCU) for vesicoureteric reflux.

ANTENATAL HYDRONEPHROSIS

Extensive use of antenatal ultrasonography has lead to increasing detection of CAKUT. On antenatal ultrasound, hydronephrosis is identified in 4–5% pregnancies. However, the majority of cases of antenatal hydronephrosis resolve without sequelae, representing transient physiological obstruction or stasis. These children require monitoring by ultrasound during the antenatal period for progressive worsening and association with oligohydramnios, which suggests severe lower urinary tract obstruction. A postnatal ultrasound is recommended during the first week of life and on day 1 in severe cases. Neonates with posterior urethral valve, solitary kidney or bilateral hydronephrosis and impaired renal function require prompt management. Neonates showing significant unilateral or bilateral dilatation should undergo a MCU at 4–6 weeks of life to detect vesicoureteric reflux; if reflux is ruled out, a diuretic renal dynamic (DTPA) scan is done to detect significant PUJ or VUJ obstruction and evaluate differential renal function. Most cases with mild to moderate hydronephrosis require only ultrasound monitoring and show spontaneous resolution by 2–5 yr of age. Surgery is indicated in presence of obstructive drainage pattern associated with low differential function, and/or recurrent UTI. Infants with vesicoureteric reflux should receive continuous antibiotic prophylaxis.

Figure 16.23 shows a proposed algorithm for postnatal evaluation and management of antenatally detected hydronephrosis. Parents of all infants with antenatal hydronephrosis should be counseled regarding increased risk of urinary tract infections and their prompt management.

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CYSTIC KIDNEY DISEASES

Polycystic kidney disease and nephronophthisis are relatively common and glomerulocystic kidney disease is increasingly diagnosed. Better delineation using high resolution ultrasonography or MRI and identification of genetic loci have enabled accurate diagnosis and improved management for these conditions.

Polycystic Kidneys

Polycystic kidneys are inherited in either the autosomal dominant or autosomal recessive form, with distinctive features. Autosomal recessive polycystic kidney disease (ARPKD), caused by mutations in *PKHD1* gene encoding fibrocystin or polyductin, is characterized by fusiform dilation of collecting tubules which are arranged radially from the cortex to medulla. Affected children usually present in the neonatal period with oliguria, respiratory insufficiency and palpable kidneys. ARPKD is sometimes diagnosed in young children presenting with hypertension, renal insufficiency and enlarged kidneys, or with portal hypertension due to associated congenital hepatic fibrosis. Ultrasonography shows enlarged 'bright' kidneys, usually without visible cysts (Fig. 16.24A). Contrast enhanced computerized tomography (CT) reveals a characteristic striate pattern of contrast excretion on delayed films.

The autosomal dominant form of polycystic kidneys (ADPKD) is caused by mutations in the *ADPKD1* (chromosome 16) or *ADPKD2* (chromosome 4) genes encoding polycystins 1 and 2, respectively, membrane proteins called that regulate tubular and vascular development in various tissues. This condition usually presents beyond the third decade of life with episodic hematuria, hypertension, palpable kidneys and gradual decline in renal function, but may be detected incidentally in childhood. Associated findings include cysts in the liver, spleen and pancreas, mitral valve prolapse and berry aneurysms of the cerebral arteries. Ultrasonography reveals cysts in the kidneys (Fig. 16.24B) in one affected parent unless they are younger than 30 yr, in which case grandparents should be screened; rare cases are due to *de novo* mutations. Therapy with angiotensin converting enzyme inhibitors helps control hypertension and limits

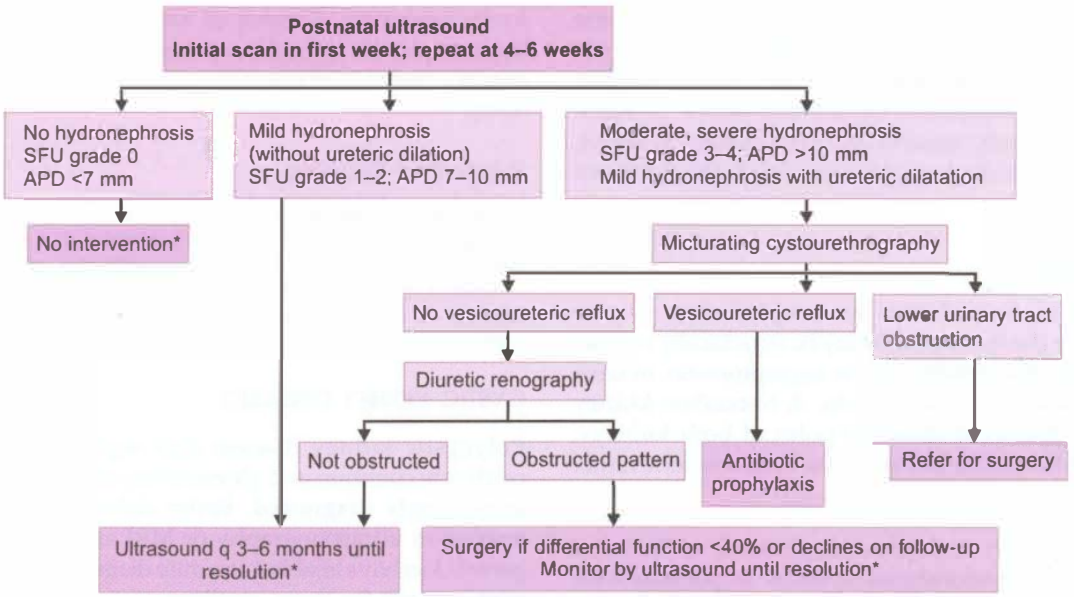
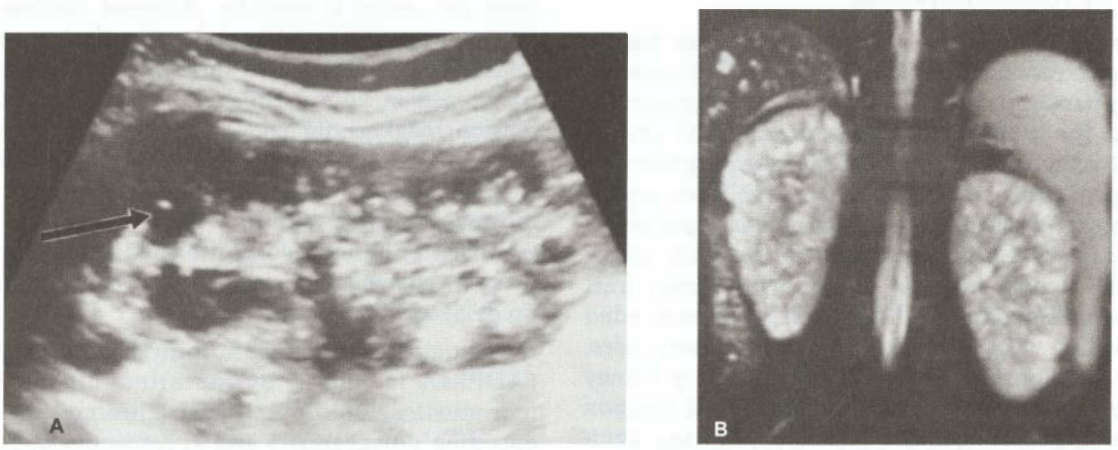


Fig. 16.23: Postnatal evaluation in patients with antenatal hydronephrosis. A postnatal ultrasound is recommended at 3–7 days except in suspected lower urinary tract obstruction, where it is done earlier. Postnatal hydronephrosis is classified using Society for Fetal Urology (SFU) grade or renal pelvic anteroposterior diameter (APD). Infants with normal findings should undergo a repeat study at 4–6 weeks. Patients with isolated mild hydronephrosis (unilateral or bilateral) should be followed with sequential ultrasounds, at 3 and 6 months, followed by 6–12 monthly until resolution; those with worsening hydronephrosis require closer evaluation. Patients with higher grades of hydronephrosis or dilated ureter(s) are screened for underlying obstruction or vesicoureteric reflux. Diuretic renography is useful in detecting pelviureteric junction or vesicoureteric junction obstruction and determining the need for surgery.

*Parents of infants with hydronephrosis should be counseled regarding the risk of urinary tract infections



Figs 16.24A and B: Findings on ultrasonography in polycystic kidney disease. (A) Note bulky enlarged kidney with increased echogenicity, loss of corticomedullary differentiation and occasional visible cyst (arrow) in a child with autosomal recessive polycystic kidney disease; (B) renal architecture is disorganized by multiple irregular cysts of varying sizes in autosomal dominant polycystic kidney disease; also note the foci of calcification

hyperfiltration and proteinuria. The role of inhibitors of the mTOR pathway such as sirolimus and everolimus is being explored.

Glomerulocystic Kidney Disease

The predominant finding in glomerulocystic kidney disease (GCKD) is cysts involving glomeruli, diagnosed most definitely on renal biopsy. Ultrasonography shows small subcortical cysts with increased kidney echogenicity and loss of cortical medullary differentiation. The condition may occur sporadically, with autosomal dominant inheritance, as a part of known syndromes (tuberous sclerosis, trisomy 13) or in association with other renal diseases such as dysplasia, ADPKD or ARPKD. Mutations in the hepatocyte nuclear factor β gene lead to the renal cysts and diabetes syndrome, characterized by

GCKD, maturity onset diabetes and genitourinary abnormalities.

Nephronophthisis Medullary Cystic Disease Complex

This group includes recessively inherited cystic disorders caused by mutations in genes, named *NPHP 1–9*, encoding cytosolic proteins called nephrocystins. Patients with nephronophthisis present during the first decade of life with polydipsia, polyuria or enuresis, growth retardation and nonspecific signs of renal insufficiency, acidosis and anemia. Extrarenal features may include retinitis pigmentosa; ocular motor apraxia, hypotonia and cerebellar or midbrain abnormalities (Joubert syndrome); skeletal chondodysplasia (Jeune syndrome); and hepatic fibrosis with pancreatic dysplasia.

The diagnosis of nephronophthisis is supported by the ultrasound or CT finding of small kidneys with corticomedullary cysts and poor corticomedullary differentiation. Renal histology shows cysts involving the collecting ducts, interstitial fibrosis and tubular dilatation with atrophy. While medullary cystic kidney disease is histologically indistinguishable from nephronophthisis, the disease is inherited in an autosomal dominant manner, and presentation is delayed to adulthood.

Renal Cysts in other Syndromes

Cystic dysplastic kidneys may be seen as a part of syndromes such as Bardet Biedl, Beckwith-Wiedemann, Meckel Gruber, Zellweger and brachiootorenal syndromes. Since the affected genes are continguous, ADPKD may be associated with tuberous sclerosis, presenting with characteristic skin lesions, periungual fibromas and seizures. The presence of retinal and central nervous system hemangioblastomas, pheochromocytoma and pancreatic cysts with cystic renal tumors suggests von Hippel-Lindau syndrome.

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17 Endocrine and Metabolic Disorders

PSN Menon, Anurag Bajpai, Kanika Ghai

GENERAL PRINCIPLES

Endocrine glands play a crucial role in maintenance of body physiology and homeostasis. The hypothalamic-pituitary axis regulates most endocrine organs including thyroid, adrenals and gonads, and processes like growth and water regulation.

Structure and Mechanism of Action

Hormones are derivatives of amino acids (e.g. peptide hormones, glycoproteins, thyroxine and epinephrine) or cholesterol (e.g. steroid hormones, vitamin D, adrenal and gonadal steroids). The peptide hormones (e.g. parathyroid hormone or PTH, growth hormone or GH and insulin) do not bind to circulating binding proteins resulting in rapid elimination and a short half-life. They do not cross the plasma membrane, but act on membrane receptors. The steroid hormones, on the other hand, bind to circulating proteins resulting in prolonged half-life. They traverse the cell membranes and act on intracellular receptors.

Hormone receptors may be extracellular (e.g. peptide hormones) or intracellular (e.g. steroid and thyroid hormones). Binding of hormones to *extracellular receptors* activates a catalytic process resulting in production of second messengers that induce structural changes in intracellular proteins, culminating in the hormone effect (Fig. 17.1). Steroids and thyroxine act on *intracellular receptors* (Fig. 17.2). The resulting hormone-receptor complex then binds to the hormone response elements in the target gene resulting in regulation of transcription. The effect of these hormones is therefore slower than those acting through extracellular receptors.

Regulation and Metabolism

Hormone secretion is regulated by a feedback system that includes regulatory hormones, hormone levels and hormone effects. The feedback operates at the level of the

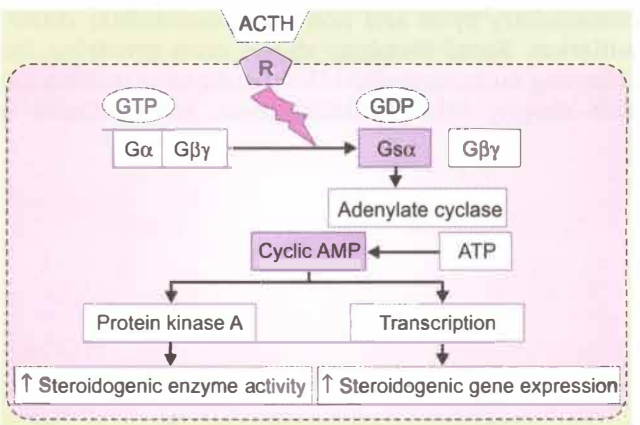

Fig.17.1: Mechanism of action of extracellular G protein coupled adrenocorticotropic hormone (ACTH) receptor. Note that ACTH has a small extracellular receptor (R). Activation of the ACTH receptor stimulates G protein Gsα subunit by hydrolysing guanosine triphosphate (GTP) to guanosine diphosphate (GDP), resulting in increased intracellular cyclic AMP that stimulate steroidogenesis by activating cyclic AMP dependent kinases. ATP adenosine triphosphate

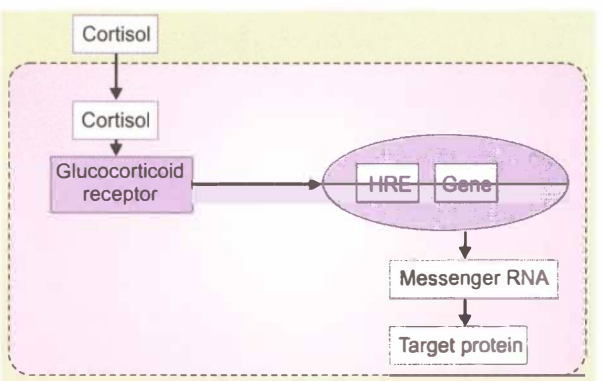

Fig. 17.2: Mechanism of action of intracellular cortisol receptor. HRE hormone response element

endocrine gland as well as the hypothalamic-pituitary axis. Peptide hormones are rapidly inactivated by plasma enzymes resulting in a short duration of action. Steroid hormones are slowly metabolized by the liver and excreted in the urine. Hormone metabolism is an important part of their regulation. Activation of hormones (e.g. androgen to estrogen, testosterone to dihydrotestosterone and calcidiol to calcitriol) is vital for their actions. Inactivation of hormones at the site of action prevents their excess effects (e.g. inactivation of cortisol by 11β-hydroxysteroid dehydrogenase prevents its action on mineralocorticoid receptor). Peripheral conversion also plays an important role in hormone function (e.g. conversion of T4 to T3).

Assessment

Endocrine assessment relies on the assessment of basal hormone levels (thyroid disorders), their metabolites (urine products in adrenal disorders), hormone effects (insulin-like growth factor-1 levels in GH deficiency and urinary osmolality for diabetes insipidus), stimulation tests in deficiency states (GH deficiency and adrenal insufficiency) and suppression tests in excess states (GH excess and Cushing syndrome). Pulsatile secretion of most hormones makes the assessment of endocrine status with a single blood test difficult.

The feedback mechanism guides assessment of endocrine disorders. In primary organ failure, pituitary hormones are compensatorily elevated, e.g. thyroid stimulating hormone or TSH in congenital hypothyroidism luteinizing hormone (LH) and follicle stimulating hormone (FSH) with delayed puberty and adrenocorticotropic hormone (ACTH) with adrenal insufficiency, while low levels suggest hypothalamic or pituitary dysfunction. The feedback mechanism also provides the basis for dynamic endocrine tests for diagnosis of hormone excess states (dexamethasone suppression test for Cushing syndrome and glucose suppression test for GH excess).

DISORDERS OF PITUITARY GLAND

Physiology

The anterior and posterior parts of pituitary gland are distinct both in embryology and function. The anterior pituitary develops from the Rathke's pouch. Posterior pituitary originates from the infundibulum, which is a downgrowth from the floor of the diencephalon.

The principal hormones produced by the anterior pituitary are TSH, ACTH, FSH, LH, GH and prolactin (PRL). These hormones regulate actions of adrenals (by ACTH), thyroid (by TSH) and gonads (by LH and FSH). The secretion of anterior pituitary hormones is in turn regulated by hypothalamic peptides (growth hormone releasing hormone or GHRH, somatostatin, dopamine, gonadotropin releasing hormone or GnRH, corticotropin releasing hormone or CRH and thyrotropin releasing hormone or TRH) and also by hormones produced by the target glands.

Posterior pituitary hormones (arginine vasopressin or AVP, and oxytocin) are secreted by neurons located in the hypothalamic nuclei. AVP, also known as the antidiuretic hormone (ADH), is the key regulator of body water and osmolality.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) may be caused by congenital CNS malformations, genetic defects or acquired neurological insults (Table 17.1.) These children have normal growth at birth. Growth retardation becomes apparent around one year of age. Midfacial crowding, round facies, mild obesity, depressed nasal bridge, single central incisor tooth and micropenis are common (Fig. 17.3). Body proportions are normal. The development of teeth is delayed. The facial appearance is 'doll like' and these children look much younger than their actual age. Bone age is delayed. Newborns may present with severe hypoglycemic seizures due to concomitant ACTH deficiency. Associated gonadotropin deficiency causes delay in sexual development and small genitalia.

Resistance to growth hormone action (*growth hormone insensitivity or Laron syndrome*) presents with almost similar features with severe growth retardation and elevated baseline GH levels.

Short Stature

Growth failure may occur as part of any long-standing systemic illness. Chronic systemic disorders and nutritional causes of growth retardation (including malabsorption) have predominant effect on weight. Height is secondarily affected. Thus weight age is substantially lower than height age in these conditions. On the contrary,

Table 17.1: Etiology of growth hormone deficiency

Congenital
Genetic defects
Isolated GH deficiency
Type I: Autosomal recessive
Type II: Autosomal dominant
Type III: X-linked recessive
Multiple pituitary deficiencies
Type I: Autosomal recessive
Type II: X-linked
Idiopathic GH releasing hormone deficiency
Developmental defects: Pituitary aplasia or hypoplasia, anencephaly, holoprosencephaly, midfacial anomalies, septo-optic dysplasia
Acquired
Tumors: Hypothalamic, pituitary or other intracranial tumors
Irradiation
Infections: Encephalitis, meningitis, tuberculosis, toxoplasmosis
Infiltration: Histiocytosis, hemochromatosis, sarcoidosis
Injury: Perinatal insult (breech), head injury, surgery
Vascular: Aneurysm, infarction

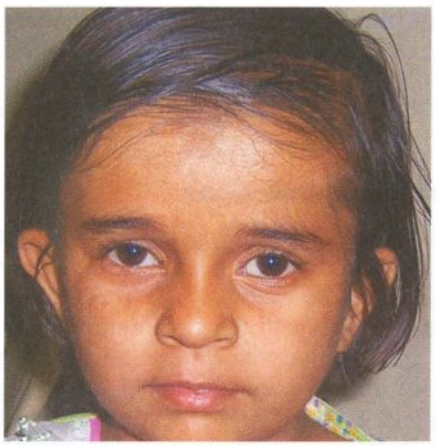

Fig. 17.3: A 6-yr-old girl with short stature due to growth hormone deficiency. Note the immature facies, midfacial hypoplasia and cherubic appearance

endocrine causes like GHD, hypothyroidism and pseudohypoparathyroidism mainly affect height resulting in disproportionately low height age (*see* Chapter 2).

Evaluation

History. Perinatal history, birth weight and length should be recorded. History of birth asphyxia, breech presentation, neonatal hypoglycemia, micropenis and prolonged jaundice are early indicators of GHD. Features of chronic infections, cardiopulmonary disorders, malabsorption and raised intracranial tension should be looked for. Presence of polyuria and polydipsia suggests diabetes insipidus, diabetes mellitus and/or renal tubular acidosis. Constipation, delayed milestones, lethargy and cold intolerance indicate hypothyroidism. Family history of short stature and/or delayed puberty suggests the possibility of familial short stature or constitutional delay of puberty and growth.

Examination. Anthropometric assessments (weight, height, weight for height and head circumference) are required. Compromised weight suggests a nutritional etiology (malnutrition, systemic illness or malabsorption) while weight is preserved in most endocrine disorders.

Body proportions are helpful in identifying skeletal dysplasia. Lower segment (LS) is measured from the pubic symphysis to the feet. Upper segment (US) is obtained by subtracting it from height. The US:LS ratio is 1.7:1 at birth and decreases by 0.07–0.1 each year to reach 1:1 by 7–10 yr of age. Increased US:LS ratio suggests hypothyroidism, achondroplasia (Fig. 17.4) or Turner syndrome while reduced US:LS ratio is seen in disorders such as Morquio syndrome and spondyloepiphyseal dysplasia. Body proportions are normal in GHD.

The clinician should look for specific features of an underlying etiology such as GHD, hypothyroidism, Turner syndrome and rickets (Table 17.2). Evaluation for dysmorphism, skeletal deformities and sexual maturity rating are essential.

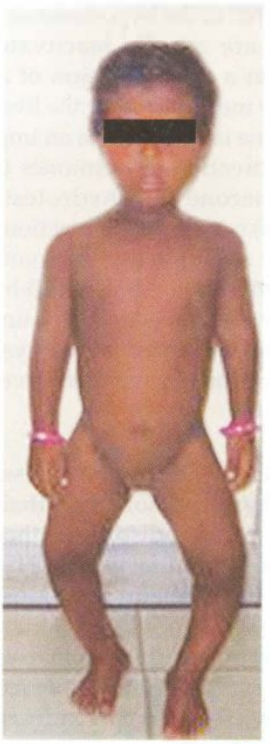

Fig. 17.4: Achondroplasia: Note the abnormal body proportions and facies

Table 17.2: Pointers to the etiology of short stature

Pointer	*Etiology*
Midline defects, micropenis	Growth hormone deficiency
Rickets	Renal failure, malabsorption, renal tubular acidosis
Pallor	Renal failure, malabsorption, nutritional anemia
Malnutrition	Protein energy malnutrition, malabsorption, celiac disease, cystic fibrosis
Obesity	Hypothyroidism, Cushing syndrome, Prader-Willi syndrome, pseudohypoparathyroidism
Metacarpal shortening	Turner syndrome, pseudohypoparathyroidism
Cardiac murmur	Turner syndrome, congenital heart disease
Mental retardation	Hypothyroidism, Down syndrome, Turner syndrome, pseudohypoparathyroidism

Investigations. Laboratory evaluation of short stature involves stepwise application of diagnostic tests to determine the etiology (Fig. 17.5).

Step 1. The first step in investigation is to rule out common causes. This involves exclusion of malnutrition, chronic systemic illnesses and recurrent infections using complete

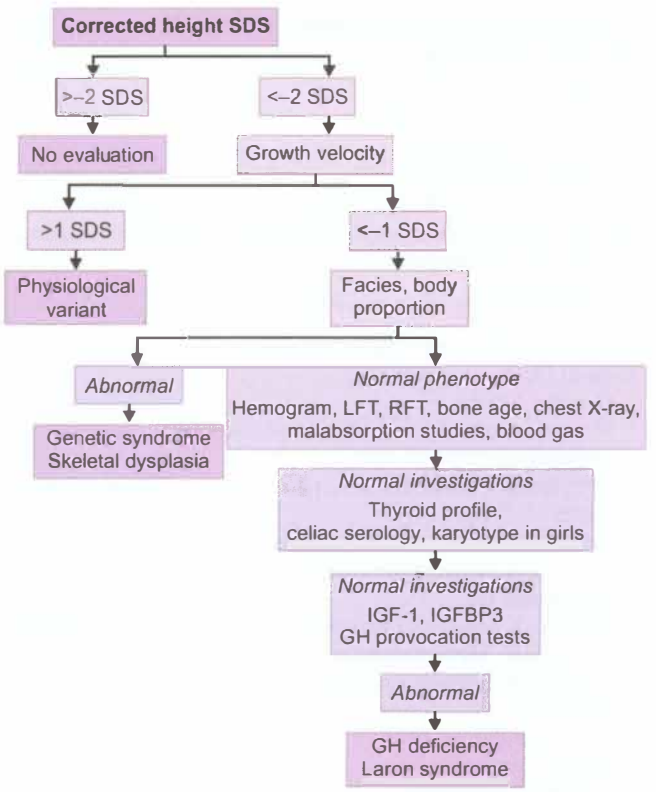

Fig. 17.5: Approach to a child with short stature.
GH growth hormone; IGF-1 insulin-like growth factor-1, IGFBP-3 IGF binding protein 3; LFT liver function tests; RFT renal function tests; SDS standard deviation score

blood counts, erythrocyte sedimentation rate, chest X-ray, serum electrolytes and liver and renal function tests. Tissue transglutaminase antibody (celiac disease) and venous blood gas (renal tubular acidosis) should be performed if these screening tests are normal.

Estimation of skeletal maturation forms an important aspect of evaluation of short stature. This is done by comparing the X-ray of left wrist with age specific norms.

Step 2. The next step in evaluation involves evaluation for hypothyroidism (free T4 and TSH) and Turner syndrome (karyotype) in all girls.

Step 3. Evaluation for GH–IGF axis is performed only after other common causes of growth retardation have been excluded. This is important as systemic illness and hypothyroidism influence the GH–insulin-like growth factor (IGF) axis. Random or fasting blood GH level measurements do not confirm the diagnosis of GHD as hormone secretion is pulsatile. The diagnosis of GHD thus requires pharmacologic stimulation tests. GHD is suspected when the peak level of GH is <10 ng/ml following stimulation. The common provocative agents used are insulin, glucagon and clonidine. Levels of IGF–1 and IGF binding protein 3 are helpful to diagnose GHD and Laron syndrome. GHD may be associated with other pituitary hormone deficiencies and appropriate investigations should be carried out to detect deficiency of these hormones if GHD is present. CT or MRI scans of hypothalamic and pituitary regions are essential to rule out developmental or acquired neurological lesions.

Management

Management of short stature involves correction of underlying cause and provision of adequate nutrition intake.

General measures Patients should be advised diet rich in protein and calorie content. They should be encouraged to increase their physical activity. Iron and vitamin deficiencies should be corrected. Zinc supplementation (10 mg/day for 3–6 months) may help in improving growth in patients with idiopathic short stature.

Specific therapy Initiation of specific treatment is effective in restoring growth in hypothyroidism (thyroxine), celiac disease (gluten free diet) and renal tubular acidosis (bicarbonate supplements). A short course of testosterone may be given to boys with constitutional delay of puberty and growth. Treatment of genetic syndromes and skeletal dysplasias is extremely difficult. Some of them do respond to GH therapy. Bone lengthening (Ilizarov technique) has been used with variable success in some forms of skeletal dysplasia.

Growth hormone GH is highly effective patients with GHD. This can result in an increase in height by 20–30 cm. The treatment is given as daily night time injections (25–50 µg/kg/day) till epiphyseal closure. The treatment is expensive and hence should be started only if it can be given regularly for at least 2 yr. The role of GH is expanding with increasing use in Turner syndrome, chronic renal failure, small for gestational age infants who fail to catchup, Russel-Silver syndrome, Prader-Willi syndrome and idiopathic short stature.

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Growth Hormone Excess

Excess of GH during childhood results in somatic overgrowth or *gigantism*. Increased GH secretion after the

fusion of skeletal epiphyses causes features of *acromegaly*. Coarse features with prominent jaw, broad nose, enlarged tongue, bushy eyebrows, thick skin and dorsal kyphosis are characteristic. Headache and visual field defects (bitemporal hemianopia and enlargement of the blind spot) are common.

The diagnosis is based on clinical examination, serial photographs of the child, growth assessment and investigations. Skull X-ray films show enlarged sella with erosion of the margins. Tufting of the phalanges and increased heel pad thickness may be present. MRI helps to confirm and determine the extent of the tumor. GH levels are elevated and are not suppressed by a glucose tolerance test.

Pituitary gigantism is rare in children. It may be the only clue to an underlying pituitary adenoma, which may be associated with isolated or multiple endocrine involvements in the setting of multiple endocrine neoplasia or McCune Albright syndrome.

GH excess should be differentiated from *Sotos syndrome* (cerebral gigantism) characterized by large size at birth, excessive growth in early childhood, and advanced height, weight and bone ages. The skull is large with prominent forehead and jaw, high arched palate, hypertelorism and antimongoloid slant of the palpebral fissure. Hereditary tall stature, obesity, precocious puberty, Marfan syndrome and lipodystrophy should be ruled out by appropriate tests.

Medical management involves the use of long-acting somatostatin analogs such as octreotide. The GH receptor antagonist pegvisomant is also useful in treatment. Partial or complete resection of pituitary adenoma is indicated if there is evidence of raised intracranial tension.

17

Diabetes Insipidus

Polyuria (urine output >5 ml/kg/hr or 2 L/m^2/day) is an important pediatric problem and may be the only manifestation of a serious disease such as diabetes insipidus, diabetes mellitus, brain tumor and renal tubular acidosis. Polyuria may result from increased solute load or impaired renal concentrating capacity (Table 17.3).

Diabetes insipidus (DI) is an important cause of polyuria. *DI presents with low urine osmolality in association with high plasma osmolality.* DI may be due to decreased production of vasopressin (central DI) or action (nephrogenic DI). Dehydration is unusual unless there is an abnormality of thirst mechanism. However, infants are at a high risk of developing hypernatremic dehydration.

Central DI is commonly associated with an intracranial pathology (Table 17.3.) Craniopharyngioma presents with DI, growth retardation and skull calcification. Germinoma located in the pituitary stalk may be missed on neuroimaging, emphasizing the need to repeat neuroimaging if no cause is found. Malformations of the central nervous system such as septo-optic dysplasia and holoprosencephaly display central DI and deficiency of anterior pituitary hormones. Histiocytosis is the commonest infiltrative disorder associated with central DI. Neurological infections including tuberculosis may cause central DI.

Table 17.3: Causes of polyuria

Increased fluid load
Iatrogenic
Compulsive water drinking
Increased solute load
Osmotic diuresis: Diabetes mellitus, mannitol treatment
Salt loss: Adrenal insufficiency, diuretics, cerebral salt wasting, aldosterone resistance
Impaired urinary concentration
Inefficient ADH action (Diabetes insipidus, DI)
Central DI (Neurogenic DI)
Genetic defects
Malformations: Septo-optic dysplasia, holoprosencephaly, anencephaly
CNS insults: Head trauma, neurosurgery, infection, brain death
Infiltrative disorders: Sarcoidosis, histiocytosis
Space occupying lesions: Craniopharyngioma, germinoma
Nephrogenic DI
Genetic: X linked (V2 receptor), AR, AD (aquaporin defect)
Acquired: Hypokalemia, hypercalcemia, obstructive uropathy, nephrocalcinosis
Tubulopathy
Renal tubular acidosis
Bartter syndrome
Gitelman syndrome

Nephrogenic DI. This condition results from inherited or acquired resistance to vasopressin. Hypokalemia and hypercalcemia are important causes of nephrogenic DI.

Water Balance and Polyuria

Maintenance of water balance involves regulation of urine output and thirst. Thirst is controlled by the hypothalamus. Urine output is determined by solute load, hydration status and urine concentration capacity. Fluid homeostasis involves close interaction of arginine vasopressin, renin–angiotensin–aldosterone system and atrial natriuretic peptide. Vasopressin is secreted by the hypothalamus in response to osmotic signals and acts on the V2 receptors in collecting duct to increase free water resorption. The renin–angiotensin–aldosterone system is central to the regulation of sodium, fluid and blood pressure.

Differential Diagnosis of Polyuria

Diabetes mellitus. Diabetes mellitus presents with polydipsia, polyphagia, recurrent infections and weight loss in addition to polyuria.

Renal disorders. Polyuria is common in obstructive uropathy. It is often the presenting feature of tubular disorders like renal tubular acidosis, Bartter syndrome and Gitelman syndrome. These conditions are associated with severe failure to thrive and rickets.

Inefficient aldosterone action. These include adrenal insufficiency, isolated aldosterone deficiency or aldosterone resistance. They present with hyponatremia, hyperkalemia and dehydration. The condition may be lethal. Failure to thrive is common. Pigmentation is characteristic of adrenal insufficiency. Polyuria and salt wasting in the neonatal period should prompt evaluation for congenital adrenal hyperplasia. Genital ambiguity in girls may be the only clue to this diagnosis.

Excessive water drinking (psychogenic polydipsia). The condition is extremely rare and is a diagnosis of exclusion.

Evaluation

Subjective estimates of urine output and nocturia may suggest polyuria; however, these cannot substitute for measurement of 24 hr urine output and fluid intake. Urine output in excess of 2 L/m^2/day or 5 ml/kg/hr confirms polyuria.

Clinical. Diabetes mellitus is suggested by polyphagia, recurrent infections and failure to thrive. Renal tubular acidosis is suspected when acidotic breathing, bony deformities or muscle weakness are present. Neurological and fundus examination should be performed. Careful search for features of histiocytosis like ear discharge, proptosis, rash, organomegaly, lymphadenopathy, bony defects and seborrheic dermatitis is essential (Table 17.4.)

Investigations. Initial investigations should include testing for urine sugar and early morning specific gravity or osmolality. Blood gas, urea, electrolytes, calcium and creatinine should be estimated. *High plasma osmolality* (>300 mOsm/kg or serum sodium >146 mmol/L) *and low urine osmolality* (<300 mOsm/kg and urine specific gravity <1.005) suggest the diagnosis of DI, which needs further classification on the basis of response to arginine vasopressin. Patients with normal plasma osmolality and low urine osmolality (<800 mOsm/kg) should undergo water deprivation test. Urinary osmolality >800 mOsm/kg (specific gravity >1.010) excludes DI.

MRI of the hypothalamic-pituitary region and anterior pituitary evaluation should be done in central DI. Evaluation of nephrogenic DI includes renal imaging and serum electrolytes.

Water deprivation test. The test is indicated in children with polyuria, low urinary osmolality and normal plasma osmolality. The aim is to increase plasma osmolality above 300 mOsm/kg (or serum sodium above 146 mEq/l) to allow opportunity for maximal renal concentration. Renal failure and RTA should be excluded before the test. Water deprivation test is not required in the presence of hypernatremia. The test should be done on an inpatient basis due to risk of dehydration. Water deprivation is started early in the morning. The child should be weighed and target weight loss calculated (5% of total body weight). Body weight, urine output and urine and blood osmolality should be monitored hourly. The test should be stopped when urine osmolality increases above 800 mOsm/kg or specific gravity is more than 1.010. Since this excludes DI, plasma osmolality increases above 300 mOsm/kg or serum sodium is above 146 mEq/l (target achieved) or weight loss is more than 5% (risk of dehydration). *Urine osmolality below 300 mOsm/kg in the presence of plasma osmolality above 300 mOsm/kg confirms DI.* These patients should be evaluated further with response to vasopressin. Children with urine osmolality between 300–800 mOsm/kg with plasma osmolality above 300 mOsm/kg may have partial central or nephrogenic DI.

Vasopressin response test. This test is performed for differentiation of complete central DI from nephrogenic DI. Urine osmolality is measured one and four hours after vasopressin injection (0.1 unit/kg). An increase in urine osmolality by more than 50% of baseline levels is diagnostic of central DI while a smaller increase suggests nephrogenic DI.

Table 17.4: Pointers to diagnosis of polyuria

Feature	*Diagnosis*
Cleft lip, cleft palate	Hypopituitarism
Metabolic bone disease	Renal tubular acidosis (RTA), renal failure
Growth failure	Nephrogenic diabetes insipidus, RTA, congenital adrenal hyperplasia, Bartter syndrome
Rash, ear discharge	Histiocytosis
Pigmentation	Adrenal insufficiency
Genital ambiguity	Congenital adrenal hyperplasia

Management

Management of polyuria is guided by the underlying cause. Treatment of diabetes mellitus (insulin), adrenal insufficiency (hydrocortisone) and renal tubular acidosis (bicarbonate supplementation) is effective in reducing urine output. Behavioral therapy is recommended for psychological polydipsia.

Central DI. Central DI is managed with vasopressin analogs. *Desmopressin (DDAVP),* a vasopressin analog has high potency and prolonged duration of action. It can be given by intranasal (2.5–10 µg 12 hourly), or sublingual or oral (50–200 µg 12 hourly) route. Patients with idiopathic DI should be followed for evolving brain tumors.

Nephrogenic DI. Hydrochlorothiazide and amiloride combination (1–2 mg/kg/day of thiazide) reduces urine output by 40%. This paradoxical effect results from decreased delivery of free water to collecting ducts and distal tubule (site of AVP action) due to increased sodium absorption in the proximal tubule. Addition of indomethacin to this regimen reduces urine output to 50–70%. This should be combined with salt restriction and reduction in solute load.

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DISORDERS OF THYROID GLAND

Physiology

Thyroid hormone biosynthesis involves interaction of iodine, tyrosine, thyroglobulin and thyroid peroxidase enzyme. Thyroid peroxidase is the rate-limiting enzyme in thyroid hormone synthesis. This process is controlled by TSH. TSH secretion is, in turn, under direct control of the thyrotropin-releasing hormone released from the hypothalamus and feedback control of thyroxine. Thyroid hormones bind to intracellular receptors and activate transcription factors. Most triiodothyronine (T3) in the circulation is produced by peripheral conversion of thyroxine (T4) by the enzyme monodeiodinase. This process is stimulated in thyroid depleted states as a protective mechanism to produce more T3. Thus T3 levels are the last to fall in hypothyroidism, and are not a reliable indicator of the disease.

Thyroid hormones are involved in the regulation of somatic and intellectual growth, intermediary metabolism and thermoregulation. There is a critical phase in the early neonatal period for the effect of thyroid hormone on mental development. This underscores the need of early diagnosis and appropriate management of congenital hypothyroidism. TSH levels increase immediately after birth, resulting in increase in T3 and T4 levels, and reach their maximum by 24 hr. Their level fall to normal in the next few weeks. TSH levels should therefore be estimated after 48 hr as part of neonatal screening for congenital hypothyroidism.

Assessment of Thyroid Function

Thyroid function is assessed by estimation of serum TSH and free and/or total T3 and T4. TSH is the most sensitive indicator of primary hypothyroidism, but is not as helpful in the diagnosis of central hypothyroidism. T4 level is a better indicator of thyroid status than T3 due to increased conversion of T4 to T3 during thyroid depleted states. Considering the wide variability in the levels of circulating thyroid binding globulin, estimation of free (F) thyroid hormone is superior to total levels in the diagnosis of hypothyroidism. Low FT4 and TSH levels suggest central hypothyroidism while high TSH levels indicate primary hypothyroidism. Persistent elevation of TSH in the presence of normal FT4 suggests subclinical hypothyroidism. Elevated FT4 and undetectable TSH levels are indicative of hyperthyroid state.

Hypothyroidism

Decreased production of thyroid hormones has significant impact on growth and development. Untreated congenital hypothyroidism has devastating intellectual and developmental consequences. Acquired hypothyroidism adversely affects growth and school performance.

Hypothyroidism could be caused by defects in the hypothalamic-pituitary axis (central hypothyroidism), thyroid gland or the peripheral sensitivity to thyroxine (Table 17.5).

Congenital Hypothyroidism

Congenital hypothyroidism is the most common preventable cause of mental retardation. Iodine deficiency is the commonest cause of congenital hypothyroidism in certain parts of India, while thyroid dysgenesis is the most common etiology in non-endemic areas (75% of all cases). The disorder encompasses a spectrum ranging from complete agenesis, partial agenesis to ectopic thyroid. Increased incidence of thyroid dysgenesis is noted in Down syndrome. Biosynthetic defects include disorders affecting iodine transport, peroxidation, thyroglobulin synthesis and deiodination. *Pendred syndrome*, a disorder of the *pendrin* gene, is associated with decreased intracellular transport of iodine and deafness. Transient congenital hypothyroidism may occur following transplacental passage of TSH receptor blocking antibodies, iodine exposure and treatment with drugs like amiodarone.

Clinical features Features of congenital hypothyroidism are nonspecific and difficult to identify in the neonatal period. They become prominent with increasing age. However, the window period for neurological intervention has elapsed in most patients by this time. *This underscores the need for neonatal screening.* Clinical manifestations include hoarse cry, facial puffiness, umbilical hernia, hypotonia, mottling of skin and lethargy (Fig. 17.6.) Prolonged jaundice, constipation and unexplained hypothermia may

Table 17.5: Etiology of hypothyroidism

Primary (Thyroid, >95%)
Autoimmune thyroiditis
Enzyme defects: Trapping, organification, thyroglobulin synthesis, deiodination
Iodine deficiency: Endemic goiter
Dysgenesis: Aplasia, dysplasia, ectopic
Thyroid injury: Surgery, radiation, infection
Goitrogens: Thiocyanates, thionamides, lithium, amiodarone
Transient causes: Maternal TSH receptor blocking antibody, iodine excess, maternal antithyroid drug
Secondary or Tertiary (Hypothalamus or pituitary, <5%)
Malformations: Septo-optic dysplasia, holoprosencephaly
Genetic defects
CNS insults: Trauma, surgery, radiation, infection
CNS tumors: Craniopharyngioma, germinoma
Peripheral (Extremely rare)
Resistance to thyroxine

TSH thyroid stimulating hormone

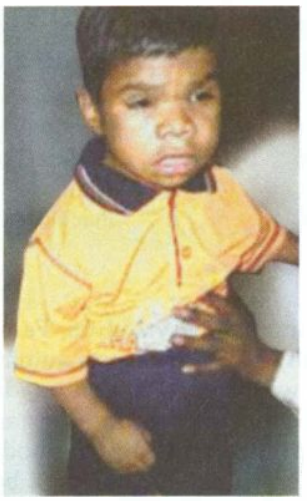

Fig. 17.6: Congenital hypothyroidism: Note the characteristic facial features

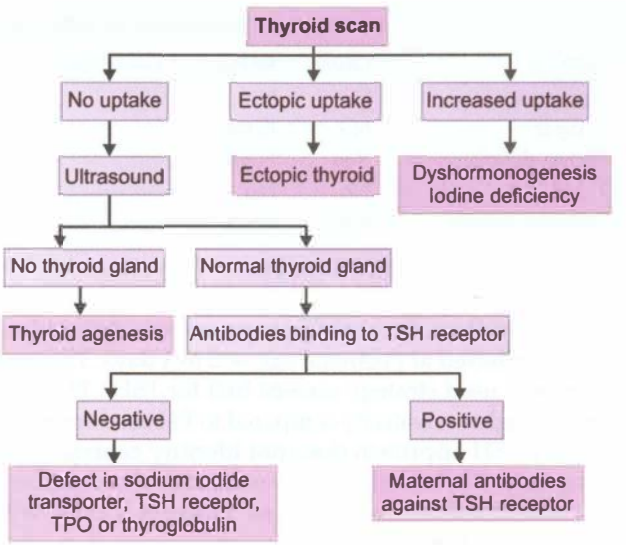

Fig. 17.7: Approach to congenital hypothyroidism. TPO thyroid peroxidase; TSH thyroid stimulating hormone

also indicate hypothyroidism. Open posterior fontanel is an important indicator of congenital hypothyroidism (Table 17.6.)

History of maternal thyroid disease or ingestion of antithyroid medications should be enquired. Family history of hypothyroidism suggests dyshormonogenesis, while recurrent transient hypothyroidism indicates disease related to maternal TSH receptor antibody. Residence in iodine deficient area may suggest the diagnosis of iodine deficiency. Goiter should prompt evaluation for transplacental passage of antithyroid drugs or disorders of thyroid hormone biosynthesis. Hypoglycemia, micropenis and midline facial defects suggest hypothalamic causes.

Evaluation Initial investigations in a child with high TSH levels should include evaluation of radionuclide uptake and thyroid ultrasound to confirm the presence of thyroid gland. Thyroid dysgenesis should be diagnosed if no thyroid tissue is visualized on ultrasound. Radiotracer uptake study with radioactive iodine or technetium should be done as soon as the diagnosis of primary congenital hypothyroidism has been established (Fig. 17.7). Children with absent radiotracer uptake but normal thyroid on ultrasound could be suffering from defects in iodine transport, TSH receptor defects or transplacental passage of TSH blocking antibody. Increased radioactive tracer uptake is indicative of iodine deficiency or dyshormonogenesis (Table 17.7). Children with low TSH levels should be worked up for other pituitary defects.

Table 17.6: Clinical features of hypothyroidism

Congenital	*Acquired*
Open posterior fontanel	Growth retardation
Umbilical hernia	Delayed skeletal maturation
Characteristic edematous facies	Delayed dental development
Constipation	Delayed puberty
Pallor	Myopathy and pseudohypertrophy
Hypothermia	Enlarged sella
Large tongue	Pseudotumor cerebri
Rough dry skin	
Hypotonia	
Large abdomen	

Management Thyroid replacement should be started immediately after diagnosis. In central hypothyroidism cortisol replacement should precede thyroid replacement as it could precipitate adrenal insufficiency. Thyroxine (T4) should be initiated at a dose of 10–15 µg/kg/day. T4 and TSH levels are expected to normalize over one week and one month, respectively, with this treatment. FT4 and TSH should be measured at each visit. Thyroxine dose should be adjusted to achieve FT4 levels in the upper normal range for the age. Lifelong thyroid replacement is required in most cases.

Thyroid replacement should be stopped for one month at the age of 3 yr in suspected transient congenital hypothyroidism. Treatment may be discontinued in the absence of persistent abnormality on investigations and normal levels of thyroid hormones.

Outcome Early diagnosis and treatment following neonatal screening has resulted in normal intellectual outcomes.

Outcome is however poor in children with congenital hypothyroidism who have been diagnosed beyond the neonatal period. Mental retardation and short stature are common sequelae.

Screening Difficulty in early identification of congenital hypothyroidism and the disastrous consequences of delayed diagnosis have led to neonatal screening for

Table 17.7: Comparison of different forms of primary congenital hypothyroidism

Type	*Goiter*	*Radioactive iodine uptake*	*Urine iodine*	*Thyroid on ultrasound*	*Diagnostic investigation*
Dysgenesis/agenesis	No	No	Normal	Absent	Radionuclide scan
Ectopic	No	Ectopic	Normal	Absent	Radionuclide scan
Iodine deficiency	Yes	High	Low	Eutopic	Urine iodine
TSHRAb*	No	No	Normal	Eutopic	Antibody
Enzyme defects	Yes	Normal	Normal	Eutopic	Perchlorate discharge

*TSHRAb antibody to TSH receptor

hypothyroidism. Screening programs use dried blood sample collected at postnatal age of 2 to 4 days. The most commonly used strategy screens first for TSH . This strategy has higher sensitivity compared to T4 based approach. Primary TSH approach does not identify central hypothyroidism. T4 first approach can identify these children, but has the disadvantage of missing cases with compensated hypothyroidism.

Acquired Hypothyroidism

Etiology Autoimmune thyroiditis is the most common cause of acquired hypothyroidism. This is more common in girls. Goiter is often nodular and firm unlike the soft and uniform goiter in dyshormonogenesis. Thyroid peroxidase antibodies are usually present. Autoimmune thyroiditis may be associated with other autoimmune endocrinopathies such as adrenal insufficiency, type 1 diabetes mellitus (DM) and hypoparathyroidism. Rarely, congenital abnormalities like thyroid dysgenesis or an inborn error of thyroid hormone synthesis may present in older children and at adolescence. Iodine deficiency and goitrogens are other causes of primary hypothyroidism in older children. Secondary hypothyroidism due to combined hypothalamic-pituitary defects could be a manifestation of neurological injury insults or tumors.

Clinical features Features of acquired hypothyroidism are subtle compared to congenital hypothyroidism. Short stature may be the only manifestation. Cold intolerance, lethargy, constipation, delay in dentition and poor school performance may suggest hypothyroidism. All children with unexplained mental retardation and short stature should be evaluated for hypothyroidism. Most patients with hypothyroidism have delayed puberty; however, uncontrolled long-standing hypothyroidism may trigger precocious puberty. Goiter is common in iodine deficiency, chronic lymphocytic thyroiditis or dyshormonogenesis. Hypothyroidism has been associated with Down syndrome, Turner syndrome, celiac disease and type 1 DM. All children with these disorders should be periodically screened for hypothyroidism even in the absence of symptoms.

Evaluation Severe short stature and mental retardation suggest congenital hypothyroidism. Round uniform smooth goiter is suggestive of iodine deficiency or disorder of thyroid hormone synthesis; firm nodular goiter indicates autoimmune thyroiditis. Family history of acquired hypothyroidism suggests autoimmune thyroiditis. Children with central hypothyroidism should be evaluated with pituitary function tests and MRI of the hypothalamic-pituitary region. Antibodies to thyroid peroxidase enzyme (anti-TPO) should be estimated in acquired primary hypothyroidism.

Management Treatment of acquired hypothyroidism should be gradual. A dose of 100 μg/m^2/day is recommended (Table 17.8). In long-standing cases initial treatment should be started at 25–50% of these doses with gradual build up every 3–4 weeks. Thyroxine should be given empty stomach in the morning. Followup should be done every three months during the first two years of therapy and six monthly thereafter. The doses should be modified to maintain TSH levels in the normal range. Most children require life long therapy. Mild elevation of TSH (below 10 mIU/l) in the setting of normal FT4 levels (subclinical hypothyroidism) is usually self resolving and does not require treatment.

Table 17.8: Recommended dose schedule of thyroxine

Age	*Thyroxine dose, μg/kg/day*
Neonatal period	10–15
1–6 mo	6–10
1–5 yr	4–6
5–12 yr	3–5
12–18 yr	2–3
> 18 yr	1–2

Goiter

Goiter refers to the enlargement of the thyroid gland. From a clinical standpoint, thyromegaly is diagnosed when the lateral lobe of the thyroid is larger than the terminal phalanx of the thumb of the child (Fig. 17.8).

Etiology Goiter may be congenital or acquired sporadic, or endemic. Goiter may be associated with diminished, normal or increased thyroid function (Table 17.9). Thyroid enlargement may represent increase in size in response to compensatory TSH secretion (hypothyroidism), infiltration (autoimmune thyroiditis, neoplasms or hemochromatosis), or presence of TSH receptor stimulatory antibody (Graves disease). Important causes of congenital

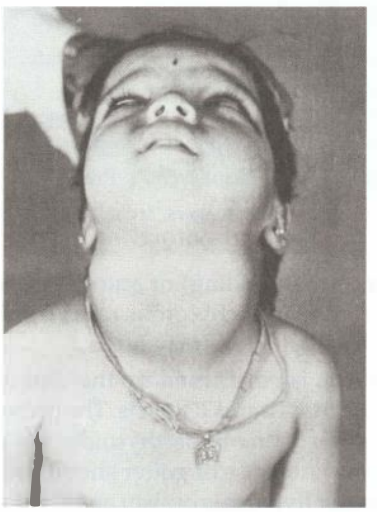

Fig. 17.8: Diffuse goiter in a child due to dyshormonogenesis

goiter include maternal antithyroid medications, dyshormonogenesis and iodine deficiency. Autoimmune thyroiditis is the most common cause in childhood, followed by iodine deficiency, dyshormonogenesis and Graves disease. Differential diagnosis includes diffuse nodular goiter, benign adenoma, thyroid cyst and, occasionally, a carcinoma.

Evaluation During clinical evaluation goiter is usually classified into diffuse and nodular goiter. Either form can be produced by autoimmune thyroiditis and colloid goiter. An acutely painful thyroid enlargement is usually due to hemorrhage or active inflammation, whereas a firm goiter is characteristic of chronic lymphocytic thyroiditis. Multinodular goiter may be seen in chronic lymphocytic thyroiditis, iodine deficiency and colloid goiter. Isolated enlargement of one lobe indicates hemiagenesis. A well-circumscribed nodule is usually due to a benign cyst. A single firm or hard painless irregular nodule is suggestive of malignancy. Diffuse goiter in the newborn may be due to Graves' disease, dyshormonogenesis or goitrogenic drugs. Investigations should include thyroid function tests. Anti-TPO antibodies should be measured to identify autoimmune thyroiditis. Positive antibodies indicate a risk of hypothyroidism even if the thyroid functions are normal. Ultrasound and fine needle aspiration should be performed if no clue to etiology is identified.

Table 17.9: Causes of goiter

Inflammatory:	Acute suppurative thyroiditis, subacute thyroiditis
Infiltration:	Autoimmune thyroiditis, neoplasm, hemochromatosis
Increased TSH levels:	Dyshormonogenesis, iodine deficiency, unilateral agenesis
TSH stimulating antibody:	Graves' disease
Colloid goiter	

Management Treatment should be directed to the cause (antithyroid medications in Graves disease; thyroxine in hypothyroidism). Children with autoimmune thyroiditis should be followed with annual thyroid function tests. Early trial of thyroxine at a dose of 100–200 µg daily may be given in children with 'physiological goiter'. This produces complete regression in about 30% of cases by two years. Caution should be taken as the dose may induce hyperthyroidism along with clinical symptoms. Surgery should be avoided unless the goiter is large enough to cause respiratory embarrassment.

Iodine Deficiency Disorders

The term iodine deficiency disorders refers to the wide spectrum of effects of iodine deficiency on growth and development. These include endemic goiter, endemic cretinism, impaired mental function in children and adults with goiter and increased rates of stillbirth and perinatal and infant mortality. These conditions can be prevented by correcting iodine deficiency. Endemic goiter is present when the prevalence of goiter in a defined population exceeds 5%. Endemic goiter is graded by the method of WHO (Table 17.10). Screening estimates of iodine intake are usually derived from 24-hr urinary iodine excretion values or urinary iodine concentration expressed in relation to creatinine concentration as given in Table 17.11.

Endemic goiter does not differ from nontoxic diffuse sporadic goiter and the diagnosis is established by epidemiologic criteria. Usually TSH is elevated with low T4 and T3 levels.

Endemic cretinism is a disorder associated with endemic goiter and severe iodine deficiency with characteristic clinical features, which include deaf-mutism, squint, mental retardation and characteristic spastic or rigid neuromotor disorder. Two types of endemic cretinism are described. *Neurological cretinism* is characterized by deaf-mutism, squint, proximal spasticity and rigidity more in the lower extremities, disorders of stance and gait with preservation of vegetative functions, occasional signs of cerebellar or oculomotor disturbance and severe mental deficiency. *Myxedematous cretinism* is characterized by retarded psychomotor development, severe short stature, coarse facial features and myxedema without deaf-

Table 17.10: Estimation of thyroid size by palpation

Stage 0	No goiter
Stage 1A	Goiter detectable only by palpation and not visible even when the neck is fully extended
Stage 1B	Goiter palpable but visible only when the neck is fully extended (this stage also includes nodular glands even if not goitrous)
Stage 2	Goiter visible when the neck is in normal position; palpation not needed for diagnosis
Stage 3	Very large goiter, which can be recognized at a considerable distance

Table 17.11: Classification of severity of iodine deficiency

Iodine deficiency	*None*	*Mild*	*Moderate*	*Severe*
Median urine iodine, µg/L	>100	50–99	20–49	<20
Goiter prevalence	<5%	5–20%	20–30%	>30%
Neonatal thyroid stimulating hormone, >5 IU/mL whole blood	<3%	3–20%	20–40%	>40%
Cretinism	None	None	Present	Present

Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. 3rd ed. 2007, WHO

mutism. The pathogenesis of endemic cretinism is poorly understood. Iodine deficiency is also associated with poor school performance in children and recurrent pregnancy loss in women.

Prevention and control Iodine deficiency disorders are best prevented as treatment is usually ineffective. Iodinated salt or iodized oil are highly efficacious in preventing iodine deficiency. Treatment of endemic cretinism may eliminate signs of hypothyroidism but neuromotor and intellectual deficiency are irreversible. Surgical removal of large goiters is indicated only to relieve airway obstruction or for cosmetic reasons.

The National Goiter Control Program of the Ministry of Health in India began in 1962 with the establishment of salt iodination plants. The program is directed towards control of iodine deficiency disorders and working to ensure that only iodized salt will be used in India. The recommended daily intake of iodine is 40–120 µg for children up to the age of 10; 150 µg for older children and adults and an additional 25 and 50 µg during pregnancy and lactation respectively. Based on an assumption of a mean intake of salt of 5 g/day, the recommended level of iodination is one part of iodine in 25,000 to 50,000 parts of salt.

17

Hyperthyroidism

Hyperthyroidism is relatively uncommon in children. It is most commonly seen in young girls, caused by *Graves' disease* (Table 17.12).

The condition should be suspected in children with weight loss with increased appetite, tremors, diarrhea, warm extremities, increased sweating and anxiety. Inability to concentrate, personality changes, mood instability and poor school performance are common. Examination reveals firm homogeneous goiter. Eye signs are common and are related to sympathetic overactivity (lid lag, ophthalmoplegia, absence of wrinkling) or auto-immune infiltration (chemosis, proptosis). Tachycardia, cardiac arrhythmia and high output cardiac failure may occur.

Table 17.12: Etiology of hyperthyroidism

Infancy
Transplacental passage of thyroid antibodies
TSH receptor activating mutation
After infancy
Graves' disease (TSH receptor stimulating antibody)
Release of preformed thyroid hormone: Subacute thyroiditis
Toxic thyroid nodule, toxic multinodular goiter
Iatrogenic
Pituitary resistance to T3

The diagnosis is confirmed by the demonstration of elevated serum free T4 and T3 levels. The presence of goiter, infiltrative eye signs and hyperthyroidism is suggestive of Graves' disease. Absence of goiter should raise the possibility of transient hyperthyroidism as part of autoimmune thyroiditis. TSH levels are usually undetectable in Graves' disease. Ultrasonography and nuclear scan for radioactive iodine uptake (RAIU) are helpful in diagnosing toxic nodule or diffuse goiter.

Antithyroid drugs are ineffective in the acute phase due to lag period in their onset of action. Propylthiouracil is contraindicated in children due to hepatotoxicity. Treatment should be started with methimazole (0.5–1.0 mg/kg/day). Beta-blockers (propranolol 2 mg/kg/day in two divided doses) are effective in ameliorating of sympathetic symptoms. Iodinated contrast (idopate 0.001 µg/kg/day) and Lugol's iodine (5% iodine and 10% potassium iodide; 126 mg/ml iodine, 1 drop 8 hourly) are effective in reversing of features of hyperthyroidism. Prednisolone (1–2 mg/kg/day) inhibits peripheral conversion of T4 to T3 and is useful in treatment of hyperthyroid storm. Cardiac failure refractory to these measures requires treatment with digitalis.

Surgery and radioiodine ablation should be considered in patients showing failure of medical management. Patients with large or toxic nodular goiter require partial or total thyroidectomy. Radioiodine (^{131}I) is now increasingly used in the management of childhood Graves' disease.

Congenital Hyperthyroidism

One percent of babies born to mothers with Graves' disease show fetal thyrotoxicosis and cardiac failure. Management includes maternal anti-thyroid drugs and digitalization. This usually occurs within the first week of life but may be delayed if mother is on antithyroid medications or has concomitant TSH receptor blocking antibody. Treatment should include antithyroid drugs, propranolol and corticosteroids. The condition is self limiting and resolves over 3–6 months.

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DISORDERS OF CALCIUM METABOLISM

Physiology

Calcium homeostasis involves interaction of gastrointestinal absorption, bone resorption and renal excretion. Most (99%) body calcium is stored in the bone and is in constant equilibrium with serum calcium. Parathyroid hormone (PTH), vitamin D and calcitonin are the key regulators of calcium metabolism (*see* Fig. 5.7).

Calcium sensing receptors present in the parathyroid gland and kidneys sense serum calcium levels. Reduced action of the receptor in the presence of low serum calcium levels results in increased PTH secretion and inhibition of renal calcium excretion.

PTH increases serum calcium by stimulating bone resorption (osteoblast), calcitriol production (proximal tubule) and renal calcium resorption (distal tubule).

Calcitriol is the only hormone that regulates calcium absorption. Calcitriol is formed by activation of vitamin D in the liver (25-hydroxylation) and kidney (1α-hydroxylation). Sunlight is the major source of vitamin D with minor contribution from dietary sources.

1α-hydroxylase enzyme in the kidneys is the rate limiting step of calcitriol synthesis.

Calcitonin, secreted by the parafollicular cells of thyroid in response to elevated calcium levels, lowers serum calcium levels by decreasing bone resorption and increasing urinary calcium excretion.

Hypocalcemia

Hypocalcemia (total calcium <8 mg/dl) is an important metabolic situation. Estimation of ionic calcium is important for confirmation of hypocalcemia (ionic calcium <1.1 mmol/l). Empirical formula for calculation of ionic calcium may be used if ionic levels are not available.

Ionized Ca^{++} = Total Ca^{++} – 0.8 × (albumin g/dl– 4)

Clinical Features

In the neonatal period, subtle clinical features like lethargy, jitteriness and poor feeding are characteristic of hypocalcemia. Seizures are common and hypocalcemia is the commonest biochemical abnormality associated with neonatal seizures.

In the postneonatal period, the commonest presentation is *tetany* (simultaneous contraction of groups of muscles). This is most commonly observed in hands (adduction of thumbs along with extension of the proximal interphalangeal joints and flexion of distal interphalangeal joints) and feet (flexion and internal rotation of lower limbs) resulting in carpopedal spasm. In milder cases, latent tetany can be detected by tests of neuromuscular excitability. Tapping the facial nerve at the angle of jaw results in contraction of facial muscles (Chvostek sign). Inflating blood pressure cuff above the systolic blood pressure for more than 5 minutes triggers spasm of the hand muscles (Trousseau sign). Hypocalcemia should be considered in children with seizures, dilated cardiomyopathy and unexplained stridor.

The diagnosis is confirmed by the demonstration of prolonged QT interval on ECG, as suggested by Q_oT_c more than 0.2 seconds, where

$$Q_oT_c = \frac{Q_oT}{\sqrt{RR}}$$

Q_oT = Interval from beginning of Q wave to beginning of T wave; RR = RR interval

Etiology

Hypocalcemia may be caused by chelation of calcium or inefficient action of PTH or vitamin D (Table 17.13).

PTH related. Inefficient PTH action caused by decreased production (hypoparathyroidism) or action (pseudohypoparathyroidism) is an important cause of hypocalcemia.

Table 17.13: Etiology of hypocalcemia

Deficiency of ionic calcium (chelation)
Phosphate load
Tumor lysis
Rhabdomyolysis
Top feeds
Total calcium deficiency
PTH deficiency (hypoparathyroidism)
Aplasia: DiGeorge syndrome
Autoimmune: Polyglandular endocrinopathy types I and II
Infiltration: Wilson disease, hemochromatosis, thalassemia
Transient: Hypomagnesemia, maternal hyperparathyroidism, post-surgery
PTH resistance (pseudohypoparathyroidism)
Vitamin D deficiency
Nutritional
1α-hydroxylase deficiency: Renal failure, VDDR* type I
Calcitriol resistance: VDDR type II
Increased inactivation: Phenytoin, phenobarbitone

*VDDR Vitamin D dependent rickets

These disorders are characterized by *high phosphate levels* due to impaired phosphaturic action of PTH.

Hypoparathyroidism may occur as part of congenital malformation or acquired destruction of the parathyroid glands. *Autoimmune hypoparathyroidism* is the most common form in older children and frequently associated with autoimmune polyendocrinopathy type 1.

DiGeorge syndrome characterized by abnormal development of third and fourth pharyngeal pouches is caused by deletion of part of chromosome 22q. This results in maldevelopment of thymus (resulting in T cell immunodeficiency), parathyroids (resulting in hypoparathyroidism), heart (resulting in conotruncal defects) and face (abnormal facies).

Hypomagnesemia is an important cause of transient hypoparathyroidism and should be excluded in children with refractory hypocalcemia.

PTH resistance (pseudohypoparathyroidism, PHP), is caused by inactivating mutation in the gene encoding for stimulatory subunit of G protein (Gsα). This presents with clinical features of hypoparathyroidism in the wake of elevated PTH levels. PHP may be associated with the phenotype of Albright hereditary osteodystrophy such as round facies, brachydactyly, short stature, obesity, short fourth and fifth metacarpals (brachymetacarpia), osteodystrophy and heterotopic ossification

Vitamin D related. Vitamin D deficiency (nutritional, malabsorption), decreased 1α-hydroxylase action (renal failure, vitamin D dependent rickets type I), increased inactivation of vitamin D (antiepileptic drugs) and calcitriol resistance (vitamin D dependent rickets type II) are associated with hypocalcemia. Phosphate levels are low due to secondary hyperparathyroidism. *Vitamin D deficiency* is the most common cause of hypocalcemia in children. Rickets may be absent. Maternal vitamin D deficiency is common in India and results in reduced calcium and vitamin D stores in children. These infants develop hypocalcemia during periods of rapid bone growth (4–8 weeks of life). Vitamin D dependent rickets presents with early onset severe hypocalcemia and rickets.

Increased chelation. Increased calcium binding results in reduction of ionic calcium and features of hypocalcemia. This is most commonly related to *high phosphate* levels (renal failure or release of intracellular phosphate due to hemolysis, tumor lysis or rhabdomyolysis). Increased phosphate levels in cow milk and commercial formula is an important cause of neonatal hypocalcemia. *Metabolic or respiratory alkalosis* increases albumin binding of calcium resulting in hypocalcemia.

Evaluation

Evaluation is directed towards identification of etiology and assessment of the severity of illness.

Clinical. Detailed history of the age of onset, presenting features, frequency of episodes of hypocalcemia and family history should be obtained. Neonates should be screened for prematurity, birth asphyxia, maternal hyperparathyroidism and initiation of top feeds. Congestive cardiac failure, recurrent infections and abnormal facies are suggestive of DiGeorge syndrome.

Investigations. Initial evaluation should include serum phosphate levels, renal and liver function tests and serum alkaline phosphatase (Table 17.14 and Fig. 17.9). Phosphate regulation is dependent on PTH and inefficient PTH action results in hyperphosphatemia. Hypocalcemia due to decreased vitamin D action is associated with secondary hyperparathyroidism and low phosphate levels. Thus hypocalcemia with hyperphosphatemia in the absence of phosphate load (exogenous or tissue lysis) and normal renal function suggests parathyroid insufficiency. Hypomagnesemia should be considered in patients with refractory hypocalcemia and normal or low phosphate levels. 25-hydroxyvitamin D levels should be measured in children with rickets to identify vitamin D deficiency.

Management

In children with severe hypocalcemia (ionic calcium <0.8 mmol/l) parenteral calcium should be administered (2 ml/kg intravenously over 5–10 min) after obtaining blood sample for calcium. Calcium gluconate (10%, 9 mg calcium per ml) is the preparation of choice. Care should be taken to administer the drug slowly (to avoid cardiac effects) and avoid extravasation (to prevent skin necrosis). Parenteral calcium should be started at a dose of 80 mg/kg/day and should be gradually tapered over two days.

Short course activated vitamin D (calcitriol or 1α-vitamin D, 20–40 ng/kg/day in three divided doses for 2 days) should be given to children with vitamin D deficiency and acute hypocalcemia. This should be combined with high dose vitamin D (300,000–600,000 IU) to replenish body stores of the vitamin. Longterm management for conditions with inefficient PTH action includes activated vitamin D (30–60 ng/kg/day) and

Table 17.14: Laboratory features of common causes of hypocalcemia

Disorder	*Phosphate*	*25-hydroxyvitamin D*	*Parathormone*
Vitamin D deficiency	Low, normal	Low	High
Renal failure	High	Normal	High
Hypoparathyroidism	High	Normal	Low
Pseudohypoparathyroidism	High	Normal	High
Hypomagnesemia	Low, normal	Normal	Low

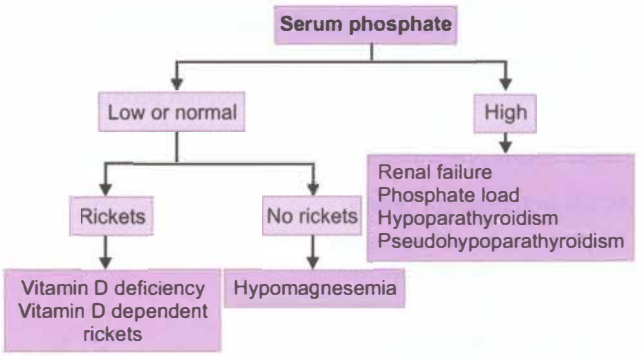

Fig. 17.9: Evaluation of a child with hypocalcemia

calcium (50 mg/kg/day) in the form of calcium carbonate. Vitamin D dependent rickets is managed with activated vitamin D and calcium phosphate. Higher doses of vitamin D may be required in patients with calcitriol resistance.

Hypercalcemia

Hypercalcemia (serum calcium >11 mg/dl) is rare in children. Its causes include increased bone resorption (hyperparathyroidism, malignancy and immobilization) or excessive vitamin D action (iatrogenic excess and increased 1 α-hydroxylase activity).

Hyperparathyroidism is the commonest cause of chronic hypercalcemia in children. Homozygous inactivating mutations of the calcium sensing receptor present with severe neonatal hyperparathyroidism. Parathyroid adenoma is rare before the age of 10 yr. Rarely, hypercalcemia may be associated with other conditions, e.g. William syndrome (supravalvular aortic stenosis, abnormal facies) or hypophosphatasia (inactivating mutation of alkaline phosphatase). Vitamin D related hypercalcemia most commonly occurs in patients with overdose of vitamin D. Increased 1α-hydroxylase activity may occur in patients with granulomatous diseases (tuberculosis, sarcoidosis) or fat necrosis.

Clinical features are often nonspecific, including muscular weakness, anorexia, nausea, vomiting, constipation, polydipsia and polyuria. Ectopic calcification in the kidney, basal ganglia and skin are common. Bony deformities and pathological fractures may be present. Infants present with failure to thrive, poor feeding, hypotonia and seizures. Serum total and ionized calcium levels are elevated with low levels of phosphate. Hyperparathyroidism is associated with elevated levels of PTH.

Treatment of acute hypercalcemia involves high fluid intake followed by diuresis (frusemide 1 mg/kg). Bisphosphonates and antiresorptive agents are indicated if there is no response to these measures. Hemodialysis may be required in refractory cases. Surgical exploration is indicated in all cases of hyperparathyroidism. Short course of glucocorticoids (prednisolone 2 mg/kg/day for 3 weeks) is indicated in children with iatrogenic vitamin D excess or increased 1α-alpha hydroxylase action (fat necrosis or sarcoidosis).

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DISORDERS OF ADRENAL GLANDS

Physiology

Adrenal cortex produces three important groups of hormones—glucocorticoids, mineralocorticoids and androgens. The process of steroidogenesis involves conversion of cholesterol to steroid hormones through a series of enzymatic processes. Cholesterol is transferred into the mitochondria in a process mediated by the steroidogenic acute regulatory protein (StAR), an ACTH-dependent protein. The most clinically relevant step in steroidogenesis is 21-hydroxylation mediated by the enzyme 21-hydroxylase (P450c21). This step is crucial for the production of cortisol and aldosterone.

Cortisol, the major glucocorticoid hormone has an important role in intermediary metabolism causing increased blood glucose levels and enhanced catabolism of proteins and lipids. *Aldosterone* acts on distal renal tubules and collecting ducts of kidneys to promote sodium and fluid reabsorption. Aldosterone deficiency causes urinary salt wasting resulting in salt wasting crisis (hyponatremia, hyperkalemia and metabolic acidosis). *Adrenal androgens* are necessary for the development of pubic and axillary hair in girls.

Adrenocorticotropic hormone (ACTH), a polypeptide secreted by the anterior pituitary, is the principle regulator of glucocorticoid and androgen synthesis. Intravascular volume, serum potassium levels and renin–angiotensin system are the chief regulators of aldosterone synthesis. ACTH has only a minor role in aldosterone regulation. ACTH deficiency as in secondary adrenal insufficiency is therefore not associated with salt wasting. ACTH secretion is stimulated by hypothalamic coriticotrophin releasing hormone and suppressed by cortisol as part of a feedback loop.

Adrenocortical Excess

The most common disorder of adrenocortical hyperfunction is Cushing syndrome. The term Cushing disease refers to hypercortisolism caused by an ACTH-producing pituitary tumor. Classic features of Cushing syndrome such as central obesity, striae, moon facies and buffalo hump are rare in children (Fig. 17.10.) Growth failure and obesity are common; other features include hypertension, hirsutism, delayed puberty, behavioral problems, bone pain and muscle weakness.

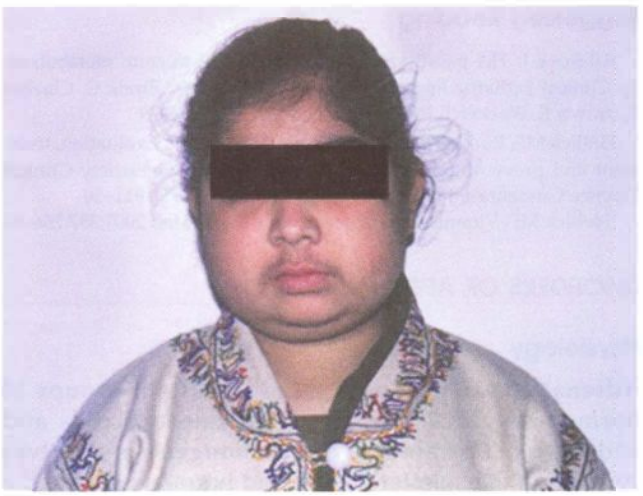

Fig. 17.10: Cushing disease secondary to pituitary adenoma. Note the moon face and hypertrichosis over forehead and upper lip

Etiology

Cushing syndrome may be caused by increased endogenous production or exogenous administration (Table 17.15). Prolonged steroid treatment is the commonest cause of childhood Cushing syndrome. Increased adrenal glucocorticoid production may be related to increased ACTH levels or represent autonomous adrenal hyperfunction. Adrenal pathology is more likely in young children, while pituitary causes are common after puberty. Ectopic ACTH production is rare.

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Evaluation

Investigations are directed towards confirming the diagnosis of Cushing syndrome and finding the etiology. The commonly used screening tests include assessment of diurnal cortisol rhythm, overnight dexamethasone suppression test (cortisol levels after a single midnight dose of dexamethasone 0.3 mg/m^2; maximum dose 1 mg) and 24 hr urine free cortisol (Table 17.16). Diagnosis can be confirmed with low dose dexamethasone suppression test (serum cortisol after dexamethasone 5 µg/kg every 6 hr for two days).

The most important part of evaluation of a child with Cushing syndrome is to differentiate ACTH-dependent causes from autonomous adrenal steroid production (Table 17.17). ACTH levels differentiate ACTH-independent (ACTH levels <5 pg/ml) from ACTH-dependent conditions (ACTH levels >15 pg/ml). Ectopic ACTH production should be suspected in children with extremely high ACTH levels (>100 pg/ml). High dose dexamethasone suppression test is based on the principle that high doses of this agent suppress ACTH production in individuals with pituitary lesions but not in those with ectopic ACTH production.

Table 17.15: Etiology of Cushing syndrome

ACTH dependent causes
Hypothalamic lesions: Increased corticotrophin production
Pituitary lesions: Microadenoma, macroadenoma
Ectopic lesions: Neuroblastoma, carcinoid tumor, Wilms tumor
ACTH independent causes
Adrenal carcinoma, adenoma
Pigmented nodular hyperplasia
McCune Albright syndrome
Exogenous administration
Glucocorticoids
ACTH

Table 17.16: Screening tests for Cushing syndrome

Test	*Sensitivity*	*Specificity*	*Cut-off level*	*Comments*
Morning cortisol	Low	Low	>10 µg/dl	Not recommended
Overnight dexamethasone suppression test	High	Low	>5 µg/dl	Screening test
Urine free cortisol	High	High	>75 µg/m^2/day	Screening test*
Low dose dexamethasone suppression test	High	High	>5 µg/dl	Diagnostic test

* Diagnostic of Cushing syndrome if level is greater than 3 to 4 times the normal range

Table 17.17: Laboratory findings of common causes of Cushing syndrome

Disorder	*Urinary free cortisol*	*High dose dexamethasone suppression test*	*Adrenocorticotrophic hormone*
Adrenal lesion			
Pituitary lesion	High	Not suppressed	Low
Microadenoma	High	Suppressed	High
Macroadenoma	High	Not suppressed	High
Ectopic ACTH	High	Not suppressed	High
Exogenous	Low	Not suppressed	Low

Adrenal tumors in children are usually large and identifiable on ultrasound. Magnetic resonance imaging of the hypothalamic-pituitary region should be performed in children with ACTH-dependent Cushing syndrome. Inferior petrosal sinus sampling is the test for identifying the source of ACTH production and should be performed in children with ACTH-dependent Cushing syndrome with normal neuroimaging.

Management

Resection of adrenal lesion is recommended for adrenal adenoma and carcinoma. Prolonged cortisol excess causes suppression of the normal contralateral adrenal gland. This mandates close monitoring for adrenal insufficiency in the perioperative period. Adrenal carcinoma is highly malignant and has a high rate of recurrence. Pigmented nodular hyperplasia should be treated with bilateral adrenalectomy. Trans-sphenoidal resection of pituitary adenoma is recommended for Cushing disease.

Medical management of Cushing syndrome with inhibitors of steroidogenesis (ketoconazole, aminoglutethimide, cyproheptadine, metyrapone and mitotane) has been tried with variable results.

Aldosterone Excess

Hyperaldosteronism is associated with fluid and sodium retention along with increased urinary loss of potassium. The most common clinical features of primary hyperaldosteronism are hypertension and hypokalemic alkalosis. Primary hyperaldosteronism due to increased adrenal aldosterone production is extremely rare. Secondary hyperaldosteronism results from factors that activate renin–angiotensin system.

Primary hyperaldosteronism may be caused by diffuse hyperplasia or adenoma. *Glucocorticoid-remediable aldosteronism* (GRA), a genetic disorder involving chimeric fusion of the promoter of CYP11B1 and the coding region of CYP11B2 genes, resulting in regulation of aldosterone secretion by ACTH and therefore, hyperaldosteronism. Primary hyperaldosteronism should be differentiated from secondary hyperaldosteronism (renal failure, congestive cardiac failure, liver disease and nephrotic syndrome and other states of minerolocorticoid excess, and apparent mineralocorticoid excess (Table 17.18).

Hypokalemic alkalosis in a child with low renin hypertension should prompt evaluation for true or apparent aldosterone excess. High aldosterone level in this setting is suggestive of primary hyperaldosteronism or GRA. Decrease in aldosterone levels and resolution of clinical and laboratory features after dexamethasone suppression suggests GRA; no effect is seen in primary hyperaldosteronism. Diagnosis of primary hyperaldosteronism should be confirmed by adrenal imaging.

Hyperaldosteronism should be managed with salt restriction and aldosterone antagonist such as, spironolactone or eplerenone. Physiological hydrocortisone replacement suppresses ACTH secretion in glucocorticoid remediable aldosteronism resulting in resolution of hyperaldosteronism and hypertension. Surgery is the treatment of choice for adrenal adenoma.

Table 17.18: Etiology of hyperaldosteronism

Primary hyperaldosteronism
Adenoma, hyperplasia
Glucocorticoid remediable hyperaldosteronism
Secondary hyperaldosteronism
Renal artery stenosis, renin secreting tumor
Cardiac failure, nephrotic syndrome, liver disease
Other causes of excessive mineralocorticoid action
Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase)
Liddle syndrome
Congenital adrenal hyperplasia due to deficiency of 17α-hydroxylase or 11β-hydroxylase

Pheochromocytoma

Pheochromocytoma is a catecholamine-secreting tumor, arising from the chromaffin cells of adrenal medulla. It can also arise from the abdominal sympathetic chain, periadrenal area, or in the thoracic cavity. The condition is rare in children and coexists with other syndromes such as neurofibromatosis, von Hippel Lindau disease and multiple endocrine neoplasia type II. Compared to adults, pheochromocytoma is more likely to be bilateral and associated with underlying genetic anomaly in children.

Excessive secretion of catecholamines results in hypertension, which is usually sustained and occasionally paroxysmal. The clinical symptoms include headache, palpitation, pallor, sweating, nausea, vomiting, visual disturbances and occasionally convulsions. The diagnosis should be considered only after other common causes of childhood hypertension like renal parenchymal disorders, renal artery stenosis and coarctation of aorta have been excluded. Diagnosis is established by demonstration of increased urinary excretion of catecholamines and their derivatives. Ultrasound, CT scan, MRI scan and ^{123}I metaiodobenzylguanidine (MIBG) scintigraphy are used for localization. Often the tumors are multiple.

Surgery is the treatment of choice. Transabdominal exploration of all the sites with removal of tumors is advocated. Preoperative alpha blockade is needed using phenoxybenzamine and prazosin. Recently, calcium channel blocking agents have been used successfully.

Adrenal Insufficiency

Adrenal insufficiency may be related to adrenal defects (primary adrenal insufficiency; autoimmune destruction, infection, steroidogenic defect, hemorrhage), decreased ACTH production (secondary adrenal insufficiency) or ACTH resistance.

Autoimmune adrenal dysfunction is the commonest cause of primary adrenal failure (Addison disease) beyond infancy. Autoimmune adrenal failure is often associated with autoimmune polyendocrinopathy type 1 and 2. Infections like tuberculosis and HIV can result in primary adrenal failure. Adrenal hemorrhage in the setting of meningococcal and other bacterial infections (Waterhouse-Friderichsen syndrome) is an important cause of insufficiency. Congenital adrenal hyperplasia (CAH) due to deficiency of 21-hydroxylase or 3-β hydroxysteroid dehydrogenase and deficient steroidogenesis due to defective steroidogenic acute regulatory protein (StAR; causing lipoid CAH) are the commonest causes in the neonatal period.

Secondary adrenal insufficiency is caused by congenital malformations (holoprosencephaly, midline defects), genetic defects or acquired insults (neurosurgery, tumor, radiation). This is usually associated with other anterior pituitary hormone deficiencies as well. In secondary adrenal insufficiency, mineralocorticoid function is preserved as aldosterone is not regulated by ACTH. Thus, salt wasting is not observed. Prolonged steroid treatment is associated with suppression of the hypothalamic-pituitary axis resulting in adrenal insufficiency after discontinuation of medications. Again, mineralocorticoid activity is preserved in these patients.

Clinical Features

Adrenal insufficiency presents with slowly progressive lethargy, vomiting, salt craving, fatigue, postural hypotension, hypoglycemia and episodes of shock during severe illness. The concomitant presence of shock, hyponatremia, hyperkalemia and hemoconcentration is characteristic of acute adrenal insufficiency and warrants immediate steroid replacement. Primary adrenal insufficiency is characterized by hyperpigmentation due to elevated levels of melanoyte stimulating hormone. Hyperpigmentation is present in sun-exposed areas such as elbows and palmar creases and areas that are normally hyperpigmented such as areola and genitalia. Pigmentation is absent in children with secondary adrenal insufficiency.

Evaluation

All patients suspected to have adrenal insufficiency should undergo urgent testing for serum electrolytes and blood sugar. Basal levels of cortisol are low but can be in the normal range. Elevated plasma renin activity indicates mineralocorticoid deficiency. ACTH stimulation test (cortisol estimation 60 minutes after 0.25 mg of intramuscular or intravenous ACTH injection) is the best test for adrenocortical reserve. Serum cortisol levels lower than 18 µg/dl are suggestive of adrenal insufficiency.

The next step in evaluation of adrenal insufficiency is estimation of ACTH levels. Elevated ACTH levels suggest primary adrenal pathology while low levels points towards pituitary defect. Further evaluation of primary adrenal insufficiency includes abdominal CT scan and workup for tuberculosis.

Management

The initial management of salt wasting crisis includes correction of shock by fluid boluses. Hydrocortisone is given immediately at a dose of 50 mg/m^2 followed by 100 mg/m^2/day in four divided doses. Frequent monitoring of hemodynamic parameters, urine output and serum electrolytes are required. Once the child is hemodynamically stable, hydrocortisone can be tapered to the physiological dose (10 mg/m^2/day). Fludrocortisone acetate (0.1 mg/day) should be added once the hydrocortisone dose is less than 50 mg/m^2/day.

Longterm management of adrenal insufficiency requires lifelong replacement of glucocorticoids and mineralocorticoids. Parents should be educated about the need of increasing dose during periods of stress. The dose of glucocorticoid should be increased 2–3 times in conditions of minor stress (fever and mild infection) and 4–5 times in severe stress (severe infection or surgery). These doses should continue throughout the period of stress. Patients with secondary adrenal insufficiency require lower dose of glucocorticoids (6–10 mg/m^2/day); mineralocorticoid replacement is not necessary.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH), a group of autosomal recessive defects in steroid synthesis, is characterized by deficiency of adrenocortical hormones on one hand and excess of steroid precursors on the other (Fig. 17.11). CAH is the commonest adrenal disorder in childhood.

21-hydroxylase Deficiency

21-hydroxylase deficiency is the commonest form of CAH accounting for over 90% of all cases. This disorder is associated with diminished synthesis of the cortisol and aldosterone. Low cortisol levels stimulate ACTH synthesis. Elevated ACTH level causes accumulation of steroid precursors (dehydroepiandrosterone), androstenedione and 17-hydroxyprogesterone). Depending on the severity of enzyme deficiency the disease forms a spectrum of presentation as highlighted below.

Salt wasting form. These patients are the most severely affected and present in the neonatal period with virilization and salt wasting. Abnormal genital appearance should prompt the diagnosis in girls. Diagnosis is often missed in boys as they lack specific clinical features. They present after second week of life with failure to thrive, polyuria, hyperpigmentation and shock. Early diagnosis is mandatory to prevent mortality. 21-hydroxylase deficiency should be suspected in neonates with ambiguous genitalia, polyuria, shock, recurrent vomiting and features of sepsis with negative septic screen. The

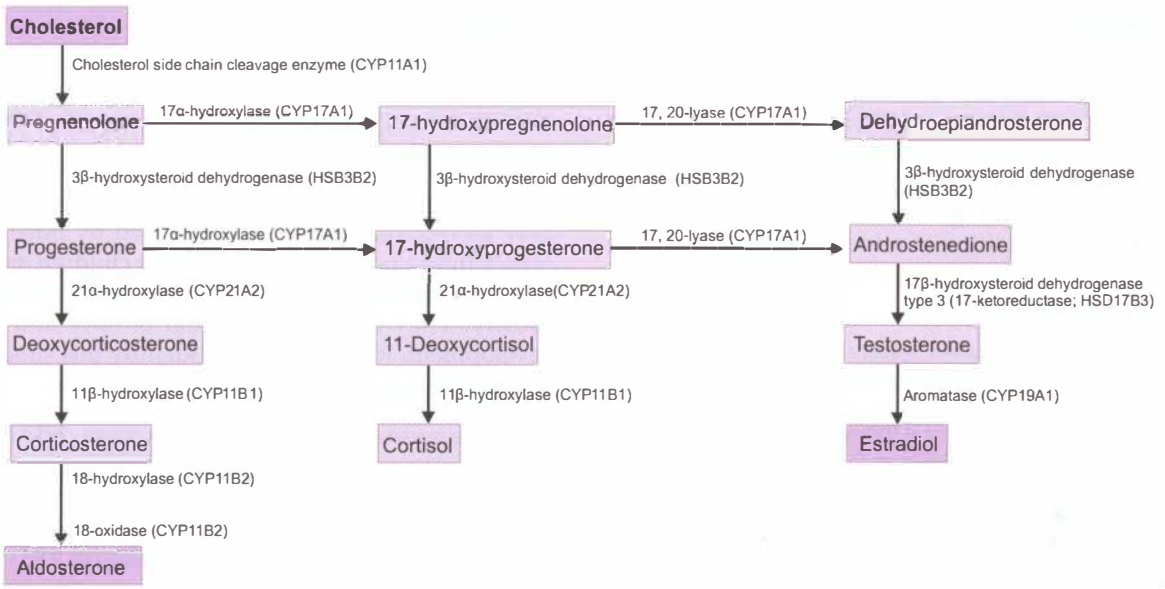

Fig. 17.11: Pathways of steroid biosynthesis. The key enzymes mediating synthesis of principal steroids are named according to their site of action; the nomenclature of cytochrome P450 enzymes is indicated in parenthesis

diagnosis should be confirmed immediately by measurement of blood levels of 17-hydroxyprogesterone. If these are not available, the child should be managed empirically in the lines of adrenal insufficiency.

Simple virilizing form. A subset of patients with 21-hydroxylase deficiency (25%) synthesizes enough aldosterone to prevent adrenal crises. These patients have features of androgen excess in the form of virilization in girls and peripheral precocious puberty in boys (Fig. 17.12).

Nonclassic form. This disorder is associated with partial 21-hydroxylase deficiency. Clinical manifestations are related to mild hyperandrogenism which presents with hirsutism, acne and menstrual irregularity.

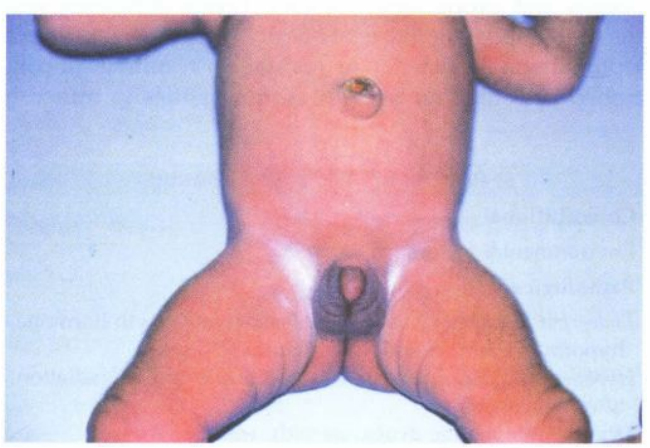

Fig. 17.12: Congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency: Note the clitoral hypertrophy, hyperpigmentation and increased rugosity of the labial folds giving a male appearance to the female genitalia

Diagnosis

Diagnosis of salt wasting form is established by demonstration of extreme elevation of 17-hydroxyprogesterone levels (10000–20000 ng/dl, normal <90 ng/dl) in presence of clinical and laboratory features of adrenal insufficiency. 17-hydroxyprogesterone levels are elevated to a lesser extent in those with simple virilizing and non classic forms. The best method of diagnosing these patients is the estimation of 17-hydroxyprogesterone levels before and 60 minutes after an intramuscular injection of ACTH (0.25 mg).

Management

These patients require lifelong treatment. Patients with salt wasting and virilizing forms should be treated with hydrocortisone (10–15 mg/m^2/day) and fludrocortisone (0.1 mg/day). After completion of growth, synthetic glucocorticoid preparations (dexamethasone, prednisolone) can be used (Table 17.19).

Table 17.19: Comparison of commonly used steroid preparations

Preparation	*Potency (compared to hydrocortisone)*			*Biological half-life*
	Gluco-corticoid	*Mineralo-corticoid*	*Growth inhibitory*	
Hydrocortisone	1	1	1	6 hr
Cortisone	0.8	1.25	1.25	5 hr
Prednisolone	4	0.25	8	8 hr
Dexamethasone	20	0	40	12 hr
Fludrocortisone	0.1	100	0.1	12 hr

Other Variants

Enzyme deficiencies other than 21-hydroxylase deficiency account for less than 10% of cases of CAH. Patients with 11β-hydroxylase deficiency and 17α-hydroxylase deficiency present with hypertension and should be managed with hydrocortisone alone. Deficiencies of StAR and 3α-hydroxysteroid dehydrogenase manifest as salt wasting crisis and require addition of mineralocorticoid.

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OBESITY

The incidence of childhood obesity has increased rapidly in the last decade. Childhood obesity has serious short and longterm medical consequences.

Criteria for Obesity

17

Obesity implies excessive fat and not merely excess weight. As methods of measuring body fat are cumbersome and expensive, several clinical and anthropometric parameters are used as markers of obesity.

Body mass index. Body mass index (BMI) is the most widely used parameter to define obesity. It takes into account weight as well as the height. It is calculated by the formula:

$$\text{BMI} = \text{Weight (kg)} \div \text{height (m)}^2$$

Children with BMI more than 85th percentile for age are considered overweight while those more than 95th percentile for age are obese. BMI is a good indicator of body fat but is unreliable in short muscular individuals.

Weight for height. This compares the child's weight to the expected weight for his/her height (*see* Chapter 2). Weight for height more than 120% is diagnosed as obesity.

Skin fold thickness. Skin fold thickness measured over the subscapular, triceps or biceps regions is an indicator for subcutaneous fat. Age specific percentile cut-offs should be used with values more than 85 percentile being abnormal.

Waist circumference. This is a marker of abdominal adiposity, a key risk factor for metabolic and cardiovascular effects of obesity.

Etiology

In most children with obesity, environmental and hereditary factors play the major role. Underlying etiology is identified in very few cases (<1%). The causes of childhood obesity are classified in Table 17.20.

Constitutional obesity. Most children with obesity do not have an organic cause. This is caused by imbalance in energy intake and expenditure. These children are tall for age, a factor that differentiates them from pathological obesity. They have proportional obesity and normal development. It is important to identify this subgroup of children to avoid unnecessary investigations.

Endocrine causes. Growth failure in an obese child indicates an endocrine etiology. *Cushing syndrome* is characterized by central obesity, hypertension, striae and retarded skeletal maturation. *Hypothyroidism* is an extremely rare cause of isolated obesity and other features like developmental delay and coarse skin are always present. In GH deficiency and pseudohypoparathyroidism, growth retardation and hypocalcemia are dominant clinical features and obesity is a less prominent manifestation.

Genetic syndromes. A variety of genetic syndromes have obesity as their major clinical feature. Many of these syndromes are associated with hypogonadism or hypotonia (Prader-Willi, Carpenter and Laurence Moon Bardet Biedl syndromes).

Hypothalamic obesity. CNS insults due to surgery, radiation, tumors and trauma results in rapid onset obesity. These disorders are associated with excessive appetite, signs and symptoms of CNS involvement and other hypothalamic-pituitary defects.

Monogenic obesity. Monogenic obesity represents a very small proportion of children with obesity. They are more likely in the presence of early onset of obesity, morbid obesity and strong family history. Leptin deficiency was the first monogenic cause of obesity identified. Inefficient leptin action (deficiency or resistance) results in uncontrolled appetite and obesity. Abnormalities in mineral-

Table 17.20: Etiology of obesity

Constitutional
Environmental factors (95% cases)
Pathological
Endocrine: Cushing syndrome, deficiency of growth hormone, hypothyroidism, pseudohypoparathyroidism
Hypothalamic: Head injury, infection, brain tumor, radiation, after neurosurgery
Drugs: Antiepileptic drugs, steroids, estrogen
Genetic syndromes: Prader-Willi, Laurence Moon Bardet Biedl, Beckwith Weidemann, Carpenter
Monogenic disorders: Leptin deficiency, or resistance, abnormalities of melanocortin-4 receptor and proconvertase

ocorticoid receptor and proconvertase have also been associated with obesity.

Evaluation

Initial evaluation is guided to differentiate constitutional from pathological obesity (Table 17.21). Normal growth, generalized pattern and lack of developmental delay or dysmorphism suggests constitutional obesity and against the need for extensive investigations.

Clinical. Family history of obesity and its complications should be recorded. Detailed history of physical activity, dietary recall and periods of inactivity should be assessed. Increased appetite in a child with recent onset obesity may indicate the possibility of a hypothalamic lesion. Features of raised intracranial tension along with history of neurologic infection, head trauma or neurosurgery suggests the diagnosis of neurologic cause of obesity. Intake of drugs linked with development of obesity like steroids and antiepileptics should be enquired. Examination should be performed for features of endocrinopathies, dysmorphic syndromes and complications such as hypertension and acanthosis nigricans. Special emphasis should be given to sexual maturity and ocular examination. Hypogonadism is an important feature of obese children with Laurence Moon Bardet Biedl syndrome and Prader-Willi syndromes (Figs 17.13, 17.14 and Table 17.22).

Table 17.21: Comparison of constitutional and pathological obesity

Feature	*Constitutional*	*Pathological obesity*
Distribution	Generalized	Usually central
Growth	Accelerated	Retarded
Bone age	Advanced	Retarded
Dysmorphism	Absent	May be present

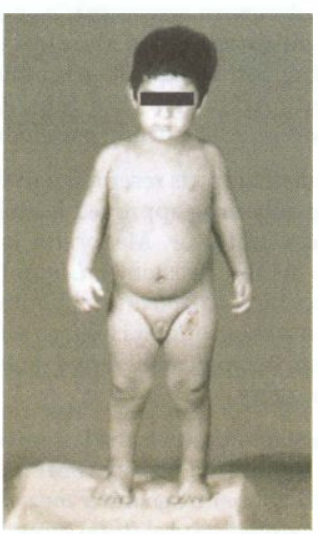

Fig. 17.13: Laurence Moon Bardet Biedl syndrome. Note the central obesity and hypoplastic genitalia

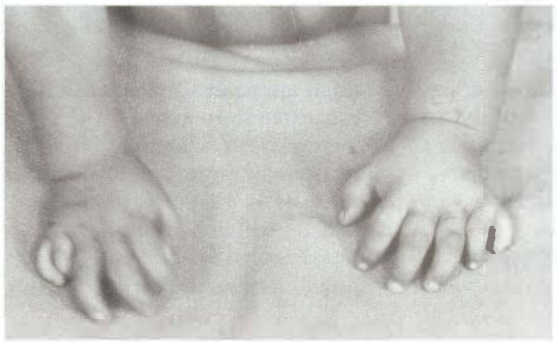

Fig. 17.14: Laurence Moon Bardet Biedl syndrome. Note the polydactyly

Investigations. Investigations are decided based on the degree of obesity and associated complications. Endocrine investigations are done only in the presence of pointers to diagnosis such as growth failure, clinical features, developmental delay and dysmorphism. Screening for complications is indicated in obese children (BMI >95th percentile). Investigations are also recommended for overweight children in the presence of family history of cardiovascular complications or type 2 diabetes mellitus or rapid increase in obesity. This evaluation should include oral glucose tolerance test, serum cholesterol and liver function tests.

Complications

Childhood obesity is associated with significant complications (Table 17.23).

Cardiovascular. Obesity has been linked with hyperlipidemia, hypertension and coronary artery disease.

Endocrine. Most important endocrine complication of obesity is insulin resistance. This presents as a spectrum of changes ranging from elevated insulin levels to impaired glucose tolerance to type 2 diabetes mellitus. A

Table 17.22: Pointers to diagnosis of obesity

Feature	*Etiology*
Hypogonadism	Laurence Moon Bardet Biedl, Prader-Willi syndrome
Retinitis pigmentosa	Alstrom syndrome, Laurence Moon Bardet Biedl syndrome
Ear lobe creases, organomegaly	Beckwith-Weidemann syndrome
Short hand and feet, almond shaped eyes	Prader-Willi syndrome
Polydactyly	Laurence Moon Bardet Biedl syndrome, Alstrom syndrome
Buffalo hump, striae	Cushing syndrome
Metacarpal shortening	Pseudohypoparathyroidism
Mental retardation	Prader-Willi syndrome, hypothyroidism, pseudohypoparathyroidism

Table 17.23: Complications of obesity

System	*Complication*
Central nervous	Benign intracranial hypertension
Respiratory	Obstructive sleep apnea
Cardiovascular	Atherosclerosis, hypertension
Hepatobiliary	Nonalcoholic steatohepatitis, gall stones
Endocrine	Polycystic ovarian disease, type 2 diabetes mellitus, dyslipidemia
Orthopedic	Slipped capital femoral epiphyses, Blount disease, osteoarthritis

characteristic clinical feature is *acanthosis nigricans*, dark and rough areas on the exposed areas of skin including back of neck, axilla and thigh (Fig. 17.15). Ovarian hyperandrogenism leading to premature adrenarche and polycystic ovarian syndrome is an important feature of obesity.

Respiratory. Obesity is associated with restrictive lung disease (decreased respiratory movements due to chest wall obesity) as well as obstructive airway disease (airway fat deposition). The most severe complication is the obesity-hypoventilation syndrome associated with hypoxia and features of cor pulmonale. Milder forms are associated with snoring, irritability, hyperactivity and daytime somnolence.

Orthopedic. Obese children are prone to slipped femoral epiphyses, flat feet, Blount disease (tibia vara) and early onset osteoarthritis.

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Hepatobiliary. Insulin resistance in obesity is associated with fatty infiltration in liver. This may vary from mild infiltration with no effect to steatohepatitis and chronic liver disease. The incidence of cholelithiasis is increased

Management

Management of childhood obesity is challenging with major impetus on lifestyle measures (Fig. 17.16.) Specific management is available for only a few conditions. Diet,

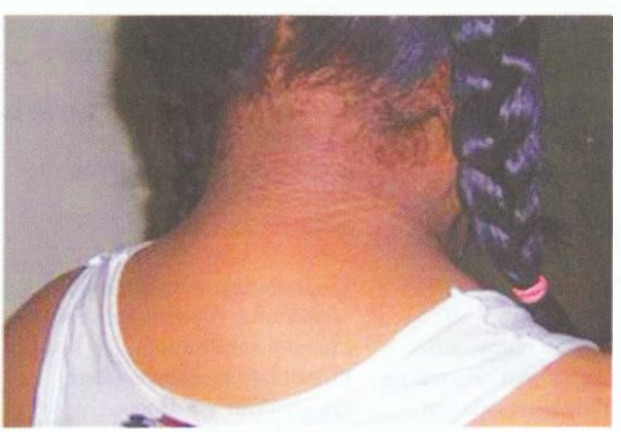

Fig. 17.15: Acanthosis nigricans on the back of neck in a girl with obesity

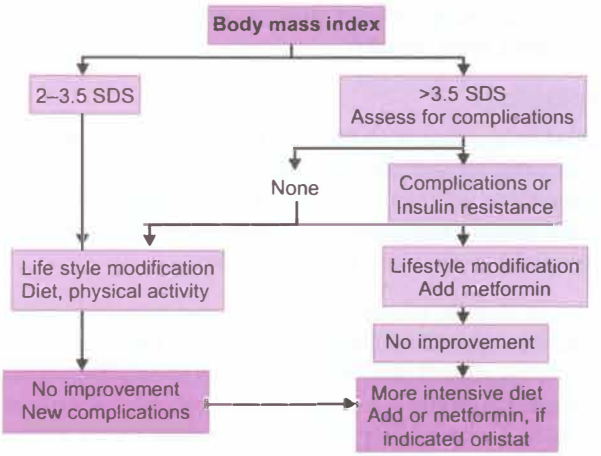

Fig. 17.16: Approach to management of obesity

activity and behavioral measures are the cornerstones of therapy, and intensive measures like drug therapy and surgery are reserved for morbid cases.

Dietary measures. Initial measures include mild caloric restriction and alteration in dietary habits. Intake of 1200–1800 Calories, depending upon the age of the individual, along with 30–40% restriction is recommended. Over-aggressive dietary restriction is associated with poor compliance and growth faltering. Apart from restricting calorie intake, efforts should be directed towards improving the nutritive value of the diet. Reduction in consumption of junk foods, carbonated drinks and saturated fat should accompany an increase in fiber, fruits and vegetable intake. Regular meal consumption with fixed portion sizes is an effective strategy in inducing weight gain.

Lifestyle modification. Increase in physical activity along with reduction in sedentary lifestyle is an useful component of obesity management. Swimming, running and playing outdoor games should be encouraged. Physical activity for at least 30–45 minutes per day is recommended. Activities like television viewing, videogames and internet surfing should be restricted.

Drugs. Pharmacotherapy is reserved only for severe cases of obesity. The only drug approved in children is *orlistat*, a gastric lipase inhibitor. *Metformin* is indicated for children with insulin resistance. *Leptin* (for those with leptin deficiency) and *octreotide* (for hypothalamic obesity) may be used in a subgroup of children with obesity. The efficacy of pharmacological therapy for obesity is modest compared to surgery.

Surgery. Surgery for obesity is the last resort in treatment. It is indicated for morbid obesity (BMI more than 40 kg/m^2 with complications) when other measures have failed, but only after completion of statural growth. Laparoscopic gastric banding is the procedure of choice and is directed at reducing gastric capacity.

Suggested Reading

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DISORDERS OF THE GONADAL HORMONES

Puberty

Puberty is the phase of life when secondary sexual characteristics appear and mature and capability of reproduction is attained. Deviations from the normal pattern of puberty have significant diagnostic and therapeutic implications.

Physiology

Puberty involves development of primary (testicular and penile growth in boys and breast and uterine growth in girls) and secondary sexual characteristics (pubic and axillary hair growth, change of voice in boys, acne and axillary odor). Sex hormones (estrogen in girls and testosterone in boys) play an important role in the development of primary sexual characteristics, while adrenal androgens are involved in the development of secondary sexual characteristics in girls.

Kisspeptin, a hypothalamic peptide, is the key regulator of puberty. Acting as the 'on-off switch' of puberty, kisspeptin initiates GnRH pulses. Initially GnRH pulses occur only during nights followed by secretion during both day and night. This results in increase in the levels of gonadotropins, and thereby, sex hormones. LH is a better indicator of pubertal status compared to FSH. Pulsatile secretion of GnRH makes basal gonadotropin levels an unreliable indicator of pubertal status. The hypothalamic-pituitary-gonadal axis is under feedback control. Thus secretion of LH is inhibited by testosterone and estrogen produced by the Leydig cells and theca cells, respectively. Inhibin produced by the Sertoli and granulosa cells inhibits FSH production.

Patterns of Pubertal Development

The pattern of pubertal development is different in girls and boys. Puberty starts at around the age of 10 yr in girls (range 8–12 yr) and is completed over 5 yr. Breast enlargement (*thelarche*) is the first event followed by the development of pubic hair (*pubarche*) and onset of menstrual cycles (*menarche*). Breast development may be asymmetrical in the initial phase. Menarche usually occurs two years after thelarche usually during stage III and IV. Discordant pubertal development (menarche within one year of thelarche) suggests hyperestrogenic states with withdrawal bleeding.

In boys, puberty starts with testicular enlargement at 11.5 yr (range 9 yr to 14 yr). This is followed by penile enlargement and pubarche. *Spermarche* occurs by the age of 14 yr.

Assessment of Puberty

The stage of pubertal assessment is assessed using Tanner staging system (*see* Figs 3.1 and 3.2). Breast development beyond Tanner II in girls and testicular volume greater than 4 mL indicates onset of puberty. Maximum growth spurt occurs during early puberty in girls (Tanner II–III) compared to boys where it occurs later (Tanner III–IV) (Table 17.24). Menstrual periods are irregular in the first few years before attainment of regular ovulatory cycles. It is important to differentiate adrenarche (pilosebaceous development related to increase in adrenal steroids) from gonadarche (genital development related to increase in GnRH) in girls.

Precocious Puberty

Pubertal onset before the age of 8 yr in girls and 9.5 yr in boys is suggestive of precocious puberty. Precocious puberty may be due to stimulation of the hypothalamic-pituitary axis (gonadotropin-dependent precocious puberty) or autonomous sex hormone production (gonadotropin-independent).

Precocious Puberty in Girls

Precocious puberty is common in girls and may represent normal variation in the age at onset of puberty. In most cases, puberty is slowly progressive with no longterm adverse effect. Endocrine workup should be restricted to girls with progressive forms of puberty.

Gonadotropin-dependent precocious puberty or central precocious puberty is much more common than gonadotropin-independent precocious puberty (Table 17.25). In more than 90% of these cases, no underlying cause is identified. It may be caused by a variety of pathologies of the central nervous system as listed in Table 17.25. *Hypothalamic hamartoma*, a neuronal migration defect, is the commonest cause of organic central precocious puberty (Figs 17.17 and 17.18). The disorder presents with early onset and rapid progression of puberty, seizures and uncontrolled laughter episodes (gelastic epilepsy).

Table 17.24: Comparison of pattern of pubertal development in boys and girls

	Girls	*Boys*
Onset	10–12 yr	12–14 yr
First sign	Breast development	Testicular enlargement
Growth spurt	Tanner II and III	Tanner III and IV
Sexual maturity	Menarche 14 yr	Spermarche 14–15 yr

Table 17.25: Etiology of precocious puberty in girls

Gonadotropin-dependent or central precocious puberty
Idiopathic
Tumors: Hamartoma, pituitary adenoma, craniopharyngioma, glioma
Infections: Neurotuberculosis, meningitis
Injury: Head trauma, neurosurgery, cranial irradiation
Malformation: Arachnoid cyst, hydrocephalus, septo-optic dysplasia
Gonadotropin-independent or peripheral precocious puberty
Hypothyroidism
Ovarian estrogen: McCune Albright syndrome, cyst, tumor, aromatase excess
Adrenal estrogen: Estrogenic adrenal adenoma
Exogenous estrogen exposure
Incomplete variants
Isolated thelarche
Isolated pubarche (adrenarche)
Isolated menarche

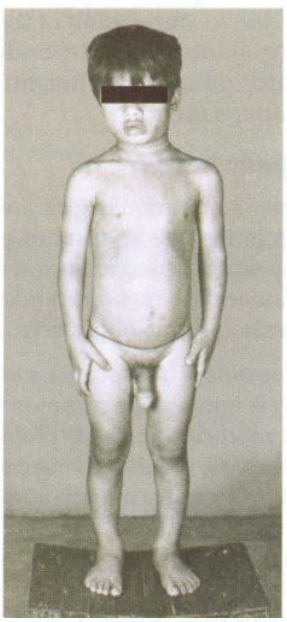

Fig. 17.17: Central precocious puberty secondary to hypothalamic hamartoma

Gonadotropin-independent precocious puberty or peripheral precocious puberty is rare and usually caused by *estrogenic ovarian cysts.* Fluctuating pubertal development and early vaginal bleeding (due to hyperestrogenic state) is common. The condition is usually self-resolving and there is no need for treatment. Recurrent ovarian cysts should raise the possibility of *McCune Albright syndrome*, a somatic activating mutation of stimulatory G protein. The condition presents with constellation of cutaneous (multiple dark brown café au lait spots), skeletal (multiple fibrous dysplasia) and endocrine abnormalities (hyperthyroidism, rickets and GH excess). Precocious puberty occurs at an early age and is rapidly progressive. Prolonged untreated primary hypothyroidism may induce early puberty due to action of TSH on FSH receptor. Delayed bone age and growth is characteristic.

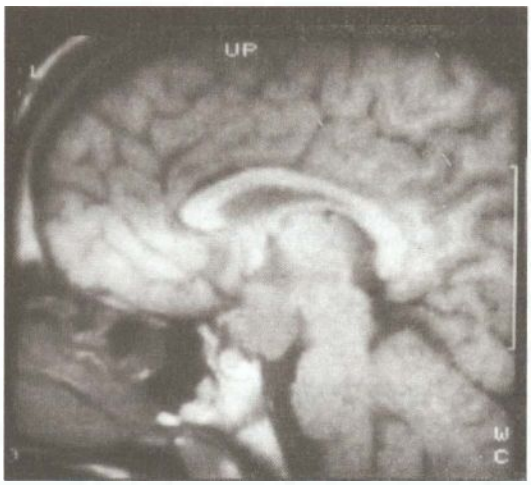

Fig. 17.18: MRI scan of brain showing an isodense mass suggestive of hypothalamic hamartoma

Evaluation

Aims of evaluation include confirmation of diagnosis, identification of underlying etiology and determination of prognosis and treatment.

Clinical. History should include the onset, progression and extent of puberty. Exposure to steroids, estrogens and androgens should be enquired. Family history of precocious puberty and early menarche points towards idiopathic central precocious puberty. Features of hypothyroidism should be assessed. Advanced growth is characteristic of precocious puberty; growth retardation indicates hypothyroidism or concomitant GH deficiency. Examination of vaginal mucosa for estrogen effect provides clues regarding the pubertal status of the patient. Red, glistening mucosa suggests lack of estrogens while pink mucosa with mucus is indicative of estrogen effect. Abdominal examination for adrenal or ovarian mass should be done. Features of McCune Albright syndrome include café au lait spots, polyostotic fibrous dysplasia, bony deformities and polyendocrinopathy.

Investigations. Assessment of pubertal status is based on basal or stimulated gonadotropin levels. Pooled gonadotropin levels are preferred due to their pulsatile secretion. LH is a better indicator compared to FSH as LH levels increase significantly during puberty. LH levels in the pubertal range with LH/FSH ratio more than 1 is suggestive of development of puberty. Ultrasound of abdomen and pelvis helps in diagnosing follicular cysts and ovarian and adrenal mass. Thyroid function should be assessed to rule out hypothyroidism. Bone age helps in assessing

the height compromise and in predicting final height. MRI of brain should be done in girls with onset of puberty before 6 yr of age, rapid progression and associated neurological features. Pituitary functions should be assessed in girls with organic GPP.

Advanced bone age (more than two years ahead of chronological age) is suggestive of progressive precocious puberty, while normal bone age indicates slowly progressive puberty. Retarded growth and skeletal maturation is diagnostic of hypothyroidism. Pubertal LH levels are suggestive of gonadotropin dependent precocious puberty and should be followed with an MRI of brain. Girls with prepubertal LH levels should undergo ultrasound of ovary and adrenals (for ovarian cyst and adrenal tumor) and skeletal survey (for fibrous dysplasia in McCune Albright syndrome).

Management

Aims of treatment include treatment of underlying cause, management of associations, puberty suppression and achievement of target height potential. The significant longterm consequence of precocious puberty is short stature. Growth is accelerated at presentation. This is associated with disproportionately advanced bone age resulting in premature epiphyseal fusion culminating in compromised final height.

Gonadotropin-dependent precocious puberty. Drugs used for pubertal suppression include medroxyprogesterone acetate (MPA), cyproterone and GnRH analogs. MPA does not improve height outcome and may be considered in girls with intellectual disability where final height is not important. Long acting GnRH analogs are the only agents effective in improving height outcome. They cause sustained stimulation and desensitization of pituitary leading to reversing of pubertal changes. GnRH analogs should be considered in girls with early onset (before 6 yr of age) rapidly progressive puberty and height compromise (bone age to chronological age difference more than two years). The treatment is discontinued at the chronological age of 11 yr and bone age of 12.5 yr. This is followed by gradual reappearance of secondary sexual characters. Menarche is attained around 12–18 months following discontinuation of treatment.

Gonadotropin-independent precocious puberty. Thyroxine replacement results in reversal of pubertal changes in hypothyroidism. Treatment for McCune Albright syndrome is directed towards inhibiting estrogen production (aromatase inhibitors like anastrazole or letrozole) or estrogen action (tamoxifen). Treatment of ovarian cysts is guided by size and morphological features.

Incomplete Variants of Precocious Puberty

These disorders represent normal variants and do not require specific treatmsent. Their identification helps in restricting the extent of diagnostic workup and counseling.

Isolated thelarche. Isolated breast development may represent isolated thelarche or first manifestation of central precocious puberty. Bone age, gonadotropin levels and pelvic ultrasound helps in differentiating the two conditions. Normal growth, prepubertal LH, age appropriate bone age and small uterine size suggest isolated thelarche.

Isolated adrenarche. Premature adrenarche refers to development of pubic hair and acne in the absence of breast development or menarche. Most cases are physiological variants. Rarely, androgen excess due to adrenal (CAH due to 21-hydroxylase deficiency, 11β-hydroxylase deficiency or adrenal tumor) or ovarian (tumor or polycystic ovarian disease) causes may be identified. Normal bone age and absence of virilization suggest premature adrenarche and no treatment.

Isolated menarche. Vaginal bleeding in the absence of thelarche is against the diagnosis of gonadotropin-dependent precocious puberty. Vaginal bleeding may occur early in course of estrogen excess states like ovarian cysts, hypothyroidism and McCune Albright syndrome. Vaginal bleeding without breast development should prompt evaluation of local causes like infection, foreign body, sexual abuse and tumors.

Precocious Puberty in Boys

Precocious puberty is less common in boys, but when present is usually associated with significant pathology. This mandates prompt evaluation and treatment of all boys with precocious puberty.

Etiology

Gonadotropin-dependent and independent precocious puberty accounts for similar number of cases in boys (Table 17.26).

Gonadotropin-dependent precocious puberty. The etiology is similar to girls with the exception that organic etiology is more common. Hypothalamic hamartoma, craniopharyngioma, hydrocephalus and tubercular meningitis are important causes. These disorders are associated with increase in testicular volume and elevated basal and GnRH stimulated LH.

Gonadotropin-independent precocious puberty. This is caused by increased androgen production by testis and adrenals in the setting of prepubertal LH levels. Adrenal overproduction due to *congenital adrenal hyperplasia* is the commonest cause of peripheral precocious puberty. Rarely adrenal tumors may present with precocious puberty. *Human chorionic gonadotropin (hCG) secreting germ cell tumors* of the liver, mediastinum or brain may present with precocious puberty. *Testotoxicosis*, a disorder associated with constitutional activation of LH receptor, presents with early onset gonadotropin-independent precocious puberty. *Androgen secreting testicular tumors* present with precocious puberty and unilateral testicular enlargement.

Table 17.26: Etiology of precocious puberty in boys

Gonadotropin-dependent or central precocious puberty
Idiopathic
Central nervous tumors: Hamartoma, craniopharyngioma, glioma
Infections: Tubercular meningitis
Injury: Head trauma, surgery, radiation
Malformation: Arachnoid cyst, hydrocephalus
Gonadotropin-independent or peripheral precocious puberty
Congenital adrenal hyperplasia: 21-hydroxylase deficiency, 11β-hydroxylase deficiency
Adrenal tumors: Adenoma, carcinoma
Testicular tumors: Seminoma, germinoma
Testotoxicosis: Activation of LH receptor
hCG secreting tumor: Germinoma, hepatoblastoma
Exogenous androgen exposure: Testosterone cream

Evaluation

Evaluation is directed towards confirming the diagnosis and establishing the underlying cause.

Clinical. History should include age at onset of pubertal development, progression of puberty, neurological features, family history of precocious puberty and androgen exposure. Detailed anthropometric and neurological examination should be performed. Pointers to CAH (hyperpigmentation and hypertension) should be identified. Estimation of testicular volume forms an integral part of assessment. Prepubertal testicular volume (less than 4 ml) is characteristic of CAH and adrenal tumors, while unilateral enlargement is seen in testicular tumors. Pubertal testicular enlargement indicates GPP while lesser enlargement is observed in hCG secreting tumors and testotoxicosis.

Investigations. Initial investigations should include LH, FSH and testosterone levels and bone age. All patients with pubertal LH levels should undergo visual field examination and MRI of brain. In the presence of prepubertal LH levels, imaging for adrenals (preferably CT scan) and 17-hydroxyprogesterone levels should be done. hCG levels should be estimated if these investigations are noncontributory.

Management

Management includes treatment of underlying neurologic pathology and GnRH analog therapy. GnRH analog should be continued till the age of 12 yr. CAH is managed with hydrocortisone and fludrocortisone. Surgery is the treatment of choice for adrenal and testicular tumors, while radiotherapy is effective in hCG secreting tumors. Aromatase inhibitors and antiandrogens are indicated in testotoxicosis.

Delayed Puberty

Delayed puberty is more common in boys than girls. Most children with delayed puberty have constitutional delay emphasizing the need for watchful monitoring and conservative approach.

Delayed Puberty in Girls

Delayed puberty is defined as lack of secondary sexual characteristics by the age of 14 yr. Absence of menarche by the age of 16 yr or 5 yr after pubertal onset also indicates pubertal delay.

Etiology

Delayed puberty may be caused by defects in the hypothalamic-pituitary axis, ovaries or genital tract (Table 17.27). Patients with anatomical defects present with amenorrhea with normal breast development. Defects in the hypothalamic-pituitary axis are associated with low gonadotropin levels (*hypogonadotropic hypogonadism*). This may be related to reversible causes like systemic diseases, malnutrition, eating disorders, hyper-

Table 17.27: Etiology of delayed puberty in girls

Hypogonadotropic hypogonadism
Transient
Systemic disorders: Renal failure, liver disease, celiac disease, renal tubular acidosis, cystic fibrosis
Nutritional disorders: Malnutrition, anorexia nervosa
Endocrine disorders: Hypothyroidism, hyperprolactinemia, type 1 diabetes
Permanent
Isolated hypogonadotropic hypogonadism
Genetic: *KAL1*, GnRH receptor, LH, FSH, *DAX1* mutations
Dysmorphic syndromes: CHARGE, Prader-Willi, Laurence Moon Bardet Biedl
Multiple pituitary hormone deficiency
Malformations: Holoprosencephaly, septo-optic dysplasia, midline defects
Genetic disorders: *PROP1*, *LH* gene deletions
Brain tumors: Craniopharyngioma, germinoma, glioma
Brain injury: Surgery, infection, radiation, trauma
Infiltrative disorders: Histiocytosis, autoimmune disorders
Hypergonadotropic hypogonadism
Gonadal dysgenesis: Turner syndrome, *SRY* deletion, trisomy 18, 13, 21
Steroidogenic defects: StAR, 17α-hydroxylase, 17β-hydroxysteroid dehydrogenase or aromatase deficiency
Ovarian insults: Surgery, radiation, alkylating agents, infections
Autoimmune ovarian failure: Autoimmune polyendocrinopathy
Gonadotropin resistance: LH and FSH receptor mutations
Isolated amenorrhea
Structural malformations: Müllerian agenesis, vaginal septum, imperforate hymen
Inefficient androgen action: Complete androgen insensitivity syndrome

DAX1 dosage sensitive sex reversal; FSH follicle stimulating hormone; GnRH gonadotropin releasing hormone; LH Luteinizing hormone; *KAL1* Kallman syndrome gene 1; StAR steroidogenic acute regulatory protein; *SRY* sex determining region on Y chromosome

prolactinemia and hypothyroidism. Irreversible defects include destruction of the hypothalamic-pituitary axis by infection, surgery, radiation or tumor. *Kallmann syndrome*, a neuronal migration defect due to mutation of KAL1 gene, is characterized by defective smell sensation, low GnRH levels and hypogonadotropic hypogonadism. *Hypergonadotropic hypogonadism* is associated with defective estrogen production by ovaries and elevated gonadotropin levels. Turner syndrome, ovarian failure and enzymatic defects in estrogen synthesis production are important causes of this condition.

Evaluation

Goals of evaluation include identification of constitutional delay, organic etiology requiring neuroimaging and decision regarding treatment.

Clinical. Family history of delayed puberty provides a clue to constitutional delay in puberty. Features of chronic systemic diseases should be inquired. Poor smell sensation is indicative of Kallmann syndrome. Amenorrhea with normal secondary sexual characteristics indicates anatomical defects and should be evaluated accordingly. Neurological examination including that for olfactory sensation should be performed. Features of Turner syndrome and hypothyroidism should be looked into. Galactorrhea points towards hypothyroidism or hyperprolactinemia.

Investigations. Initial workup is directed towards excluding systemic disorders such as liver disease, renal disease and malabsorption. This should be followed by measurement of FSH levels. Karyotype should be done if FSH levels are high. Steroidogenic defects are likely, if karyotype and pelvic ultrasound are normal. In patients with low/normal FSH levels, prolactin and thyroid profile should be measured to exclude reversible causes. Neuroimaging and pituitary function tests should be done if these levels are normal.

Management

All patients with hypergonadotropic hypogonadism and irreversible hypogonadotropic hypogonadism need hormone replacement. Hormone replacement should be deferred till the bone age of 12 yr to avoid deleterious effects on height. The goal of treatment is to initiate and maintain sexual characteristics and to prevent osteoporosis. Treatment should be started with low dose estrogens (5 µg ethinyl estradiol or 0.3 mg conjugated estrogen every day) and gradually increased every 3 months till adult doses (20 µg of ethinyl estradiol or 1.25 mg of conjugated estrogen daily by 2 yr) are reached. Medroxyprogesterone acetate (MPA 5–10 mg from day 11 to 21) should be added two years after initiation of treatment or once withdrawal bleeding has started.

Delayed Puberty in Boys

Delayed puberty is more common in boys than girls and is usually due to a constitutional delay. Lack of pubertal changes by the age of 14 yr is suggestive of delayed puberty.

Etiology

Constitutional delay in growth and puberty is the commonest cause of delayed puberty in boys (Table 17.28). These boys have growth retardation and delayed bone age. Family history of delayed puberty is present. Gonadotropin levels are prepubertal similar to hypogonadotropic hypogonadism.

Hypogonadotropic hypogonadism may be reversible due to systemic illnesses or permanent due to neurological insult (infection, surgery, radiation or tumor). *Kallmann syndrome* is an important cause of isolated gonadotropin deficiency and presents with impaired smell sensation. Delayed puberty is common in dysmorphic syndromes like Prader-

Table 17.28: Etiology of delayed puberty in boys

Hypogonadotropic hypogonadism
Transient
Constitutional delay of puberty and growth
Systemic disorders: Renal failure, liver disease, celiac disease, renal tubular acidosis, cystic fibrosis
Nutritional disorders: Malnutrition, anorexia nervosa, bulimia nervosa
Endocrine disorders: Hypothyroidism, hyperprolactinemia, type 1 diabetes mellitus
Permanent
Isolated hypogonadotropic hypogonadism
Genetic disorders: *KAL1*, GnRH receptor, LH, FSH, *DAX1* mutations
Dysmorphic syndromes: CHARGE, Prader-Willi, Laurence Moon Bardet Biedl, Robinow
Multiple pituitary hormone deficiency
Malformations: Holoprosencephaly, septo-optic dysplasia, midline defects
Genetic disorders : *PROP1, LH* gene deletions
Brain tumors: Craniopharyngioma, germinoma, glioma
CNS insults: Surgery, infection, radiation, trauma
Infiltrative disorders: Histiocytosis, sarcoidosis, hemochromatosis
Hypergonadotropic hypogonadism
Chromosomal abnormalities: Klinefelter syndrome, gonadal dysgenesis
Steroidogenic defects: StAR, 17α-hydroxylase, 17β-hydroxysteroid dehydrogenase deficiency, Smith Lemli Opitz syndrome
Testicular insults: Radiotherapy, chemotherapy, trauma, torsion, infections
Malformations: Vanishing testis syndrome, cryptorchidism
Inefficient testosterone action: 5α-reductase deficiency
Resistance to testosterone action: Androgen insensitivity syndrome

DAX1 dosage sensitive sex reversal; FSH follicle stimulating hormone; GnRH gonadotropin releasing hormone; LH luteinizing hormone; KAL1 Kallman syndrome gene 1, stAR steroidogenic acute regulatory protein

Willi, Laurence Moon Bardet Biedl, Noonan and Robinow syndromes.

Hypergonadotropic hypogonadism (testicular failure) may be related to chromosome abnormalities (Klinefelter syndrome), partial gonadal dysgenesis, steroidogenic defects and acquired testicular injury (infection, radiation, chemotherapy) (Fig. 17.19).

Evaluation

Clinical. Family history of delayed puberty provides a clue to constitutional delay in puberty. History of delayed growth spurt and onset of shaving in father and brothers is common. A history of continued growth in adult years is often present. Features of any systemic disease should be enquired. History of head injury, neurosurgery and intracranial space occupying lesions suggest a defect in the hypothalamic-pituitary axis. CNS examination including olfactory sensation should be performed. Features of dysmorphic syndromes are usually evident on examination.

Investigations. Initial step includes estimation of LH, FSH and testosterone levels. Elevated gonadotropin levels (hypergonadotropic hypogonadism) should be followed up by karyotype and evaluation for biosynthetic defects. Individuals with low LH and FSH levels may have constitutional delay in puberty or hypogonadotropic hypogonadism. They may be distinguished by hCG stimulation test or GnRH stimulation tests (Table 17.29). However, these tests are nondiscriminatory in most cases and followup after a course of testosterone is the best strategy. Patients with hypogonadotropic hypogonadism should undergo evaluation of hypothalamic-pituitary axis and neuroimaging.

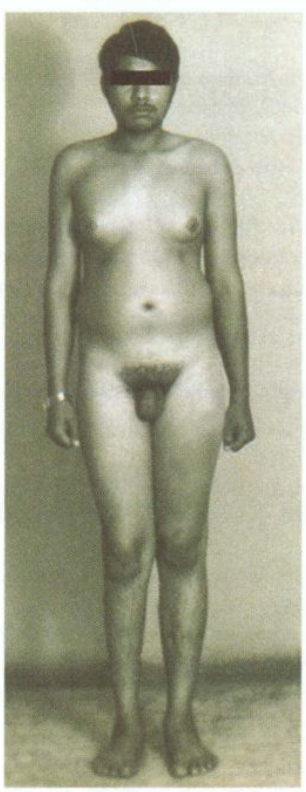

Fig. 17.19: Klinefelter syndrome. Note the tall stature and gynecomastia

Table 17.29: Differentiation of constitutional delay from permanent hypogonadotropic hypogonadism

Features	*Constitutional delay*	*Permanent hypogonadotropic hypogonadism*
Family history	Common	Rare
Adrenarche	Usually absent	May be present
DHEAS	Usually low	Low/high
Bone age	Marked delay	Mild delay
Early morning testosterone	May be elevated	Low
GnRH agonist test	Positive response	No response
hCG test	Increase in testosterone	No response
Followup	Spontaneous puberty	No spontaneous puberty

DHEAS dehydroepiandrosterone synthase

Management

Testosterone treatment should be deferred till the age of 14 yr and bone age of 13.5 yr. Children with suspected constitutional delay in puberty should receive three monthly injections of testosterone enanthate (100 mg). This should be repeated if adequate response is not achieved. Serum testosterone levels should be estimated three months after the last dose of the drug. Low testosterone levels indicate hypogonadotropic hypogonadism and the need for continued treatment.

Turner Syndrome

Turner syndrome is the most important cause of hypergonadotropic hypogonadism in girls. The disorder affects 1 in 2,500 newborn phenotypic females. These girls present with short stature, classical phenotypic features and delayed puberty. Most common karyotype is 45, X. Mosaic forms like 45, X/46, XX and 45, X/46, XY have also been observed. Premature atresia of ovarian follicles and bilateral streak gonads are features of this condition.

Clinical Features

Short stature is the most frequent finding. Turner syndrome may be identifiable at birth by the presence of lymphedema, cystic hygroma and left-sided obstructive cardiac lesions. Features of Turner syndrome in childhood include cubitus valgus (wide carrying angle), shield chest with widely spaced nipples, webbed neck and short fourth metacarpal (Table 17.30). Cardiac associations like

Table 17.30: Features of Turner syndrome

Endocrine	Growth retardation, delayed puberty, amenorrhea, hypothyroidism, type 1 diabetes mellitus, obesity
Skeletal	Wide carrying angle, shield chest, Madelung deformity, brachymetacarpia, low posterior hair line, hyperconvex nails
Cardiovascular	Hypoplastic left heart syndrome, coarctation of aorta, aortic stenosis, bicuspid aortic valve, hypertension, aortic aneurysm
Renal	Duplication of renal pelvis, horse shoe kidney
Hearing	Sensorineural and conductive hearing loss
Dysmorphism	Antimongoloid slant, epicanthic fold, mandibular hypoplasia
Edema	Cystic hygroma, lymphedema, webbing of neck

coarctation of aorta, mitral valve prolapse and aortic stenosis are common. Renal malformations like horseshoe kidney, reduplication of renal pelvis and agenesis may also be present. Endocrine associations of the disease include hypothyroidism and diabetes mellitus.

Assessment

Ultrasound pelvis reveals hypoplastic uterus and poorly developed ovaries. FSH levels are elevated. Karyotype is indicated in all patients with Turner syndrome to exclude the presence of a Y chromosome, which is associated with gonadoblastoma in 25–30% cases. Echocardiography and ultrasound for kidneys should be done in all patients for screening cardiac and renal malformations. Thyroid profile and blood sugar should be done at baseline and yearly. Periodic hearing evaluation for deafness is recommended (Table 17.31).

Management

GH therapy (0.1–0.15 unit/kg/day) is indicated in Turner syndrome for improving stature. Estrogen treatment should be deferred till the age of 12 yr to ensure adequate growth. Gonadectomy is recommended in patients with a Y chromosome in view of high risk of gonadoblastoma.

Table 17.31: Evaluation for associations of Turner syndrome

Association	*Initial workup*	*Followup*
Growth retardation	Growth monitoring; GH stimulation not required	Growth, bone age
Pubertal delay	Clinical evaluation FSH after 12 yr	Annual FSH levels, pelvic ultrasound
Cardiovascular	Examination Echocardiography	Blood pressure Echocardiography
Renal disorders	Ultrasound, radionuclide scan	Ultrasound
Hypothyroidism	TSH, T4	Annual TSH
Hearing	Audiogram	Annual audiogram
Diabetes	Blood glucose after 12 yr	Annual blood glucose

Suggested Reading

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Disorders of Sexual Differentiation

Disorders of sexual differentiation (DSD) previously termed as intersex disorders, are rare but constitute a medical, social and psychological emergency.

Physiology

Sexual differentiation is a complex process involving a close interaction of genetic, phenotypic and psychological factors. Usually genetic sex guides gonadal sex, which is responsible for the determination of phenotypic manifestations and gender identity (Fig. 17.20.) Any deviation from this pattern results in DSD.

Gonadal differentiation. Germ cells arise from the celomic epithelium of hindgut and migrate to the gonadal ridge at 4–6 weeks of gestation. These cells combine with

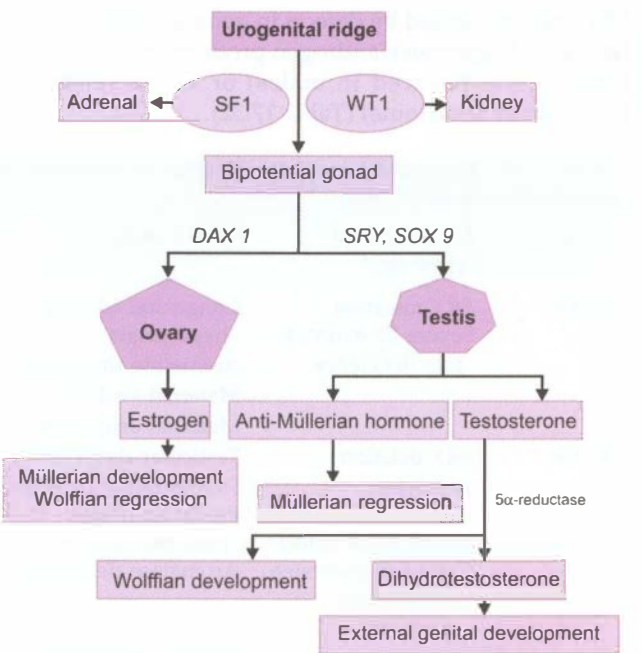

Fig. 17.20: The process of sexual development and its disorders. *Dax1* dosage sensitive sex reversal; *SF1* steroidogenic factor 1; *SOX9* transcription factor related to *SRY*; SRY sex determining region on the Y chromosome; *WT1* Wilms tumor 1 gene

somatic cells to give rise to the bipotential gonad. A transcriptional factor present on Y chromosome called the sex determining region of the Y chromosome (*SRY*) is one of the most important regulators of sexual differentiation. *SRY* acts in conjunction with other genes like Wilms tumor gene 1 (*WT1*), *SOX9* (a transcription factor on X chromosome) and dosage-sensitive sex reversal (*DAX1*) gene to induce testicular development. In the absence of *SRY*, the bipotential gonad develops into ovary.

Genital differentiation. Following development of testis, antimüllerian hormone secreted by Sertoli cells induces regression of müllerian ducts. Testosterone produced by Leydig cells is responsible for sustenance of Wolffian ducts. Dihydrotestosterone (DHT), produced by action of 5α-reductase on testosterone, is responsible for male external genital development (scrotal fusion and development of corpus spongiosum and penile corpus cavernosa). Feminization is the default process of sexual development. In the absence of antimüllerian hormone and testosterone, müllerian ducts differentiate into fallopian tubes, uterus and the upper third of the vagina. Labioscrotal swellings and urethral folds do not fuse and give rise to labia majora and minora respectively. The genital tubercles form the clitoris while canalization of the vaginal plate creates the lower portion of the vagina. Prenatal exposure to androgens may lead to labioscrotal fusion, while exposure thereafter usually causes clitoromegaly alone and no labial fusion.

Classification

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DSD may be caused by defects in gonadal differentiation (gonadal dysgenesis), androgen production (increased in females and reduced in males) or action (androgen insensitivity syndrome) (Table 17.32).

Table 17.32: Karyotype based classification of disorders of sexual differentiation (DSD)

Karyotype	*Normal genital appearance**	*Genital ambiguity*
46,XX	*SRY* insertion Severe 21-hydroxylase deficiency	Congenital adrenal hyperplasia Aromatase deficiency Maternal virilization Maternal drug intake
46,XY	*SRY* deletion *SF1* defect Gonadal dysgenesis Severe StAR defect Complete androgen insensitivity syndrome	Testicular dysgenesis Steroidogenic defects Partial androgen insensitivity syndrome Aromatase deficiency
46,XY/45,X		Gonadal dysgenesis Ovotesticular DSD

SF1 steroidogenic factor 1, SRY sex determining region on the Y chromosome, stAR steroidogenic acute regulatory protein

* Discordant to genotypic sex

Increased androgen production. Excess androgen production during the critical period of fetal development may result in masculinization of a female. These disorders are the commonest form of DSD. *Congenital adrenal hyperplasia* should be excluded in all children with DSD. *21-hydroxylase deficiency* is characterized by deficiency of glucocorticoids and mineralocorticoids with elevated androgen levels. Delay in diagnosis could be fatal, underscoring the importance of early diagnosis. *11β-hydroxylase deficiency* and *3β-hydroxysteroid dehydrogenase* deficiency are the other forms of CAH that present with virilization. Transplacental androgen exposure due to maternal medications or hyperandrogenism may lead to virilization in newborn. These disorders are readily identifiable by history of virilization in mother. Rarely aromatase deficiency may be associated with virilization of mother during pregnancy and DSD in newborn.

Disorders of gonadal differentiation. These disorders are associated with abnormal gonadal development. The gonad is usually streak (no functional gonadal tissue). Combinations of partially functional testis or ovary or ovotestis may be observed. *SRY* gene deletion results in normal female phenotype with 46,XY karyotype. Mutations in genes involved in the testicular differentiation (*WT1*, *SOX9*, steroidogenic factor *1* and *DAX1*) are other causes of 46, XY gonadal dysgenesis. These disorders are associated with renal (*WT1* mutation), skeletal (*SOX9*) and adrenal abnormalities (*DAX1*). 46, XY gonadal dysgenesis is associated with risk of development of gonadoblastoma. Asymmetric gonadal location may result in asymmetric genital appearance. 46, XX gonadal dysgenesis is usually caused by *SRY* translocation and presents as normal appearing male. *Ovotesticular DSD*, new term for true hermaphroditism, is characterized by the presence of both ovarian and testicular tissue in the same individual.

Inefficient androgen action. These disorders result from decreased production, activation or action of androgens. *Androgen insensitivity syndrome*, previously referred to as testicular feminization syndrome, an X-linked disorder of androgen action, is the commonest cause and is characterized by resistance to androgens. The disease forms a spectrum ranging from a normal female to boy with hypospadias, to a male with infertility. Complete androgen insensitivity presents in the neonatal period as a girl with inguinal masses and primary amenorrhea in older girls. Absent or sparse pubic and axillary hair is common. Müllerian structures are absent. High dihydrotestosterone levels are diagnostic. *5α-reductase deficiency* is associated with reduced dihydrotestosterone production. Increased testosterone during puberty acts on the androgen receptor leading to virilization. High testosterone and low dihydrotestosterone levels are diagnostic. *Testosterone biosynthetic defects* include deficiency of StAR, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase and 17β-hydroxysteroid dehydrogenase enzymes. Diagnosis

requires estimation of testosterone precursors and basal and hCG stimulated testosterone and androstenedione levels.

Evaluation

DSD workup is indicated in the infants with genital ambiguity, girls with inguinal masses (probable androgen insensitivity syndrome), boys with cryptorchidism (probable 21-hydroxylase deficiency), penoscrotal hypospadias (probable undervirilization disorder) and adolescent girls with amenorrhea (probable androgen insensitivity syndrome). 21-hydroxylase deficiency should be excluded by estimating serum electrolytes and blood levels of 17-hydroxyprogesterone.

Clinical. Family history of genital ambiguity is suggestive of genetic disorders such as 21-hydroxylase deficiency or androgen insensitivity syndrome. CAH is likely if there is a history of fetal losses and sibling deaths and family history of consanguinity. On the other hand, history of similar disorder in healthy male relatives (brothers and maternal uncles) is suggestive of androgen insensitivity syndrome. Gonads in complete androgen insensitivity syndrome might have been mistaken for inguinal hernia and operated. Intake of progestational drugs during first trimester and features of virilization in mother should be enquired. Failure to thrive, polyuria and lethargy indicate 21-hydroxylase deficiency (Table 17.33). Virilization during puberty is suggestive of 5α-reductase deficiency, while feminization indicates androgen insensitivity syndrome. General examination should include assessment for facial dysmorphism and hyperpigmentation. Maternal examination for features of hyperandrogenism like hirsutism, acne and change in voice should be done.

Genital examination. The most important step is identification of gonads. Bilaterally rounded structures below the inguinal canal are most likely testis. Unilateral gonads are suggestive of mixed gonadal dysgenesis. The labioscrotal region should be evaluated for the extent of fusion (Fig. 17.21). Müllerian structures can be confirmed by rectal examination. The length of phallus and number of openings in the urogenital region should be recorded.

Table 17.33: Clinical pointers to etiology of disorders of sexual differentiation (DSD)

Pointer	*Likely diagnosis*
Pigmentation	Congenial adrenal hyperplasia, SF1 defect, StAR defect
Polydactyly	Smith-Lemeli-Optiz syndrome
Skeletal dysplasia	*SOX9* defect
Genital asymmetry	Mixed gonadal dysgenesis, ovotesticular DSD
Hypertension	11β-or 17α-hydroxylase defect
Hemihypertrophy	*WT1* mutation
Renal failure	Denys Drash syndrome

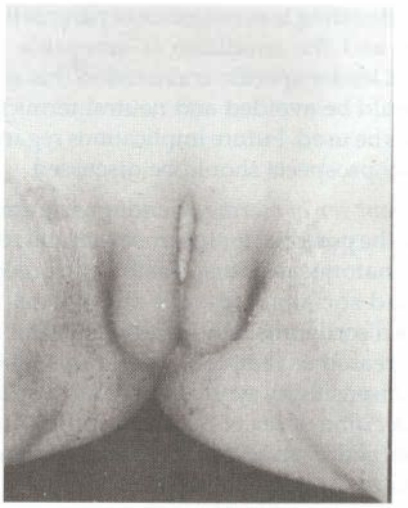

Fig. 17.21: Partial androgen insensitivity syndrome. Note the female appearance of the genitalia with an underdeveloped buried penis and poorly developed scrotum and testes

Asymmetrical labioscrotal region is suggestive of gonadal dysgenesis or ovotesticular DSD. The genitalia should be staged according to the classification proposed by Prader from grades I to V with grade I representing female with clitoromegaly and V male with cryptorchidism.

Investigations. Initial investigations should include karyotyping, estimation of electrolytes, serum 17-hydroprogesterone and pelvic ultrasound. Fluorescent in situ hybridization can be used to delete the presence of Y chromosome. Identification of Müllerian structures is an important part of evaluation of ambiguous genitalia. Genitogram is helpful in determination of level of fusion, which is of surgical importance. Further investigations are guided by clinical and laboratory evaluation.

Müllerian structures with no palpable gonads indicate androgen excess state and need for estimation of 17α-hydroxyprogesterone. Absence of Müllerian structures is suggestive of inefficient testosterone action and should be evaluated with estimation of testosterone and dihydrotesterone. The presence of both Müllerian structures and palpable gonads indicate gonadal dysgenesis or ovotesticular DSD. Absent gonads and Müllerian structure may be caused by vanishing testis syndrome or dysfunctional intra-abdominal testis. Estimation of levels of anti-Müllerian hormone and hCG stimulation test are helpful in differentiating the two conditions. Children with vanishing testis will have low levels of anti-Müllerian hormone and inappropriate response to hCG stimulation.

Management

Management involves parental counseling, decision about sex of rearing, timing of surgical correction and gonadectomy.

Parental counseling. Birth of a child with DSD generates significant parental anxiety and stress. The most important

aspect of counseling is reassurance of parents that the child is healthy and the condition is amenable to surgical treatment. Gender specific connotation (his or her, testis, ovary) should be avoided and neutral terms like gonads and phallus be used. Future implications regarding sexual and fertility prospects should be discussed.

Decision about sex of rearing. Gender assignment should depend on the potential for future sexual and reproductive function, anatomical status, feasibility of reconstructive surgery and social acceptance and norms. Girls with virilization disorders usually have potential for fertility and should be reared as females. Individuals with complete androgen insensitivity syndrome should also be reared as females. Decision of sex of rearing is difficult in disorders of inefficient androgen action. This should depend on genital appearance and surgical feasibility.

Surgery. There has been a trend of performing early surgeries before gender identity is established. Most centers perform clitoroplasty at the age of 1 yr with vaginoplasty reserved during puberty for girls with vaginal stenosis. Gonadectomy should be done in gonadal dysgenesis or ovotesticular DSD, if a Y cell line is present.

Cryptorchidism (Undescended Testes)

Cryptorchidism is present in about 3% of full-term infants and 20% of premature infants. In most of these cases testes descend spontaneously by the age of one year with a decrease in the prevalence to 1%. Spontaneous testicular descent is unlikely after the age of one year and the prevalence in adult population is 0.8%.

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Etiology

Most children with undescended testis do not have an identifiable underlying cause. Endocrine causes account for only a small proportion of boys with undescended testis. The possibility of salt wasting 21-hydroxylase deficiency presenting with sex reversal should be considered in newborns with bilateral cryptorchidism. Undescended testis may be associated with hypopituitarism, dysmorphic syndromes and disorders of androgen production and action.

Evaluation

It is important to differentiate true undescended testis from retractile or ectopic testis due to therapeutic and prognostic implications (Fig. 17.22). Poorly developed scrotum and inability to bring down the testis to the scrotal sack suggests true undescended testis. *Retractile testis* is an otherwise fully descended testis that has an active cremasteric reflex, which retracts it into the groin.

Penoscrotal hypospadias and genital ambiguity is suggestive of disorders of androgen production or action. The hCG stimulation test should be done in boys with bilateral nonpalpable testis to differentiate abdominal testis from anorchia.

Management

Undescended testis is associated with significant complications like torsion, trauma, inguinal hernia, testicular dysfunction and development of malignancy. These children should be treated early because of the increased risk for malignancy and infertility in later life. *The optimal time of therapy is before the age of one year*. The commonly used medical treatment is human chorionic gonadotropin (hCG) 250 units below 1 yr, 500 units between 1 and 5 yr and 1,000 units above 5 yr administered twice a week for 5–6 weeks. Good response occurs within a month. Retraction rate of testes after cessation of therapy is high. If the response to hCG is poor, patient should be treated early with orchiopexy.

Micropenis

A penis whose length in stretched position is less than 2 SD below the mean for the age is termed micropenis. Most often it is the result of primary or secondary testicular failure.

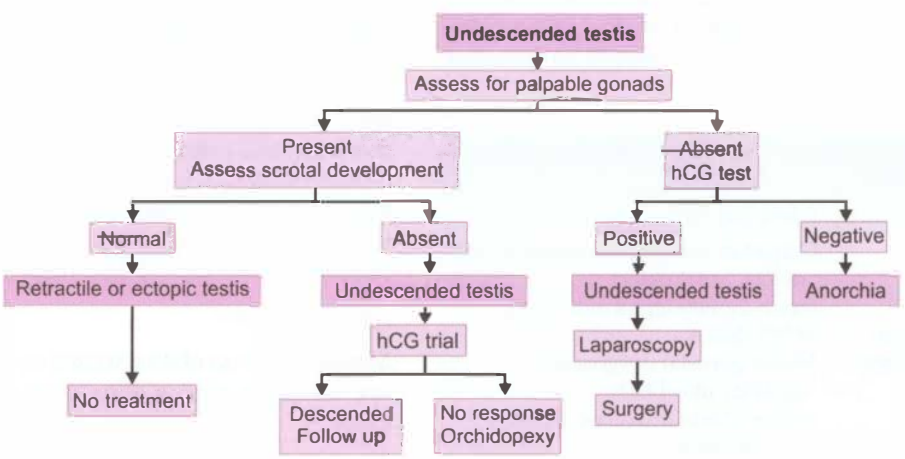

Fig. 17.22: Approach to cryptorchidism; hCG human chorionic gonadotropin

Etiology

Micropenis results from decreased androgen action during fetal life. It may be due to hypogonadotropic hypogonadism as in Kallmann syndrome, Prader-Willi syndrome, septooptic dysplasia, or Klinefelter syndrome. It may also be a manifestation of partial androgen insensitivity syndrome or testosterone biosynthetic defects.

Evaluation

Penile length should be measured in a fully stretched state by grasping the glans between thumb and forefinger. A firm ruler or caliper should be pressed against the pubic ramus to depress the suprapubic fat pad. The measurement should be made along the dorsum to the tip of the glans penis excluding the length of foreskin. Penile size is often underestimated in boys with obesity (due to the suprapubic fat) and hypospadias (due to chordee). Investigations should include estimation of gonadotropin and testosterone levels. Low gonadotropin and testosterone levels indicates hypogonadotropic hypogonadism. Elevated gonadotropin levels (hypergonadotropic hypogonadism) should prompt evaluation for testicular dysgenesis, steroidogenic defects or androgen insensitivity syndrome.

Management

All boys with micropenis are treated with a course of low dose testosterone (25 mg testosterone enanthate or cypionate monthly for three doses). The aim of this short course of testosterone treatment is to increase penile length and not to induce puberty. Boys with micropenis should be reared as males as normal sexual function is usually attainable with early intervention.

Suggested Reading

Houk CP, Hughes IA, Ahmed SF, Lee PA. Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics 2006;118:753–7

DIABETES MELLITUS

Diabetes mellitus is a metabolic disorder that is characterized by hyperglycemia and glycosuria. Several distinct types of diabetes mellitus exist resulting from pancreatic dysfunction caused by genetic and environmental factors. The factors that contribute to hyperglycemia include decreased insulin secretion, decreased insulin action and increased glucose production.

Hyperglycemia resulting from diabetes mellitus causes damage to multiple organs resulting in multi organ damage. Diabetes mellitus is the leading cause of end stage renal disease, nontraumatic leg amputation and adult blindness.

Classification

Classification of diabetes mellitus is shown in Table 17.34. Most patients can be clearly classified as type 1 or 2 diabetes mellitus. However, occasionally an adolescent with type 2 diabetes may present with ketoacidosis, and patients with type 1 diabetes mellitus may present late and progress slowly.

Table 17.34: Classification of diabetes mellitus

Type 1 diabetes mellitus	Absolute insulin deficiency resulting from β-cell destruction
Type 2 diabetes mellitus	Progressive insulin secretary defect in the background of insulin resistance
Gestational diabetes mellitus	Diabetes mellitus manifesting in pregnancy
Other specific types of diabetes mellitus	Genetic defects in β-cell function or insulin action, diseases of exocrine pancreas and drug or chemical induced diabetes

Epidemiology

Diabetes has been more commonly diagnosed over the past two decades. The prevalence rates of impaired fasting glucose are also increasing. Type 2 diabetes is increasing in prevalence more rapidly than type 1 due to increasing obesity and less active lifestyles of children. There is a significant geographic variation in the incidence of diabetes mellitus. Scandinavia has the highest incidence, with Finland having the incidence of 35/100,000/yr. China and Japan have a much lower incidence of 1–3/100,000/yr. Indian data suggest an incidence of 10.5/100,000/yr. India would have 79 million diabetics by 2030, the highest for any country in the world. The variability in incidence in type 1 diabetes is believed to be due to differences in frequency of high-risk HLA alleles in various ethnic groups. Type 1 diabetes is uncommon in infants. The incidence of diabetes mellitus increases in children with advancing age all the way to adolescence, with peaks at 5 and 12 yr of age. Seasonal variation has been noted with a higher incidence in spring and fall.

Pathogenesis

Type 1 diabetes develops consequent to immune-mediated destruction of pancreatic cells, resulting in severe impairment of insulin secretion in genetically susceptible children.

Genetic factors Genetic, environmental and autoimmune factors are believed to result in the development of type 1 diabetes. Genetic susceptibility to diabetes involves multiple genes (polygenic inheritance). Polymorphisms in the HLA complex account for almost 50% of the genetic risk for type I diabetes. Certain haplotypes confer significant risk of acquiring diabetes, yet others are protective. Most children with diabetes in United States have either the DR3 and/or DR4 antigens. Association with DR3 has been reported in Indians.

Concordance of type I diabetes in identical twins ranges from 30–70%. 7% of children whose fathers have type 1

diabetes develop type 1 diabetes. Mothers with type 1 diabetes do not confer a similar risk. Siblings are not at higher risk of developing type 1 diabetes.

Environmental factors Many environmental agents are thought to trigger the development of type 1 diabetes mellitus, including viruses, bovine milk protein and nitrosourea compounds.

Autoimmune factors and autoimmunity Individuals susceptible to development of diabetes have normal β cell mass at birth. Autoimmune destruction affects only the β cells of the islets, even though the α and delta cells are functionally and embryologically similar. The pancreatic islets are infiltrated with lymphocytes 'insulinitis'. Once the islet cells are completely destroyed inflammation abates and the islet cells atrophy. Clinical diabetes occurs when the pancreas loses 80% or more of its insulin secretary ability.

Islet cell antibodies (ICA) can be measured in the serum of 70–80 % of Caucasian patients at the time of diagnosis. These include antibodies directed at pancreatic islet molecules such as insulin, IA-2/ICA-512 and GAD-65. The presence of these antibodies predates the clinical presentation of diabetes and declines after clinical disease has manifested. Autoantibody production in Indian children is less common and their titres are lower as compared to Caucasian children.

Clinical Features

Children and adolescents usually present with symptoms of diabetes that have often been ongoing for a month or two prior to seeking physician contact, with an acute increase in symptoms over the last week. Symptoms of type 1 diabetes mellitus include polyuria, nocturia, polydypsia, recent weight loss, polyphagia and fatigue. Recent acute infection is often noted at presentation. Approximately 50% children present with acute complication of diabetes or diabetic ketoacidosis.

Diagnosis

The National Diabetes Data group and the World Health Organization have outlined diagnostic criteria for diabetes mellitus (Table 17.35).

Random blood sugar of 200 mg/dl or more associated with the classic symptoms of diabetes mellitus (polydipsia, polyuria and weight loss) is diagnostic. Oral glucose tolerance is not routinely recommended. Fasting blood sugar is also reliable and convenient test. Elevated glycated hemoglobin (HbA1C) is diagnostic of diabetes mellitus. However, it is not completely reliable when dealing with mild elevations of blood sugars.

Table 17.35: Criteria for diagnosis of diabetes mellitus

Symptoms of diabetes and a random blood glucose concentration ≥11.1 mmol/l (200 mg/dl) *or*
Fasting blood sugar ≥ 7 mmol/l (126 mg/dl) *or*
Two hour plasma glucose ≥11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test

Screening

Epidemiologic studies indicate that diabetes is often present for over a decade in patients eventually diagnosed with type 2 diabetes mellitus. 50% or more patients with Type 2 diabetes have one or more of the complications of diabetes at the time of diagnosis. High risk adolescents should therefore be screened for diabetes.

Course of Illness

Most children respond to insulin therapy. Once insulin is initiated, blood sugars gradually decline. Often, after around a week of insulin therapy, the need for exogenous insulin declines, due to a transient recovery of insulin secretion. This phase is called the "honeymoon phase of diabetes". Some children can go completely insulin free during this time. The honeymoon phase lasts from a few days to a month. It can rarely extend as long as one year. Insulin needs increase over time till such time as when the pancreas can no longer secrete insulin. At this point the daily insulin requirement plateaus at 0.8–1 unit /kg/day.

Treatment

The goals of therapy of type 1 and 2 diabetes mellitus are to:

- Eliminate symptoms related to hyperglycemia
- Reduce and delay the complications
- Achieve a normal lifestyle and normal emotional and social development
- Achieve normal physical growth and development
- Detect associated diseases early

A comprehensive approach is adopted to achieve these goals. Symptoms of diabetes abate with blood sugars <200 mg/dl; making the first goal relatively easier to achieve. However, achieving the other goals require focus on diabetes education, medical nutritional therapy and well-planned appropriate insulin therapy that is customized to the needs of each patient. The availability of insulin analogs and insulins with long duration of action with minimal/absent peaks allows insulin therapy to match glucose excursions with meals and at the same time provide baseline insulin for endogenous glucose production without significant hypoglycemia. Advances in self blood glucose monitoring, development of insulin pumps for accurate insulin delivery, continuous glucose monitoring systems and development of a team approach to the management of diabetes care has greatly improved diabetes care. These developments and strategies have allowed many children and adolescents to achieve glycemic goals of near normal blood sugars; goals that were previously almost impossible to achieve, with conventional insulin therapy of two injections a day.

The current therapeutic regimen; which involves frequent blood sugar monitoring and multiple insulin injections or continuous subcutaneous injection infusion, along with dietary modifications, is called intensive insulin therapy. Intensive insulin therapy involves frequent communication between the physician and the diabetes educator to accomplish insulin adjustments in a timely manner, with the goal of achieving near normal blood sugar at all times. Intensive therapy result is better blood sugars, and reduced late complications of diabetes by 39–60%

Insulin therapy Current insulin preparations are generated using recombinant DNA technology. Animal insulins should be avoided. Amino acid substitutions on human insulin will alter insulin pharacokinetics and this has been used to synthesize 'designer' insulin preparations with particular desired characteristics. The insulin analog Lispro [Lys(B28) Pro(B29) human insulin] allows better control of blood sugar as its onset of action is faster than regular insulin and duration of action is shorter. Insulin Aspart also has rapid onset of action but duration of action is longer than Lispro insulin. These modifications in insulin enable improved glycemic control during fasting as well as postprandial state. Table 17.36 provides the pharmacokinetics and specific characteristics of currently available insulins.

Insulin prescription Insulin requirements generally range from 0.5–1 unit/kg/day. At diagnosis, insulin therapy is initiated with four doses of short-acting insulin. The dose is evaluated and an appropriate home regimen of insulin is planned. The goal of therapy is to provide background insulin to maintain glycemic control during the fasting state, and to punctuate this with multiple boluses of short-acting insulins to maintain euglycemia during post-prandial states in a titratable manner.

Currently, the most accurate method of achieving glycemic control uses the *insulin pump*. It utilizes insulin delivery devices to accurately deliver a small baseline continuous infusion of insulin, coupled with parameters for bolus therapy—related to food intake and activity levels. The bolus insulin is determined by the amount of carbohydrate intake and the blood sugar level

In most traditional regimens, intermediate or long-acting insulin is utilized to provide background insulin to maintain glycemic control during the fasting state. Short-acting insulin is used to provide glycemic control in the postprandial state. Insulin regimens in varying combinations are utilized to achieve near normal blood sugars at all times with minimal hypoglycemia. There are two main classes of insulin regimen: (i) NPH with short-acting insulin analogues and (ii) Long-acting insulin, typically insulin Glargine (Lantus) with short-acting insulin, as depicted in Fig. 17.23.

In the NPH regimen two to three injections are given daily. This includes a combination of NPH and short-acting insulin before breakfast, short-acting preparation at dinner and NPH at dinner or bedtime. In this regimen usually two-thirds of the total daily insulin is prescribed in the morning prior to breakfast and one-third is given in the evening. Hence, before breakfast, two-thirds of the morning insulin is given as NPH and one-third as short-acting insulin. Pre-dinner 1/2–2/3 of the evening insulin

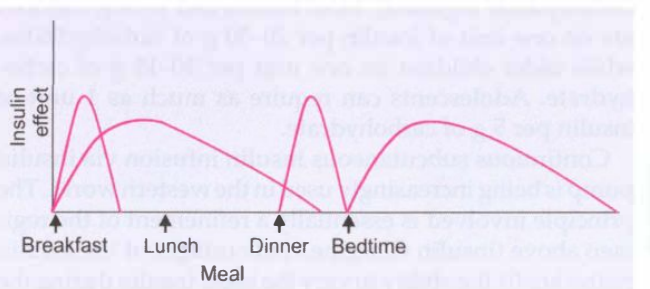

Fig. 17.23: Intermediate and short-acting insulin regimen

Table 17.36: Features of different insulin preparation

Preparation	*Properties*	*Onset*	*Peak*	*Effective duration*
Short-acting				
Lispro	Faster onset; shorter duration	15 minutes	0.5–1.5 hr	3–4 hr
Insulin Aspart	Faster onset	15 minutes	0.5–1.5 hr	3–6 hr
Regular		30 minutes	2 hr	3–6 hr
Intermediate				
NPH insulin	Slower onset; longer duration	2–4 hr	6–10 hr	10–16 hr
Lente	Slower onset; longer duration	3–4 hr	6–12 hr	12–18 hr
Long-acting				
Ultra Lente	Slower onset; longer duration	6–10 hr	10–16 hr	18–20 hr
Glargine (Lantus)	Slower onset; longer duration No peak	4 hr	—	24 hr

Combinations of intermediate and short-acting insulin as 70% + 30% and 50% + 50%, respectively are available in value of 70:30 and 50:50

is given as NPH and 1/3–1/2 of the evening insulin is given as short-acting insulin prior to dinner. When drawing up a mixed dose of insulin, short-acting insulin is drawn before intermediate acting (cloudy) insulin, as accidental introduction of longer-acting insulin in short-acting insulin can result in increasing the duration of effect of short-acting insulin. A meal is planned incorporating three meals and two or three snacks.

Insulin is adjusted by reviewing blood sugars. Blood sugars are monitored at least four times a day (prior to meals and at bedtime). It is important to follow the diet outlined in the plan and to adhere to meal timings. Variation in meal amounts and timings can result in wide fluctuations in blood sugars, with high blood sugars from eating excessively and low blood sugars with insufficient food intake and delayed meals. Variations in physical activity and exercise will also affect the insulin/blood sugar dynamics.

A more physiologic insulin regimen utilizes multiple daily injections of Lispro or Aspart with baseline insulin levels achieved using Glargine insulin. Insulin Glargine is given once daily either in the morning or evening. Short-acting insulin is given with every meal and snack. The dose of the short-acting insulin is determined by the amount of carbohydrate intake and the level of blood sugar. The dose of the short-acting insulin is calculated based on a carbohydrate ratio (units of insulin per g of carbohydrate ingested). Most infants and young children are on one unit of insulin per 20–30 g of carbohydrates, while older children on one unit per 10–15 g of carbohydrate. Adolescents can require as much as 1 unit of insulin per 5 g of carbohydrate.

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Continuous subcutaneous insulin infusion via insulin pump is being increasingly used in the western world. The principle involved is essentially a refinement of the regimen above (insulin Glargine). Advantages of the insulin pump are (i) the ability to vary the basal insulin during the day and night by using multiple basal rates allowing adjustment of insulin for nocturnal and daytime requirements; (ii) usefulness in preventing early morning hyperglycemia secondary to Dawn phenomenon due to morning hormonal surges; (iii) allowing alteration of basal rates during exercise and hence preventing postactivity hypoglycemia; (iv) allowing boluses to be given in different wave forms to account for variable absorption from different foods. High fat foods takes longer to metabolize and result in delayed hyperglycemia which can be addressed using complex boluses with dual wave infusion with a greater proportion of insulin given two hours after food intake. Extended boluses are used for food consumed over two–three hours or longer in small portions.

Nutrition Therapy

Nutrition therapy in diabetes is important in preventing and treating existing diabetes. The goal of therapy is to match intake with appropriate insulin. Insulin therapy and self blood glucose monitoring are integrated with appropriate nutrition and caloric intake. Flexibility in caloric intake, especially to allow exercise is desired. Nutritional plan which allows deviation in food intake incorporating individuals likes and dislikes is implemented. Simple sugars are discouraged. Foods with a low glycemic index and fiber is encouraged. The intake of saturated fats should be limited and the intake of trans fats should be minimized. Five sweeteners (acesulfame, aspartame, neotame, saccharin, sucralose) are approved for use in children. Excessive use should be avoided.

Exercise

Physical activity is important for children with diabetes. It increases glucose utilization and insulin sensitivity, improving metabolic control. It also builds self esteem. Longterm outcome of children with diabetes is better with regular exercise. Recommended activities include walking, jogging, swimming and organized sports.

Sick Day Care

Children with diabetes require careful monitoring at home when they are ill or ketotic. If timely intervention is not provided they can develop diabetic ketoacidosis (DKA) a serious and life-threatening complication of diabetes. Children who are noted to have high blood sugars >240 mg/dl and or are ill should be tested for ketosis. Beta-hydroxybutyrate and acetoacetic acid can be measured in blood or urine. Based on the level of ketosis additional insulin is provided every 2 hr. This ranges from 5–20% of the total daily dose as short-acting insulin. Blood sugar is monitored and parents are advised to administer additional oral fluids. Parents are advised to bring the child to the emergency if the child has altered sensorium, rapid breathing, fruity odor, signs of dehydration, persistent vomiting or persistent ketosis.

Type 2 Diabetes

The incidence of type 2 diabetes in children and adolescents is rising and parallels the increase in childhood obesity, at least in the West and in the more affluent sections of Indian society. Change in dietary habits and lifestyle changes seem to have contributed to this increase. Increase in TV watching, increase in time spent playing videogames rather than outdoor play have resulted in children acquiring a sedentary lifestyle. Distinguishing between type 1 and 2 diabetes in children can be difficult (Table 17.37). Often children with type 2 diabetes may have weight loss and ketoacidosis as the presenting feature. Sometimes autoantibodies are also present in children with type 2 diabetes. However, most of these children are overweight, have family history of type 2 diabetes and show acanthosis nigricans. Children who present with ketosis are treated with insulin initially and transitioned to oral hypoglycemics once their endogenous glucose secretion

Table 17.37: Distinguishing features of type 1 and type 2 diabetes mellitus

Features	*Type 1*	*Type 2*
Onset	Rapid	Slow
Age of onset	Before age 30 yr	After 30 yr
Obesity	Usually thin; weight loss	Usually overweight
HLA association	+++	Not increased
Family history	10%	+++
Concordance in twins	25–50% >80%	50–70% <5%
Islet cell autoimmunity	Frequent	Absent
Ketoacidosis	Rare at diagnosis	May be present at diagnosis
Microvascular complications	100%	Many yr after diagnosis

recovers. These children and adolescents should be evaluated for hyperlipidemia, diabetic retinopathy and nephropathy at diagnosis. It is recommended that children at risk of type 2 diabetes be screened for diabetes.

Plasma Blood Sugar and Hemoglobin Goals

Goals need to be set, but nevertheless are individualized and planned. Blood sugar goals may need to be higher for children with hypoglycemic unawareness (*see* below) or who have frequent and serious hypoglycemia. Goals may be set lower if achievable without complication and risk. Younger children have a higher risk of hypoglycemia. Prepubertal children are at a lower risk for longterm complication than are postpubertal children. Therefore, goals for an acceptable range for blood sugars and for glycosylated hemoglobin can safely be set a little higher for younger children.

Table 17.38: Goals of blood sugar and glycated hemoglobin (HBA1c)

Toddlers and Preschoolers (0–6 yr)

Pre-meal glucose: 100–180 mg/dl
Bedtime and overnight glucose: 110–200 mg/dl
HbA1c: <8.5%

School age (6–12 yr)

Pre-meal glucose: 90–180 mg/dl
Bedtime and overnight glucose: 100–180 mg/dl
HbA1c: <8.0%

Adolescents and young adult

Pre-meal glucose: 90–130 mg/dl
Bedtime and overnight glucose: 90–150 mg/dl
HbA1c: <7.5%

The goals of blood sugar and glaycated hemoglobin recommended by the ADA are shown in Table 17.38.

Complications of Diabetes

Acute Complications

Diabetic ketoacidosis, a serious acute complication due to insulin deficiency is discussed below.

Hypoglycemia is defined as blood sugar less than 60 mg/dl. Low blood sugar usually occurs when the child has been unusually active and insulin and/or food has not been adjusted for increase in activity. Counter-regulatory hormones, namely adrenaline, glucagon and cortisol, are secreted to correct the hypoglycemia. Adrenergic symptoms such as tremors, pallor, tachycardia and sweating can be seen. If left untreated, more severe symptoms may occur dut to neuroglycopenia (decreased availability of glucose to the brain), including seizures, fainting and coma. Prevention of hypoglycemia should be discussed with the patient and family during diabetes education sessions. Treatment follows a rule of 15, i.e. 15 g of free sugar are given in form of sugar, honey, juice or carbonated drink, followed by recheck of blood sugar in 15 minutes. If the child is unconscious glucagon is administered intramuscularly. The dose is dependent on the age and weight of the child as follows: infants 0.3 mg, child <25 kg, 0.5 mg and child >25 kg 1.0 mg. If glucagon is unavailable intravenous dextrose is given.

Intermediate Complications

Lipoatrophy is fat atrophy at the injection site. This can be prevented by rotation of injection sites.

Limited joint mobility is typically noted in the hands. This occurs due to flexion contractures of the metacarpophalangeal and proximal interphalangeal joints.

Growth failure occurs in children whose diabetes is not well controlled. Mauriac syndrome occurs with poor control of diabetes. These children have hepatomegaly, pale skin and extreme short stature.

Delay in sexual maturation is associated with inadequate control of diabetes and delayed bone age.

Hypoglycemic unawareness is caused by frequent hypoglycemia associated with tight metabolic control of diabetes. It is due to impaired counter regulatory response to hypoglycemia. Raising blood sugar targets and prevention of hypoglycemia usually causes reversal of hypoglycemic unawareness.

Chronic Complications

Retinopathy in diabetes is characterized by microaneurysms and proliferative disease. Previously 80–90% of individuals developed eye disease by 15 yr of diabetes.

With intensive management of diabetes this complication is delayed to beyond childhood.

Ophthalmologic examination should be conducted once the child is ≥10 yr of age and has had diabetes for 3–5 yr. Annual followup is suggested.

Peripheral neuropathy is unusual in children and adolescents. This results in decreased nerve conduction velocity and sensory changes. An abnormality in vibration perception may be the first finding.

Nephropathy It is defined by albuminuria in the urine and is preceded by microalbuminuria. It causes significant morbidity and mortality in adulthood. Annual screening of microalbuminuria is initiated once the child is 10 yr of age or has had diabetes for 5 yr. If screening shows an elevated ratio of spot urine microalbumin to creatinine, 24 hr urine microalbumin is estimated. Patients with elevated microalbumin to creatinine ratio should receive ACE inhibitors to delay the progression of nephropathy.

Dyslipidemia Fasting lipid profile is performed on all prepubertal children >2 yr of age at the time of diagnosis (after glucose control is achieved) if there is a family, history of elevated cholesterol (>240 mg/dl) and/or a cardiovascular event before age 55 yr in the family. If there are no concerns of hyperlipidemia in the family, screening is performed after onset of puberty (>12 yr). If LDL is <100 mg/dl, a lipid profile is repeated every 5 yr. For pubertal children (>12 yr of age), a fasting lipid profile is performed at diagnosis after glucose control is achieved. If LDL is <100 mg/dl, lipid profile is checked in 5 yr. If lipids are abnormal, annual monitoring is recommended in both age groups. Intervention is needed if fasting LDL is >100 mg/dl once glucose control is established. Initial therapy is nutritional modification with decrease in saturated fat in diet. A pharmacologic agent is added for LDL of >160 mg/dl, and in patients at risk of cardiovascular disease and LDL values 130–159 mg/dl after initiation of dietary changes and lifestyle intervention. The goal of therapy is LDL value of <100 mg/dl.

Celiac disease Evaluation of celiac disease involves testing for serum IgA, antigliadin antibodies and transglutaminase antibodies. Further evaluation is suggested if these antibodies are elevated.

Specific Recommendations for Longterm Followup

Scheduled followup visits at 3 month intervals with diabetes team is recommended. At these visits the following is planned:

- Assessment of growth, weight and puberty
- Physical examination with specific focus on thyroid, injection sites, fundus, foot and neurological examination.
- Assessment of blood sugar records checked typically pre-meals and at bedtime. Periodic measurements should be advised at 2 AM and postprandially if blood sugar range is inconsistent with glycated hemoglobin. Insulin adjustments are performed, if needed.
- Ongoing diabetes education is necessary, including prevention and management of hypoglycemia and discussion of sick day principles.
- Eye examination is advised annually, if initial eye exam was normal.
- Glycated hemoglobin is checked at 3 month intervals.
- Fasting serum lipids are evaluated annually, and more frequently if abnormal.
- Thyroid function tests are done yearly to assess for hypothyroidism, and more frequently if abnormal.
- Psychological assessment is conducted and referral to psychology advised, if necessary
- Urine microalbumin is assessed (normal 30–399 mg/24 hr).
- For a child receiving continuous subcutaneous insulin infusion): specific education is reviewed and pump function assessed. One should consider the need for continuous glucose monitoring devices.
- At each visit, one should assess nutrition, revisit nutritional plan and advise regarding physical activity.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the most severe complication of diabetes mellitus. It is a state of hyperglycemic dehydration and ketotic acidemia. It is characterized by hyperglycemia, acidosis and ketosis. Blood sugar is typically over 250 mg/dl, ketonemia is present (ketones positive at greater than 1:2 dilution), serum pH is <7.3 and serum bicarbonate <15 mEq/l. In moderate DKA, serum pH is <7.2 and bicarbonate <10 mEq/l. Severe DKA is characterized by serum pH < 7.1 and bicarbonate <5 mEq/l. It can occur in both type 1 and type 2 diabetes. Hyperglycemic hyperosmolar state is a hyperglycemic state seen primarily in adolescents with type 2 diabetes. Both disorders are associated with absolute or relative insulin deficiency, volume depletion and acidosis.

DKA can occur as the initial presentation of type 1 diabetes; 15–70% of all newly diagnosed children present with DKA. The overall rate of DKA among pediatric patients has remained about 25%. The prevalence of DKA decreases from 36% in children <5 yr of age to 16% in those >14 yr. Mortality rates in children vary from 0.15–0.3%; cerebral edema accounts for 60–90% of all DKA related deaths in children.

DKA most commonly occurs in children and adolescents who are non compliant to insulin therapy. Recently, it has also been seen in patients using insulin pumps due to acute interruption of insulin infusion due to pump malfunction. In young patients with type 1 diabetes, psychological problems complicated by eating disorders are a contributing factor in 20% of recurrent cases. Infection may be a precipitation factor.

Pathophysiology

The most important factor that contributes to pathogenesis of DKA is insulin deficiency. This coupled with an increase in counter-regulatory hormones namely glucagon, growth hormone and cortisol augments glucose production from glycogenolysis and gluconeogenesis while limiting glucose utilization. These hormonal alterations result in hyperglycemia and lipolysis resulting in increased free fatty acid production. Oxidation of fatty acids in liver generate β-hydroxybutyrate and acetoacetic acid (ketones) which results in acidosis and ketosis. Hyperglycemia results in osmotic diuresis causing dehydration and hypovolemia and can progress to severe dehydration and shock. Dehydration also causes lactic acidosis which increases acidosis. Ketosis and acidosis results in electrolyte imbalance and other most diagnostic mani-festations of DKA including fruity odor and rapid respirations (Kussmaul breathing). Acidosis causes shift of intracellular ions, most importantly potassium, and phosphate, to the extracellular compartment. These are lost in urine in excess amounts resulting in total body potassium and phosphate depletion. However, serum levels of potassium are variable, depending on the stage of DKA. Initially serum potassium levels are high, and once treatment with insulin is initiated the child becomes hypokalemic. Phosphate is a major component of 2, 3 DPG and its depletion results in decrease in 2, 3 DPG and reduced oxygen delivery to the tissues. Hypertriglyceri-demia and hyperglycemia also falsely lower serum sodium resulting in pseudohyponatremia. Each 100 mg/dl elevation in blood sugar lowers sodium by 1.6 mEq/dl.

Clinical Features

The symptoms and physical signs of DKA are listed in Table 17.39.

Though the metabolic derangements of DKA may take a long time to develop, the signs and symptoms develop in 24 hours. Nausea and vomiting are almost always present. Abdominal pain is usually severe and mistaken for acute appendicitis and other causes of severe abdominal pain are considered. Dehydration is usually severe. Hypotension and shock can be seen in severe DKA. Acidosis and acetone accumulation result in classic signs of DKA; with rapid respiration (Kussmaul breathing) and fruity odor. Lethargy and cerebral depression may evolve into coma. Cerebral edema is a serious complication of DKA and is more frequently seen in children. Children may also have signs of infection, including fever, which precipitate DKA.

Laboratory Evaluation

Criteria for confirmation of diagnosis of DKA include blood glucose >250 mg/dl, blood pH <7.3 and serum bicarbonate <15 mEq/l. Serum potassium may be normal initially but declines with therapy. Serum sodium is low. An elevated creatinine usually reflects dehydration. Leukocytosis and hypertriglyceridemia are common. Serum ketones are elevated being positive even in 1:8 dilution. The levels of β-hydroxybutyrate are higher than acetoacetate, but the latter is preferentially detected by the nitroprusside strip test. Plasma assays of β-hydroxy-butyrate more accurately reflect the true ketone levels.

Management

The goal of treatment is slow correction of dehydration and acidosis to prevent the development of cerebral edema.

A practical approach to the (fluid, electrolyte and IV insulin therapy) management of diabetes ketoacidosis is shown in Table 17.40.

Cerebral Edema

This is complications of DKA, is characterized by headache, bradycardia, altered neurological status and desaturation in an otherwise improving child. The condition most commonly occurs during the first 5–15 hr of therapy. The rate of fluid administration should be reduced. Either IV mannitol (0.25–1 g/kg) over 20 min) or hypertonic (3%) saline (5–10 ml/kg over 30 min) is given to reduce edema.

Nonketotic Hyperosmolar State

This condition is characterized by severe hyperglycemia (usually >600 mg/dl), hyperosmolality (>350 mOsm/kg), low plasma ketones (negative or positive at <1:2 dilution) and dehydration. Although usually seen as a complication of non-insulin dependent diabetes, it can occur in type I diabetes in children if insulin is present to prevent ketoacidosis, but is insufficient to control the blood sugar. The principles of treatment include judicious fluid replacement, regular insulin and fluid therapy.

Table 17.39: Manifestations of diabetic ketoacidosis

Symptoms	*Physical findings*
Abdominal pain	Tachycardia
Nausea and vomiting	Dry mucous membrane, reduced skin turgor, hypotension
Polyuria	Tachypnea, Kussmaul respiration, respiratory distress
Shortness of breath	Abdominal tenderness
Polydipsia	Lethargy, cerebral edema, coma

Table 17.40: Principles of acute management of diabetic ketoacidosis

A. Fluids and electrolytes (Goal: Correct dehydration over 24–48 hr)

1. Initial fluid bolus should be determined based on blood pressure and capillary refill
   - Administer 10–20 ml/kg of normal saline bolus over one hr
   - If hypovolemia present, repeat normal saline for another hr
2. Calculate fluids based on 10% dehydration, not exceeding 4000 ml/m^2/day. Infuse 0.45% saline until blood sugar is ≤300 mg/dl. Dextrose containing fluid (5%) should be added once the blood glucose fall below 250–300 mg/dl and 10% glucose is administered when glucose is <180 mg/dl.
3. Potassium (20–40 mEq/l KCl) is added once urine flow is established and serum K^+ is <5.5 mEq/l

B. Use of bicarbonate

1. Bicarbonate is not used routinely in management of ketoacidosis
2. Therapy with sodium bicarbonate is considered if pH does not improve and arterial pH remains <7.0 (or venous pH <6.9) and serum bicarbonate is <5–10 mEq/l
3. Calculate deficit as follows: Total deficit = (Expected bicarbonate – actual bicarbonate) × 0.6 × patient weight in kg
4. Plan **half correction** of deficit in IV fluid over 24 hr, targeting total bicarbonate 25 mEq/l (27 mEq/l for venous blood)
5. Discontinue bicarbonate in IV fluids when serum bicarbonate reaches ≥10 mEq/L and serum pH >7.1

C. Insulin therapy

1. Following initial hydration, start insulin drip at 0.1 units/kg/hr. If patient is a known diabetic and has received insulin subcutaneously, start at lower insulin dose (0.05 U/kg/hr)
2. When blood glucose is <300 mg/dl, change IV fluids to 5% dextrose with 0.45 saline
3. If blood glucose drops to <180 mg/dl, despite 5% dextrose, change IV fluid to 10% dextrose in 0.45 saline
4. If blood glucose drops to <150 mg/dl, reduce insulin drip in decrements of 0.02 unit/kg/hr
5. The rate of fall of plasma glucose should be 80–100 mg/dl/hr or 40 mg/dl/hr in the presence of severe infection. If there is no change in plasma glucose in 2–3 hr, increase the insulin infusion to 0.15 U/kg/hr
6. When patient is acidotic and ketotic, do not decrease insulin infusion below 0.05 U/kg/hr and do not discontinue insulin infusion until after subcutaneous insulin has been given
7. Monitor blood glucose every 30 minutes when changing insulin drip, or if blood glucose drops to <150 mg/dl
8. Insulin must be continued until pH >7.36 or serum bicarbonate is >20 mEq/l

D. Monitoring

1. Monitor vital signs every hr; neurological signs every 1–2 hr
2. Fluid balance: intake and output monitored hourly
3. Blood sugar, electrolytes pH, bicarbonate: initially 1–2 hr, then every 4 hr
4. Calcium, phosphate and magnesium every 12 hr
5. Also send for glycated hemoglobin; lipid profile; insulin autoantibodies
6. Screen for infections with appropriate cultures, X-rays

Suggested Reading

American Diabetes Association position statement: Standards of medical care diabetes 2011. Diabetes Care 2011, S1:34

Dunge, DB, Sperling MA, Acerini CL, et al. ESPE/LWPES Consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004;89:188–94

International Society for Pediatric and Adolescent Diabetes. Clinical practice consenus guidelines. Pediatric Diabetes 2009;10:1–210

Central Nervous System 18

Veena Kalra

APPROACH TO NEUROLOGICAL DIAGNOSIS

History

An accurate and sequential clinical history and detailed neurological and developmental examination may provide more information than expensive investigations.

Onset of illness. The mode of onset gives clues about the etiology. Head trauma, vascular causes, acute demyelinating encephalomyelitis (ADEM) and acute infections are sudden in onset. Subacute onset is characteristic of infections with organisms of low virulence and neurodegenerative processes. Meningococcal meningitis has a galloping course, whereas tuberculous meningitis may go on for weeks. A relapsing and remitting course can occur in multiple sclerosis and Devic disease. A progressive course indicates degenerative and neoplastic disorders.

Developmental history. A sequential development history helps to define the time of onset and rather ailment. All the developmental milestones are delayed if the disease begins at or near the time of birth of the child. Milestones may regress with acquired insults or degenerative disease of the nervous system. Always ask for consanguinity and family history of neurological disorders.

Physical Examination

Inspection is a crucial part of neurological examination. Observe posture, quality and symmetry of spontaneous movements, behavior, apathy, interest in surroundings, hyperkinesis, involuntary movements such as tremors, athetosis, chorea, myoclonus and convulsions.

Cranial nerves. Response to light stimuli and pupillary reflexes show integrity of second and third cranial nerves. Ophthalmoplegia and paralytic squint indicate involvement of third cranial nerve. Down and out movement of the affected eye indicates fourth cranial nerve involvement. Fifth nerve integrity can be checked by conjunctival or corneal reflex. Sixth nerve paralysis, diagnosed by a convergent paralytic squint, may be a false localizing sign. Facial asymmetry, loss of nasolabial fold on the ipsilateral side, pulling of the angle of the mouth on contralateral side and drooling of saliva indicates paralysis of seventh nerve. The integrity of cochlear division of eighth nerve is checked by auditory tracking. Ninth and tenth nerve integrity is determined by gag reflex and palatal movements. If the child can shrug his shoulders and turn his neck from side to side, eleventh nerve (accessory) is intact. In twelfth nerve palsy, the tip of the tongue is deviated to the side of the lesion.

Motor Examination

Best power in all limbs during spontaneous movement should be recorded in infants and toddlers. Detailed assessment of power should be attempted in older children. Assessment of tone helps in the localization of lesion.

Deep tendon reflexes. These are best elicited when the concerned muscle groups are relaxed. Exaggerated deep tendon reflexes imply upper motor neuron lesions and diminished reflexes are observed in lower motor neuron disease. Cerebellar lesions cause pendular knee jerks.

Developmental Examination

In infancy, tone, posture, neonatal reflexes, appearance of postural reactions are to be assessed. In addition, gross and fine motor functions, socioadaptive and language evaluation should be done using standard tests or charts of development. Hearing and vision evaluation is also mandatory.

Lumbar Puncture

Lumbar puncture is indicated in inflammatory CNS disorders, neonatal sepsis, malignancies (to determine CNS spread and for therapy), autoimmune diseases, demyelinating illnesses, slow virus infections specially

subacute sclerosing panencephalitis (SSPE), and for lactate, neurotransmitters and glycine in neurometabolic and neurotransmitter disorders. Lumbar puncture is not indicated in febrile convulsions except in infants to exclude meningoencephalitis. Lumbar puncture has both diagnostic and therapeutic utility in pseudotumor cerebri.

Fundus must be examined prior to procedure to exclude papilledema, as sudden release of cerebrospinal fluid pressure following lumbar puncture may result in medullary coning and cardiorespiratory arrest. Aseptic precautions should be maintained while doing lumbar puncture. Cerebrospinal fluid (CSF) opening pressure evaluation is useful.

CSF is examined for its color; microscopy for number and type of cells. Protein, sugar/chloride estimation is routinely performed. Blood sugar estimation should be performed at time of lumbar puncture for comparison. Culture, serology and newer diagnostic tests for antigen/antibody detection should be done if infection is suspected.

Electroencephalogram (EEG)

Electroencephalogram is a commonly employed test. Electrical activity is recorded by placing a set of electrodes on the scalp in a specific arrangement. Recorded rhythms are evaluated by their rate (Hz), amplitude (μV), symmetry, synchrony and morphology. The various rhythms include beta rhythm at 14–20 Hz (cycles/sec), alpha rhythm at 8–13 Hz, theta rhythm at 4–7 Hz and delta at 1–3Hz. Activity faster than beta can be an artifact from the scalp muscles. Figure 18.1 depicts a normal EEG record.

Indications. EEG is useful in classifying, supporting and confirming diagnosis of epilepsy and epilepsy syndromes. It distinguishes between seizure and nonseizure states, e.g. fainting spells, hypoxic episodes and breath holding spells. EEG is especially helpful for diagnosis of absence attacks, myoclonic epilepsies, nonconvulsive status, epilepsy syndromes, SSPE and herpes encephalitis. EEG is not indicated in typical febrile convulsions.

Abnormalities. The common abnormalities of background include slow/abnormal or asymmetric rhythms; these may be generalized, localized or lateralized to one side and thus help to localize anatomic lesions. In addition, spikes, sharp waves, polyspikes or hypsarrhythmia may be seen in certain epilepsy syndromes/epilepsies (Fig. 18.2).

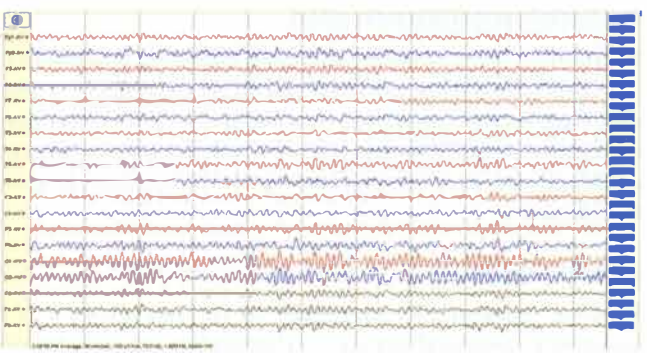

Fig. 18.1: Normal EEG, in a 5-yr-old child. Note normal posterior dominant alpha background activity

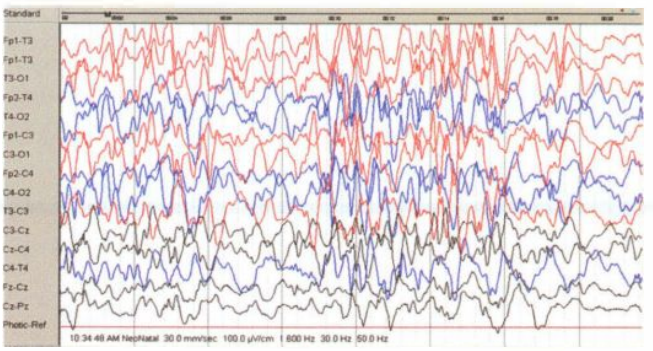

Fig. 18.2: Abnormal EEG, in a 4-month-old, showing abnormal slow chaotic background with multifocal spikes suggestive of hypsarrhythmia

Spikes are transient discharges that stand out from background, last less than 70 milliseconds and often accompanied by a slow wave. When spikes occur very closely, they are called polyspikes. Sharp waves have a duration of 70–200 milliseconds and are less pointed. A *three per second spike and wave discharge* is observed in typical absence attacks (Fig. 18.3). Brief bursts of polyspikes are common in myoclonic epilepsies. In benign focal epilepsies of childhood, clusters of high amplitude, spike wave complexes are seen in rolandic areas. High voltage (>100 μV), generalized, chaotic slow waves (hypsarrhythmia) and multifocal spikes are common in infantile spasms.

Subacute sclerosing panencephalitis (SSPE) is characterized by periodic epileptiform discharges recurring at similar intervals throughout the record. The discharges are similar in morphology and amplitude and often superimposable (Fig. 18.4).

Herpes encephalitis may be associated with periodic lateralized slow waves or high voltage complexes. Focal

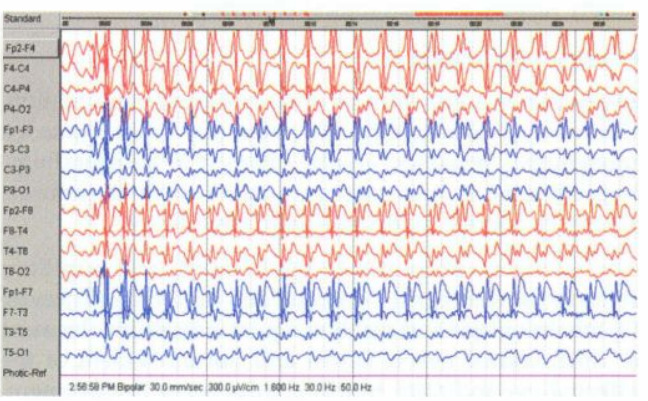

Fig. 18.3: Synchronous 3 Hz spike wave discharges in a child with absence epilepsy

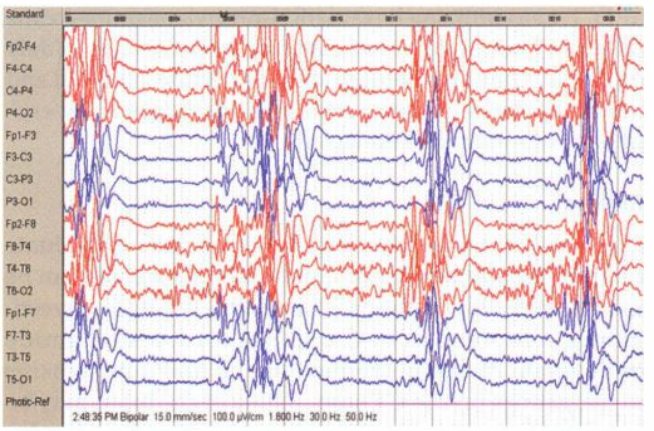

Fig. 18.4: High amplitude periodic sharp waves in a child with subacute sclerosing panencephalitis (SSPE)

slowing may be observed in inflammatory granulomas, cerebral abscesses and infarction. Generalized slowing of the background may be seen in encephalitic syndromes. Barbiturates and benzodiazepines produce generalized fast beta activity.

Limitations of EEG. Two percent of the normal population may have abnormal EEG records with spikes that have no clinical consequence or diagnostic utility. Patients with epilepsies may have normal interictal records. Treatment should not be based on EEG alone; correlation with the clinical condition is important. EEG is not essential for decision to stop antiepileptic drugs in epilepsy, though it may be useful in predicting the risk of recurrence after discontinuation of anticonvulsants.

Video EEG and EEG telemetry are useful in identifying surgical foci of epilepsy and in management of intractable epilepsies. Magnetoencephalography records the magnetic field generated instead of electrical potentials and can localize the focus three dimensionally.

Evoked Potential Response

Evoked potentials in response to visual, brainstem, auditory or somatosensory stimuli are useful tools to assess conduction, processing of information and integrity of specific sensory pathways. It also helps to determine the site of pathology. Brainstem auditory evoked potentials (BAEP) and otoacoustic emissions (OAE) can detect early defects of hearing and postkernicteric damage to the newborn. Visual evoked responses (VER) are useful to determine site and severity of neurological visual loss. These tools have diagnostic utility in deeply comatose patients and neurodegenerative disorders.

Electromyography

The technique of electrical recording from the muscle is called electromyography (EMG). Concentric needle electrodes are inserted into the muscle to be studied. Normally the resting muscle is electrically silent. Insertion of electrode causes a brief burst of electrical potentials called insertional activity. When the muscle contracts, the motor unit action potential is recorded. This is a triphasic record, which usually ranges from 200 to 500 μV with duration of 2–15 min.

Abnormal spontaneous activity such as fasciculations or fibrillations indicate denervation, e.g. spinal muscular atrophy. Large amplitude, polyphasic and prolonged duration potentials may be seen in neurogenic abnormalities. In myopathies, these units are of low voltage, shorter duration with early recruitment. Myasthenic syndromes reveal a decremental response on repetitive nerve stimulation test. When requisitioning an EMG, a partly involved muscle should be sampled rather than an atrophic or a normal muscle.

EMG is especially helpful to distinguish between neurogenic and myogenic weakness in a floppy infant.

Nerve Conduction Study

Nerve conduction studies are useful for diagnosing specific nerve lesions, neuropathies and in systemic disorders which alter motor and sensory nerve function. Diminished nerve conduction velocities, which imply diseases of myelin, can be observed in patients with peripheral neuropathies and dysmyelinopathies. Nerve conduction studies are useful in distinguishing polio-myelitis from Guillain-Barré syndrome.

Neuroimaging

Ultrasonography is an investigation of choice in newborns and infants with a neurological illness through open anterior fontanel. It can be performed at bedside and provides quick and useful information. The ventricles, part of cortex and periventricular tissue are very well visualized with ultrasonography. The peripheral cortex and posterior fossa is poorly visualized. A color Doppler ultrasound evaluates many vascular malformations and congenital anomalies in a two-dimensional way.

Computerized tomography (CT scan) The cross-sectional images are computed into two mm sections of the brain. Newer modifications and sophisticated scanners provide 3-D images, volumetric data and quick sequential images. CT evaluates anatomy of supratentorial brain structures reasonably well. Myelination, posterior fossa and brain stem structures are not well visualized. Calcification is best evaluated by CT images (Fig. 18.5).

Indications. (i) Hypoxic ischemic encephalopathy; (ii) head injury; (iii) craniofacial anomalies; (iv) inflammatory disorders: CNS tuberculosis, neurocysticercosis, pyogenic abscesses and other inflammatory lesions; (v) suspected space occupying lesions; (vi) vascular causes–infarcts, sinus thrombosis, malformations; (vii) degenerative brain disorders; (viii) hydrocephalus, porencephaly and structural malformations.

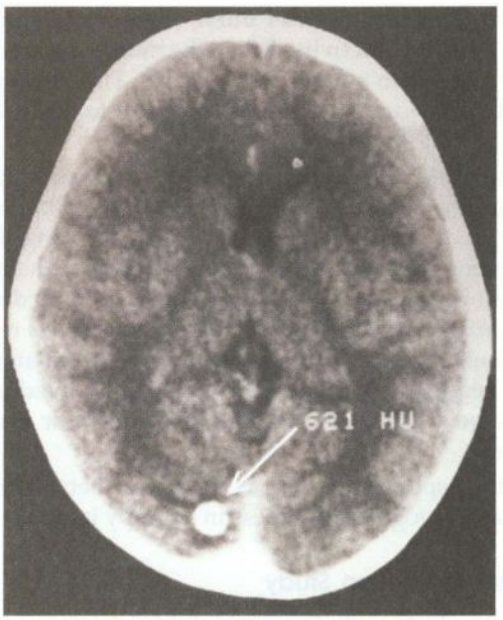

Fig. 18.5: Noncontrast enhanced CT of brain showing a calcified cyst (*Courtesy*: Dr. Atin Kumar, Deptt. of Radiodiagnosis, AIIMS)

CT is not very useful in a large proportion of neurometabolic, neuromigration and genetic disorders. In vascular, inflammatory, infectious or neoplastic lesions a plain scan followed by contrast enhanced scan improves diagnostic yield.

Magnetic resonance imaging (MRI) MRI provides anatomical delineation, gray-white matter distinction, detection of myelination, congenital abnormalities, vascular anomalies and migration defects with far greater diagnostic detail than CT. The midline structures, posterior fossa and brainstem structures can be visualized well. Sagittal and coronal views permit volume evaluation of CNS structures. Some degenerative disorders can be picked up early by MRI. MRI is also of particular use in patients with intractable epilepsy as it helps in anatomic localization of lesion. Newer MR techniques–MR spectroscopy that identifies metabolites like NAA, choline, lactate in specific voxels of the brain is useful for diagnosis of metabolic disorders, cystic lesions and tumors and is being increasingly used as an investigative tool.

Functional scans Functional scans like *positron emission tomography* (PET) help to demonstrate perfusion, oxygen and glucose uptake in different parts of brain like cerebrum, cerebellum, thalamus and basal ganglia. These scans have utility in identifying surgically resectable intractable epilepsies, cerebral tumors and head injuries. PET scans can be modified to assess cerebral blood volume, cerebral blood flow, oxygen and cerebral glucose metabolism. These have been used as research tools for assessing brain development, speech and vision dysfunction. PET is extremely useful for localization of an anatomic focus in presurgical work up of intractable epilepsy.

SPECT scans utilizing hexamethyl-propyleneamine oxime (HMPAO) and ethyl cysteinate dimer (ECD) are widely available. They are useful to identify perfusion in ictal and interictal states, and are important presurgical investigations of intractable epilepsies.

Others

Digital subtraction cerebral angiography is done to evaluate cerebrovascular disorders. *Carotid Doppler* studies can be used to study flow patterns. *Myelography* is used for investigating compression of the spinal cord. Metrizamide myelogram can be performed to evaluate compressive myelopathies on the CT scan. *Biopsy* of the brain may be indicated for malignant or degenerative disorders. *Psychometric tests* are carried out for measuring cognitive ability and intelligence of patients with suspected mental retardation.

SEIZURES

Seizures (convulsions, fits) are caused by abnormal electrical discharges from the brain resulting in abnormal involuntary, paroxysmal, motor, sensory, autonomic or sensorial activity. About 5 percent children experience convulsions during the first five years of life. Motor movements consisting of tonic and clonic components are the most commonly observed phenomenon, except in the newborn period.

Several times, a child may present with a condition that can mimic or be misinterpreted as a seizure. These conditions include convulsive syncope with or without cardiac dysarrhythmia, decerebrate posturing, psychogenic events, dystonia and migraine. Seizures should be differentiated from these conditions as misdiagnosis can have significant therapeutic implications.

Neonatal seizures often present with twitching of the limbs, fluttering of the eyelids, sucking movements and conjugate deviation of the eyes. These should be distinguished from jitteriness, tremors, startle response to stimuli, sudden jerks on awakening and tremulousness of the hungry child.

Common causes of convulsions are better classified according to the age at onset (Table 18.1).

Approach to a Child with Convulsions

A good description of the seizures including mode of onset, details of aura, type of seizure, automatism, associated behavioral abnormalities and the postictal phase should be obtained. An accurate seizure description is more informative than detailed neurological examination or investigations. Perinatal, developmental, and family history of seizures help in determining the cause. The child should be examined for evidence of raised intracranial tension, degenerative, metabolic or congenital disorders.

Table 18.1: Causes of convulsions

Early neonatal period (0–7 days)

Birth asphyxia, difficult obstructed labor
Intraventricular, intracerebral hemorrhage
Pyridoxine dependency, hypoglycemia, hypocalcemia
Inborn errors of metabolism
Maternal withdrawal of medications
Injection of local anesthetic into the fetal scalp during the paracervical block given to the mother

Neonatal period (7–30 days)

Transient metabolic: Hypocalcemia, hypomagnesemia, hypoglycemia, dyselectrolytemia
Developmental malformations
Infections: Meningitis, septicemia, tetanus neonatorum, intrauterine infections
Metabolic errors: Phenylketonuria, maple syrup urine disease, galactosemia, urea cycle disorders

Beyond neonatal period

Simple febrile convulsions
Epilepsy syndromes
Infections: Bacterial meningitis, intrauterine infections, tuberculous meningitis, aseptic meningitis, encephalitis, cerebral malaria, Reye syndrome
Metabolic causes: Dyselectrolytemia, hypocalcemia, hypomagnesemia, inborn errors of metabolism
Space occupying lesions: Neoplasm, brain abscess, tuberculoma, cysticercosis
Vascular: AV malformations, intracranial thrombosis, hemorrhage
Miscellaneous: Hypertensive encephalopathy, sequelae of birth trauma and birth asphyxia, gray matter degeneration, storage disorders
Drugs, poisons: Phenothiazines, salicylates, phenytoin, strychnine, carbon monoxide, lead

Role of Investigations

Estimation of glucose, calcium and screening tests for neurometabolic causes usually suffice. Detailed metabolic studies, including screening of amino acids, blood ammonia, blood and CSF lactate/pyruvate levels are indicated if inborn errors of metabolism are suspected and in familial seizures.

Electroencephalography (EEG). It is the best supplementary test for classification and diagnosis of epilepsy. It should be used to support the diagnosis of seizure, diagnose certain epilepsy syndromes, localize an epileptic focus and determine its anatomical basis. EEG does not always help in determining the duration of therapy. Focal EEG abnormalities justify the need for imaging.

Cranial imaging. X-ray films of the skull are not helpful, except in microcephaly, scattered calcification, suture evaluation and thickening of the calvarium. MR imaging, CT scans and functional imaging are indicated in partial seizures, seizures with focal neurological deficits, dysmorphic features, or skin lesions suggesting neuroectodermatoses and in the presence of raised intracranial pressure.

STATUS EPILEPTICUS

Status epilepticus (SE) implies prolonged single seizure or multiple episodes of seizures lasting more than 30 min without regaining consciousness in between. Impending status epilepticus refers to any seizure lasting more than 5 min.

SE can be classified as *convulsive* (tonic-clonic, clonic, tonic, or myoclonic) or *nonconvulsive* (absence, non convulsive, speech sensorial alteration). Convulsive SE is the most common and is associated with significant morbidity and mortality. The neurological sequelae following SE depend upon etiology, age and duration of SE. The risk of complications increases substantially with duration (>60 min). Neurological residua include mental retardation, focal neurological deficits, behavioral disorders and chronic epilepsy. Seizures recur in 25–75% of patients. The mortality rate is 10%; most deaths are attributable to the patient's underlying pathology.

In over 50% of cases, SE is the patient's first seizure. About 3% of epileptics experience a SE in their lifetime. Approximately 25% of childhood SE is idiopathic, 25% is associated with fever or meningoencephalitis, while 50% of patients have neurodevelopmental abnormality, head trauma, stroke, drug intoxication, subarachnoid bleed, pyridoxine deficiency or metabolic abnormality (hypoglycemia, hyponatremia).

Pathophysiology

SE results from excessive and persistent excitation, or ineffective recruitment of inhibition. Excitatory neurotransmitters include glutamate, aspartate and acetylcholine and the dominant inhibitory neurotransmitter is gamma-aminobutyric acid. The blockage of N-methyl-D-aspartate (NMDA) channels by magnesium ions seems to be important in the pathogenesis of neuronal damage in SE. Associated hypoxia, hypotension, acidosis and hyperpyrexia exacerbate the neuronal damage.

Evaluation in the Emergency Department

History is taken for description of the event, associated symptoms, duration and the postictal period, prior history of seizures, noncompliance with antiepileptic drugs (AEDs) or change of AED and history of prior neurological development.

If postictal confusion does not resolve search for other causes, e.g. hypoglycemia, dyselectrolytemia, CNS infection, CNS vascular event, drug toxicity, psychiatric disorders and nonconvulsive status epilepticus (SE). Nonconvulsive SE can be diagnosed by EEG monitoring.

Investigations

Patients who are in convulsive SE require comprehensive diagnostic testing which includes serum glucose, electrolyte, urea, creatinine, calcium, magnesium (if indicated), complete blood cell count, malarial parasite and culture (if fever), arterial blood gas analysis, determination of anticonvulsant level (if on anticonvulsants), renal and liver function tests. Lumbar puncture is essential in suspected CNS infections. If meningitis is suspected but lumbar puncture cannot be performed, antibiotics should be administered immediately.

Neuroimaging. It is an important investigation. The yield varies from 3 to 41%, may be higher in developing countries because of neuroinfections and neurocysticercosis. A head CT is informative for acute head trauma, malignancy, meningoencephalitis, neurometabolic disorders, persistent headache or in presence of focal neurological signs.

Electroencephalography (EEG). An urgent EEG is recommended for patients with SE especially if nonconvulsive SE is suspected.

Management

There are four goals of therapy: (i) ensure adequate vitals, systemic and cerebral oxygenation, (ii) terminate seizure activity, (iii) prevent seizure recurrence, and (iv) establish the diagnosis and treat the underlying disorder.

Emergency Supportive Treatment

Secure the airway, maintain oxygenation, ensure perfusion, obtain intravenous access and protect the patient from hypoglycemia, hyperthermia and injury. Head and neck should be positioned to keep the airway open. If necessary, airway should be suctioned. Oxygen by nasal cannula or mask, if needed, is administered, endotracheal intubation may be required. Two IV access should be established. Blood samples should be sent for laboratory studies, and 10–25% dextrose (2 ml/kg) should be given empirically. Systolic BP should be maintained at normal levels. Hyperthermia occurs frequently in SE; temperature should be recorded and treated promptly.

Anticonvulsant Treatment

The goal of treatment is rapid termination of clinical and electrical seizure activity by the prompt administration of appropriate drugs in adequate doses, with attention to the possibility of complicating apnea, hypoventilation and other metabolic abnormalities. The dosage schedule, route and rate of administration of the common anticonvulsant drugs used to treat acute seizures and SE are outlined in Tables 18.2 and 18.3.

Early and effective treatment is essential to prevent a refractory status and longterm neurological sequelae. Every institution should have a well-established treatment protocol depending upon the local availability of drugs. A proposed management protocol is shown in Fig. 18.6.

Domiciliary treatment Prehospital treatment with anticonvulsants is advocated for all children with recurrent prolonged seizures to reduce hospitalization episodes and complications. Drugs used are oral or intranasal midazolam or rectal diazepam.

Hospital treatment Any child who presents actively convulsing to emergency room is assumed to be in SE and managed aggressively. The drug recommended is IV

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Table 18.2: Anticonvulsants in management of acute seizures

Drug	*Route*	*Intial dose (mg/kg)*	*Rate of infusion*	*Remarks*
Diazepam	IV	0.1–0.3	1 mg/min	Followed by phenytoin loading; can cause apnea, respiratory depression
	Rectal	0.2–0.5		
Lorazepam	IV	0.05–0.1	1 mg/min	Longer duration of action; less respiratory depression than diazepam
	Rectal	0.1–0.4		Slower onset of action
Midazolam	IV	0.05–0.2	1–18 µg/kg/min	Non-IV midazolam is safe and effective in treating SE
	IM	0.1–0.2		
	Buccal	0.1–0.2		
	Nasal	0.1–0.2		
Valproic acid	IV	20	5 mg/kg/min	Used in status epilepticus
Paraldehyde	IM	0.15 ml/kg		Use glass syringe
	Rectal	0.3 ml/kg		Dilute one part with three parts of olive/coconut oil
Phenytoin	IV	15–20	0.5–1 mg/kg/min	Mix only in normal saline, may cause dysarrhythmia and hypotension
Fosphenytoin	IV/IM	15–20 PE/kg	3 mg/kg/min	Less risk of hypotension
Phenobarbitone	IV	10–20	1–2 mg/kg/min	Hypotension, respiratory depression, especially with benzodiazepines
Levetiracetam	IV	20	5 mg/kg/min	Safe drug

IM intramuscular; IV intravenous; PE phenytoin equivalents

Table 18.3: Drugs for management of refractory status epilepticus

Drug	*Initial IV dose (mg/kg)*	*Maintenance infusion*	*Remarks*
Pentobarbital	5–15	1–5 mg/kg/hr	Titrate drip to seizure control/burst suppression on EEG
Propofol	1–3	2–10 mg/kg/hr	Rapid infusion can cause hypotension
Midazolam	0.05–0.2	1–18 µg/kg/min	Few hemodynamic adverse effects
Diazepam	0.1–0.3	0.1–1 mg/kg/hr	Cardiorespiratory monitoring
Lignocaine	1–2	3–5 mg/kg/hr	Proconvulsant at higher doses

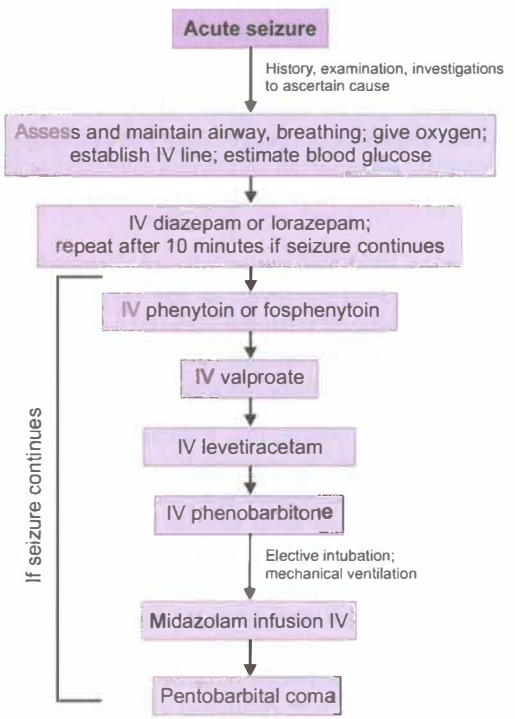

Fig. 18.6: Management of status epilepticus. Following initial assessment, patients need to be treated with anticonvulsants. If required, more than one agent may be administered sequentially. Patients should be monitored for respiratory difficulty and might need assisted ventilation

lorazepam, midazolam or diazepam. If diazepam is used when treating SE, a long acting anticonvulsant such as phenytoin must be administered concurrently with diazepam to prevent recurrent convulsions. Seizure control occurs within 5 min of benzodiazepine administration in 80% of patients. The usual IV dosage for diazepam is 0.1 to 0.3 mg/kg given at a rate of 1 mg/min. This dose can be repeated two times every 5 to 10 min if seizures persist up to a maximum dose of 10 mg. Lorazepam (0.05–0.1 mg/kg IV) is the preferred first line anticonvulsant as it has a longer duration of action (12–24 hr), less respiratory depression and repeated doses are less often required than with diazepam. A second long-acting anticonvulsant is also not required because of longer duration of action. Maintenance drugs should be added to control further seizures. If IV access cannot be immediately obtained, then other routes of administration (rectal, oral) should be considered.

Midazolam is an important drug for the initial management of acute seizure. It can be used IM or intranasal if IV access is not available at a dose of 0.1 to 0.2 mg/kg.

Phenytoin is used for maintaining a prolonged antiseizure effect after rapid termination of seizures with a benzodiazepine. The loading dose is 20 mg/kg infused at a rate of 0.5–1 mg/kg/min (maximum 50 mg/min). A therapeutic effect can be seen in 20 min. Saline solution should be used for dilution as phenytoin precipitates in dextrose. Side effects include hypotension, cardiac dysarrhythmia, phlebitis and tissue necrosis from extravasation, movement disorder and cerebellar ataxia.

Fosphenytoin is a water-soluble ester of phenytoin that is rapidly converted to phenytoin by systemic phosphatases and can be administered intramuscularly. The dose of fosphenytoin is expressed in phenytoin equivalents (PE) and is 15–20 mg/kg, infused at a rate of no more than 3 mg/kg/min (maximum 150 mg/min). Phlebitis is less common with fosphenytoin but its primary disadvantage is high cost.

If no response to benzodiazepines and phenytoin, *phenobarbitone* is administered at a loading dose of 10 to 20 mg/kg at a rate of 1 to 2 mg/kg/min. Potential side effects include hypotension, respiratory depression and sedation. Phenobarbitone is the drug of choice in neonatal seizures, hypersensitivity to phenytoin and cardiac conduction abnormality.

In patients on oral phenytoin or phenobarbitone, 5–10 mg/kg of the drug should be given if drug withdrawal is the likely cause of SE.

Paraldehyde is generally not available; can be administered per rectally or intramuscularly with a glass syringe.

If signs and symptoms of raised intracranial pressure are present, mannitol can be administered at a dose of 5 ml/kg (20%) IV over 10 min to decrease cerebral edema. Maintenance therapy should be simultaneously started with appropriate AED.

Refractory Status Epilepticus

When the seizure do not respond to at least two doses of benzodiazepines, followed by phenytoin/valproate and phenobarbitone or midazolam infusion beyond 60 min after treatment has been started, it is labeled as refractory SE and must be ideally managed in a tertiary health care

center with intensive care unit where facility for artificial ventilation is available. Treatment of refractory SE include barbiturate coma, midazolam infusion, lignocaine, intravenous valproate, propofol and inhalation anesthesia.

In a recent meta-analysis, midazolam infusion was found to be a good choice for initial treatment of refractory SE with fewer hemodynamic consequences and lesser need for invasive monitoring and mechanical ventilation. A bolus dose of 0.15 mg/kg of midazolam is followed by continuous infusion at a rate of 1 µg/kg/min increasing by 1 µg/kg/min every 15 min until a maximum of 18 µg/kg/min or seizure control. The optimum rate of infusion at which seizure control is achieved is maintained for a period of 48 hr. Subsequently the infusion rate is gradually decreased by 1 µg/kg/min every three hr with frequent EEG review. Any seizure activity during the weaning period requires an immediate resumption of the infusion to achieve again a seizure-free period of 48 hr.

Both pentobarbital and thiopental have been used for barbiturate coma. Patients requiring barbiturate coma must be intubated and mechanically ventilated with close hemodynamic and continuous EEG monitoring. Pentobarbital is given in a loading dose of 5 mg/kg followed by an infusion of 0.5–3 mg/kg/hr. The patient is monitored for a burst suppression pattern by EEG. The patient remains in barbiturate coma for 12 to 24 hr. The patient is then weaned and observed for recurrence of seizure activity. If seizure recurs, the patient is placed back into the barbiturate coma and weaning is again tried after another 24 hr. Barbiturate coma is advantageous over the use of general anesthesia. Continuous EEG is necessary to ensure that burst suppression has occurred.

Longterm anticonvulsant drugs The decision for therapy is based on the underlying cause and predicted risk of seizure. When no etiology is identified and the EEG is normal, the recurrence risk is 24% at 2 yr. Patients with abnormal neuroimaging/EEG or focal seizures have a 65% risk of recurrence and should receive longterm anticonvulsant therapy.

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FEBRILE CONVULSIONS

Febrile convulsions are the commonest provoked seizures affecting 3–5% children. They are defined as seizures during fever occurring between 6 months and 5 yr age in the absence of infection of the central nervous system in a neurologically normal child. Febrile seizures are frequently genetically determined. The convulsions are not related to the degree of temperature, but are frequent if temperature rises abruptly. Febrile convulsions may be (i) simple, benign; or (ii) atypical, complex.

Simple febrile convulsions. The seizure occurs within 24 hr of the onset of fever, last less than 15 min and are usually single per febrile episode. Convulsions are generalized. There is no postictal neurological deficit.

Atypical febrile seizures. Atypical or complex febrile convulsions should be distinguished from simple febrile convulsions. Presence of family history of epilepsy, neurodevelopmental retardation and atypical episodes increase recurrence risk of febrile seizures and subsequent epilepsy.

Convulsions in developmentally challenged children may be precipitated by fever, as the cerebral threshold for seizures is reduced with the elevation of temperature. These are distinct from febrile convulsions, which occur in a neurodevelopmentally normal child.

Differentiation from meningitis. Infections of the central nervous system such as meningitis or encephalitis, are important causes of convulsions associated with fever and can be easily confused with simple febrile convulsions. Lumbar puncture should be performed in the first episode of febrile seizure, in infants below 1 yr who are not immunized with Hib and pneumococcal vaccine, or if immunization status is not known and where meningitis is suspected. In all patients with febrile convulsions, a lumbar puncture is not required routinely. EEG and neuroimaging have no role in febrile seizures.

Treatment. Febrile convulsions are managed by prompt reduction of temperature with antipyretics or hydrotherapy to comfort the patient. Maintenance of airway, breathing and circulation should be ensured. In case of prolonged febrile seizures, IV access should be established to maintain adequate hydration and to administer anticonvulsant medication. Possibility of meningitis should be excluded by a lumbar puncture if indicated. Injection of midazolam or diazepam (0.2–0.3 mg/kg/dose) is given for control of seizures.

Febrile Seizure Prophylaxis

Prophylaxis may be continuous or intermittent. Intermittent prophylaxis of febrile convulsions is indicated if 3 or more febrile seizures in 6 months, or 6 or more in 1 yr, febrile seizures lasting more than 15 min or requiring pharmacological therapy to control seizures.

Intermittent prophylaxis is currently prescribed during episodes of fever. A drug that attains drug levels quickly and prevents febrile convulsions should be used. Oral

clobazam (0.75–1 mg/kg/day) is an effective prophylactic and is given for 3 days during fever episodes. Antipyretics, hydrotherapy and meticulous temperature recording should be advocated for all patients. Domiciliary care is recommended.

Continuous prophylaxis with antiepileptic drugs is advocated in the event of failure of intermittent therapy, recurrent atypical seizures and in particular, when parents are unable to promptly recognize the onset of fever. Only sodium valproate (10–20 mg/kg/day) or phenobarbitone (3–5 mg/kg/day) are effective for febrile seizure prophylaxis. Carbamazepine and phenytoin are ineffective. The duration of therapy should be for 1–2 yr or until 5 yr of age.

Prognosis. Recurrence risk of febrile convulsions varies from 30 to 50%. Risk factors that can predict the recurrence of simple and complex febrile seizures are early age of onset (<15 months), epilepsy or fevers in first-degree relatives, frequent fevers and low temperature at the onset of the febrile seizure. About 1–2% of children with simple febrile convulsions and up to 5% of those with recurrent complex seizures are likely to develop epilepsy. Parents of the child should be reassured that the risk of epilepsy after simple febrile seizure is not significantly greater than the general population. The risk of developing epilepsy is higher if the seizures are atypical, electroencephalogram is persistently abnormal, if the child has abnormal neurodevelopment or a family history of epilepsy. Complex partial seizures may manifest after several years of prolonged atypical febrile convulsions.

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EPILEPSY

Epilepsy is characterized by recurrent, episodic, paroxysmal, involuntary clinical events associated with abnormal electrical activity from the neurons. The patient may present with motor, sensory or psychomotor phenomena, often with alteration in sensorium.

Epidemiology and Classification

Five percent of children may experience one or more seizures in childhood, less than 1% have epilepsy. The incidence is highest in the preschool years. Intrafamilial recurrence of convulsions, especially simple febrile convulsions, is common.

Epilepsy is classified by appraisal of (i) seizure type, (ii) etiology, and (iii) electroencephalographic data. If an underlying etiology is identified it is symptomatic epilepsy otherwise it is called idiopathic. In cryptogenic epilepsy, a cause is presumed. A simplified modified version of the classification proposed by the International League Against Epilepsy (ILAE 1981) is given in Table 18.4.

Clinical Features

Epilepsy is described as generalized or partial (focal). Generalized seizures may be (i) tonic; clonic or tonic-clonic; (ii) absence (petit mal); (iii) atonic, and (iv) myoclonic.

Tonic-Clonic Seizures (Grand Mal Type)

Generalized tonic-clonic seizures are the most frequent form of childhood epilepsy. Classic form has four phases viz. (i) aura; (ii) tonic; (iii) clonic; and (iv) postictal phase.

Aura. A transitory premonitory symptom or aura heralds the onset of a seizure. Aura may be sensory, visceral, motor or autonomic. Only one-third of patients can describe the aura properly.

Tonic phase. During this phase, skeletal muscles go into a sustained spasm. The muscular rigidity is most marked

Table 18.4: Classification of epilepsy

Generalized

Generalized epilepsy may be (i) tonic-clonic (grand mal), (ii) tonic, (iii) clonic, (iv) absence, (v) atonic, (vi) myoclonic

Idiopathic: (i) benign neonatal convulsions, (ii) childhood absence, (iii) juvenile absence, (iv) juvenile myoclonic epilepsy, (v) grand mal seizures on awakening, (vi) generalized idiopathic

Symptomatic/Cryptogenic: (i) West syndrome (infantile spasms), (ii) Lennox -Gastaut syndrome (childhood epileptic encephalopathy), (iii) myoclonic astatic seizures, (iv) myoclonic absences

Partial

Simple partial (elementary symptoms, no impairment of consciousness) with (i) motor, (ii) sensory, (iii) autonomic, (iv) psychic

Complex partial (impaired consciousness): (i) simple partial followed by loss of consciousness; and (ii) with impaired consciousness at onset

Partial seizures evolving to secondary generalized seizures

Syndromes

Idiopathic: Benign childhood focal epilepsy with centrotemporal spikes (Rolandic epilepsy); epilepsy with occipital paroxysms
Symptomatic: (i) chronic progressive epilepsy; (ii) epilepsia partialis continua; (iii) progressive myoclonic epilepsy

Undetermined syndromes

Neonatal seizures
Severe myoclonic epilepsy of infancy, migratory partial seizures of infancy
Epilepsy with continuous spike waves during slow wave sleep
Acquired epileptic aphasia

in the antigravity muscles, such as flexors of arms and extensors of lower extremities. The child becomes unconscious, falls, face appears pale, pupils are dilated and eyes are rolled and there is frothing from the mouth. Urine or stools may be passed involuntarily. This phase lasts for about thirty seconds.

Clonic phase. It is characterized by rhythmic alternating contractions of muscle groups. In many patients, epileptic phases overlap each other.

Postictal phase. The child may complain of headache, confusion and has little recollection later. Rarely, the child develops a transient paresis, may lose bladder/bowel control or injure himself. EEG shows generalized burst of spikes and irregular 4–6 Hz spike-wave complex.

Absence Seizures

Absence seizures start abruptly in childhood; the peak prevalence is between 6–8 yr. Absence seizures are not preceded by aura. The patients have a brief abrupt lapse of awareness or consciousness, sudden discontinuation of the activity being performed with staring spell, eye fluttering, or rhythmic movements. The seizure lasts less than 30 seconds. There is no loss of posture, incontinence of urine/stools or breathing difficulty. Other neurological manifestations and postictal phenomena are absent and development is normal. Unaware of the nature of their illness, school teachers may consider them inattentive pupils.

Hyperventilation for 3 min often precipitates the attacks. Absence seizures may occur in multiples, everyday. Attacks following in close succession indicate *petit mal* status or *pyknolepsy*.

About half of patients become seizure free and the rest develop tonic-clonic fits. Learning disabilities and behavior disorders when present are probably related to associated conditions. EEG shows a characteristic 3 per second spike and slow wave pattern. Absence fits are distinguished from complex partial seizures by shorter duration (10 seconds), absence of aura and abrupt return of full consciousness.

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Partial Seizures

Partial seizures account for 60% of seizures in childhood. Common causes include inflammatory granulomas, atrophic lesions, vascular insults, birth asphyxia, head trauma and neoplasms. In some geographic areas including India, neurocysticercosis has emerged as a common cause. Neurocutaneous syndrome, arteriovenous malformations and infarcts are less frequent. Magnetic resonance imaging may help to clarify the etiology more accurately than CT scanning.

Partial seizures are classified as

i. *Simple partial* without loss of consciousness, with motor, sensory, autonomic or mixed symptoms
ii. *Complex partial* with impairment of consciousness and automatisms, psychomotor or limbic system symptoms
iii. *Partial with secondary generalization*

Simple partial seizures begin with a focal epileptiform discharge, howsoever brief. The symptoms may be motor or sensory, include tingling, pain, sensation of cold, burning. Sometimes visual, olfactory, auditory or taste hallucinations may be complained of. Consciousness is not impaired. When the simple seizure spreads unilaterally as per the motor cortex, it is called *Jacksonian march*.

Complex partial seizures. Originate from parietal or temporal lobe and may be associated with automatisms, or with loss of consciousness, even if seizures are not generalized.

Complex partial seizures originating from temporal lobe (psychomotor epilepsy). Symptoms are very protean and misdiagnosed for absence seizures, behavior problems or malingering. Brief visceral, olfactory or visual aura are followed by peculiar posture, tonic jerks of the face and limbs, or one-sided dystonia. Patients may perform lip smacking, chewing or complex automatisms or acts. There is no memory for the events and consciousness is impaired. It manifests, as memory disturbances like forced thinking or dreamy states, transitory fear, visual or other hallucinations. Vasomotor changes are often present. Tonic or clonic movements may follow in about 15%.

Benign childhood epilepsy with centrotemporal spikes The syndrome is characterized by (i) onset between 2 and 13 yr; (ii) no neurological or intellectual deficit; (iii) seizures generally occur in sleep, are partial and involve mouth area. Speech involvement, dysarthria and somatosensory symptoms are common; (iv) interictal EEG shows a spike focus over the centrotemporal or rolandic area; and (v) may be self limiting with spontaneous remission around adolescence. These comprise about one-fourth childhood epilepsy and have autosomal dominant inheritance.

Neonatal Seizures

Incidence ranges from 1 to 2% to almost 20% in preterm infants. Poor myelination and incomplete dendritic arborization result in clinical manifestations that are different from older children.

Neonatal seizures present in decreasing order of frequency as (i) subtle; (ii) focal clonic; (iii) multifocal clonic; (iv) generalized tonic; and (v) myoclonic. Subtle seizures may manifest as eyelid blinking, fluttering or buccal-lingual movement. There may be pedaling or automatic movements because of subcortical neuronal discharges.

The common causes are hypoxic ischemic encephalopathy (almost 50% cases), sepsis and bacterial meningitis.

Metabolic seizures due to hypoglycemia, hypocalcemia, dyselectrolytemia and hypomagnesemia account for almost one-fourth. Intracranial bleeding, developmental anomalies and inborn errors of metabolism need to be excluded. Malformations and dysgenetic states are important causes of tonic or myoclonic type of jerks. About one-third are multifactorial and idiopathic.

It is important to establish the cause of neonatal seizures; investigations for hypoglycemia, hypocalcemia, hypomagnesemia, hypoxia, sepsis should be performed. Lumbar puncture for the diagnosis of meningitis is advised. Hypoglycemia and hypocalcemia should be corrected before the administration of anticonvulsants.

Myoclonic Epilepsies

West syndrome (infantile spasms). The onset is usually between 3–8 months of life. It is characterized by a combination of salaam spells (sudden dropping of the head and flexion of arms), developmental retardation and hypsarrhythmia on EEG. Common causes of infantile spasms are: (i) hypoxic ischemic encephalopathy; (ii) neurocutaneous syndromes specially tuberous sclerosis; (iii) perinatal infections; (iv) hemorrhage; (v) injury; (vi) metabolic disorders; and (vii) localized structural malformations; and (viii) idiopathic. The spasms occur in clusters usually on waking. Prognosis for normal mental development is poor. ACTH and corticosteroids frequently help, the course varies from 2–12 weeks, depending upon response. Vigabatrin is the drug of choice, especially in tuberous sclerosis.

Lennox-Gastaut syndrome. Onset is usually in late infancy or childhood, is characterized by mixed seizures, including myoclonic, atypical absence, generalized tonic-clonic or partial seizures. Intellectual regression is invariable. Very slow background and generalized slow and spike wave discharges (2.5 per second) are observed on EEG. This diffuse form of encephalopathy may result from factors such as head injury, anoxia, cardiopulmonary arrest, post-vaccinal encephalopathy/neurogenetic disorder and neurlogical infections. Drugs of choice are valproic acid, benzodiazepines and ACTH. Prognosis is often unsatisfactory. Newer antiepileptic drugs, lamotrigine, topiramate and zonisamide are promising.

Common Errors in Diagnosing Epilepsy

A wrong label of epilepsy may be given to 20–30% children reporting to epilepsy clinics. A variety of paroxysmal disorders, which mimic seizures, should be excluded. These include syncope, breath holding spells, acute psychiatric states, migraine variants, abnormal movement disorders, paroxysmal disturbances of sleep like night terrors, narcolepsy and lastly hysteria. Careful history and EEG are useful to rule out these conditions. Treatment should be deferred until the diagnosis becomes obvious on followup of the natural course of the disease.

Management of Epilepsy

Epilepsy management includes drugs, psychosocial and lifestyle management. Epilepsy requires management for a period 1 to 4 yr.

Drug Therapy

The first line antiepileptic drugs (AED) include phenytoin, phenobarbitone, sodium valproate and carbamazepine. The indications, dose and side-effects of commonly used drugs is depicted in Table 18.5. Age, sex, economic factors and seizure type determine choice of AED.

Tonic-clonic seizures. Carbamazepine is an effective drug for partial and generalized tonic-clonic seizures. It has the advantage of very few side-effects. Phenobarbitone is the drug of choice in the first year of life. Almost 20% develop hyperactive behavior and learning disabilities after first year of life. Phenytoin is often used as initial choice if economic constraints exist. Therapy should be initiated with lowest anticonvulsant doses. The drug dose should be increased gradually. If seizures control is inadequate or toxicity appears, an alternate antiepileptic drug should be tried and the initial drug tapered. Polytherapy should be discouraged unless monotherapy fails.

Antiepileptic drug level monitoring is not required routinely. It helps in better and safer control of therapy: (i) if high doses are being used; (ii) in mixed seizure disorders; (iii) polytherapy; (iv) to assess drug compliance; and (v) to determine plasma level before discontinuing a major drug.

Complex-partial seizures. The drug of choice is carbamazepine or oxcarbazepine, 10–30 mg/kg/day in 2–3 divided doses. It has a positive psychotropic effect. Slow release preparations may have advantage. Newer drugs and surgery should be restricted for selected patients.

Absence seizures. Effective agents include ethosuximide, sodium valproate, lamotrigine and benzodiazepines

Myoclonic and atonic seizures. Sodium valproate, levetiracetam, benzodiazepines such as clonazepam, nitrazepam or clobazam may be used.

Infantile spasms. In West syndrome, intramuscular ACTH 40 to 60 unit per day may be given 4–6 weeks and then tapered off. On the other hand oral prednisolone at 2 mg/kg/day in 2 divided doses may also be used. These agents abolish spasms and may result in resolution of hypsarrhythmia.

Newer antiepileptic drugs. Lamotrigine and topiramate have wide spectrum and are useful adjunct after primary failure in partial and generalized epilepsies. Familiarization of drug use and side effects is essential. Oxcarbazine may be useful for partial epilepsies; and vigabatrine for infantile spasms.

Surgical Treatment

Medically resistant cases of epilepsy may be treated surgically after a careful selection and work up. Possible

Table 18.5: Medications used in epilepsy

Medication	*Indication*	*Dose*	*Half-life*	*Side effects; remarks*
Carbamazepine	Partial, tonic clonic, atonic, akinetic	10–30 mg/kg/day; start with low doses	13–18 hr	GI symptoms, hepatitis, rash, bone marrow depression
Phenytoin	Tonic-clonic, atonic akinetic	5–10 mg/kg/day; 1–2 doses	2–20 hr	Hirsutism, gingival hyperplasia; toxicity if blood level >20 µg/ml. Ataxia, nystagmus, diplopia, drowsiness, seizures (phenytoin encephalopathy), rash. Interferes with calcium metabolism, can cause megaloblastic anemia
Sodium valproate	Broad spectrum	10–60 mg/kg/day; 2–3 doses	7–11 hr	Idiosyncratic fatal hepatic necrosis (especially infants); use L-carnitine if dose >30 mg/kg/day or high blood ammonia. Nausea, sedation, weight gain, hair loss
Ethosuximide	Absence seizures	20–25 mg/kg; 1–2 doses	4–30 hr	Photophobia, leukopenia, drowsiness, nausea. Rarely, blood dyscrasia, myasthenia syndrome
ACTH	West syndrome	20–40 U/day IM for 4–6 weeks; reduce dose next 3–6 mo		Hypercortisolism
Clonazepam	Atonic, resistant absence seizures	0.02–0.2 mg/kg/day; 2–3 doses		Fatigue, somnolence, hypotonia, excessive secretions
Phenobarbitone	Tonic-clonic, akinetic, febrile seizures	5–10 mg/kg; single dose	20–80 hr	Not a preferred agent; drowsiness, hyperkinesia, drug dependency
Lamotrigine	Broad spectrum	5–10 mg/kg/day; 1–5 mg/kg/day single dose with valproate; 5–15 mg/kg/day with enzyme inducers	14–50 hr	Dizziness, drowsiness, blurred vision, rash, Stevens-Johnson syndrome
Topiramate	Refractory partial, secondary generalized seizures	2–10 mg/kg/day; 2–3 doses	18–23 hr	Weight loss, acidosis, neuropsychiatric symptoms
Vigabatrin	Simple partial; complex partial; infantile spasms in tuberous sclerosis	50–150 mg/kg/day; 2–3 doses	5–8 hr	Drowsy, fatigue, loss of peripheral vision, retinal degeneration, aggravates absence seizures
Levetiracetam	Partial, generalized seizures; myoclonus; photosensitive epilepsy	10–60 mg/kg/day; 2 doses	6–8 hr	Behavioral changes, sedation
Zonisamide	Refractory infantile spasms; progressive myoclonic epilepsy; partial seizures	2–10 mg/kg/day; 2 doses	24–60 hr	Weight loss, renal stones
Clobazam	Partial, generalized epilepsy (add on)	0.3–2 mg/kg/day; 1–2 doses		Sedation, ataxia, drooling, hyperactivity
Tiagabine	Partial seizures, (add on)	Starting dose 0.2 mg/kg/day; 4–6 mg/kg/day	4–7 hr	Exacerbate primary generalized seizures, unsteadiness; avoid in hepatic disease
Acetazolamide	Refractory seizures	10–20 mg/kg/day; 2–3 doses	4–10 hr	Metabolic acidosis, paresthesias, anorexia, weight loss

surgical choices include lesional resection of epileptic areas, resection of corpus callosum and focal resection of parts of cerebral cortex such as temporal lobe and extratemporal regions involved in epileptogenesis. Surgical treatment should be increasingly used by identification of anatomic lesions to cure epilepsy.

Duration of Therapy and Prognosis

Drug withdrawal should be attempted after a seizure free interval of 2 yr, gradually over a period of 3 months. About 10–15% patient relapse after the withdrawal of anticonvulsant. Risk of recurrence is low in patients with easily controlled seizures, generalized seizures, normal development, normal neuroimaging, normal EEG and certain genetic epilepsies. Treatment has to be continued lifelong in patients with juvenile myoclonic epilepsy. Seizures are refractory in patients with underlying structural pathology in brain. Normal neurological and psychological profile indicates better prognosis.

Social Aspects

Encourage full participation in educational and extracurricular activities except certain sports/games like unsupervised swimming without buddy, playing kite on roof and riding bicycle in traffic, which may endanger the child's life. Patients are advised regarding the necessity of regular treatment and continuous followup.

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COMA

A clinical definition of coma entails an altered state of consciousness combined with reduced arousal, decreased responsiveness to visual, auditory and tactile stimulation. Usually results from pathological states (Table 18.6) affecting reticular formation of the brainstem, the hypothalamus or the cerebral hemispheres.

Pathophysiology

Consciousness requires interplay between the cerebral cortex and subcortical structures in the diencephalon, midbrain and upper pons. The arousal system is the ascending reticular pathway that constitutes the central core of the brainstem and extends from the caudal medulla to the rostral midbrain.

Table 18.6: Causes of coma

Causes without focal neurological signs
Cerebrospinal fluid is normal
Poisonings, narcotic agents, toxins
Metabolic disorders, e.g. hypoglycemia, diabetic acidosis, uremia, inborn metabolic errors, Reye syndrome, hepatic encephalopathy
Head injury, concussion
Septicemia, cerebral malaria, dengue
Postictal
Hyperpyrexia, febrile encephalopathy
Water intoxication
Cerebrospinal fluid is abnormal
Meningitis
Encephalitis
Subarachnoid hemorrhage
Cerebral vein thrombosis
Midline cerebral tumors
Causes associated with focal neurological signs
Demyelinating disorders
Postictal coma
Intracerebral bleed, vascular malformation
Tumors, infarcts, strokes
Infections: Brain abscess, subdural empyema, encephalitis
Head injury, intracranial hemorrhage
Miscellaneous
Systemic illnesses, hypertension, shock

Grades of Coma

Stage 1 or stupor. The patient can be aroused briefly and shows verbal or motor responses to stimuli.

Stage 2 or light coma. The patient cannot be aroused easily, except with painful stimuli.

Stage 3 or deep coma. There is no response to painful stimuli. The limbs may be kept in a primitive reflex posture. Cortical control over the motor functions is lost. When the brainstem is intact, the arms are flexed on the chest, the fists are closed and legs are extended (*decorticate posture*). In dysfunction of the midbrain, the comatose child adopts a *decerebrate posture*. The arms are rigidly extended and pronated and legs are extended.

Stage 4 or brain death. All cerebral functions are lost. Pupillary reflexes are absent. There is no spontaneous respiratory effort. However, local spinal reflexes may be preserved.

Glasgow Coma Scale

The score is useful for evaluating progress of cases with disturbed consciousness and is calculated from the figures given in parenthesis.

E. Eye opening. Spontaneous (4), in response to call (3), in response to painful stimuli (2), no response (1).

M. Best motor response. Obeys commands (6), localizes (5), withdraws limb on irritation (4), abnormal flexion of

extremities (3), extension response to painful stimuli (2), no movement (1).

V. Best verbal response. Well oriented (5), confused conversation (4), inappropriate words are spoken (3), incomprehensible sounds (2), no vocal response (1).

Diagnosis of Coma

The airway, breathing and circulatory status should be documented by respiration, blood pressure, capillary refill time recording and any compromise should be immediately attended. Intravenous access should be obtained. A detailed neurologic examination should be carried out to rule out involvement of cranial nerves, motor deficits and bladder/bowel dysfunction. If respiratory depression or circulatory collapse is present, appropriate therapy is necessary.

History. A detailed history of events preceding coma, background illnesses, exposure to drugs and toxins provides useful information. The onset, presence of fever, history of trauma and possible bacterial, viral, or parasitic infestations is important. Immunocompromised states or malignancy may suggest opportunistic infections; and history may suggest tuberculosis, malaria or dengue. Headache, vomiting and diplopia suggest raised intracranial pressure. Failure to thrive, vomiting, peculiar skin and urinary odor suggest a metabolic cause. Endocrine dysfunction, dyselectrolytemia, hypo or hyperglycemic states, uremia and hyperammonemia suggest a metabolic cause. History of preceding seizure may indicate postictal coma.

Onset. Sudden onset may be due to trauma, poisoning, intracranial vascular episodes, postictal phase, acute hypoxia or hydrocephalus due to obstruction of cerebrospinal pathway in cases of brain tumor.

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Systemic examination. This includes measurement of vital signs, pupil size and reactivity, coma scale, airway patency, pattern and adequacy of respiration. Skin and mucosa are inspected for bleeding diathesis, exanthem or systemic disease. Organ failure is suggested by associated jaundice, anemia, etc.

Respiration. Periodic or *Cheyne-Stokes breathing* indicates bilateral damage to the cerebral cortex with an intact brainstem. It occurs in transtentorial herniation, congestive cardiac failure and some metabolic disorders. It is attributed to an abnormally increased ventilatory response to CO_2 followed by apnea.

Hyperventilation. Occurs in metabolic coma with acidosis and in brainstem lesions. *Prolonged inspiration followed by expiratory pause* indicates pontine lesions. *Irregular or ataxic* breathing indicates involvement of respiratory center in the medulla.

Depth of unconsciousness. Presence of yawning, swallowing or licking movements of the lips, is an evidence of intact functioning of the brainstem and deep coma is unlikely However, flexion and extension movements may be seen in comatose patients as they are mediated at lower spinal reflex level.

Involuntary movements. Repetitive, multifocal, myoclonic jerks or seizures are seen in anoxic, metabolic, toxic encephalopathies or CNS infections.

Pupillary signs. Pupils are generally *small, equal* and *reactive* in toxic, metabolic cause of coma. Pupils are *moderately dilated* in midbrain damage; they do not react to light but fluctuate slightly. *Pinpoint pupils* indicate pontine lesion or morphine poisoning. *Bilateral fixed dilated pupils* are seen in terminal states or severe ischemic brain damage, atropine or belladonna poisoning. *Unilateral unreactive dilated pupils* indicate third nerve damage, often associated with transtentorial herniation of the temporal lobe or traction of third cranial nerve against posterior cerebral artery.

Eye movements. Stimulation of cortical center for gaze, results in conjugate eye movements to the contralateral side, whereas ablation produces conjugate deviation of the eyes to the ipsilateral side.

Doll's eye response. If the head is suddenly turned to one side, there is a conjugate deviation of eye in the opposite direction indicating that brainstem is intact. Doll's eye movement is not seen in normal conscious infants and is absent when brainstem centers for eye movements are damaged.

Oculovestibular response. If the external auditory canal is irrigated with cold water, the eyes normally deviate towards the stimulated side. This response is lost in pontine lesions, labyrinthitis and coma due to drugs such as sedatives and phenytoin.

The hallmark of metabolic encephalopathy consists of loss of oculocephalic and oculovestibular reflexes with preservation of the pupillary light reflex.

Motor responses. Structural lesions involving cortical or subcortical motor areas lead to contralateral hemiparesis, hemifacial weakness, partial seizures or tone changes.

Flexion of upper extremities with or without extension of the legs (decorticate posture) denotes a cerebral cortical and subcortical disturbance with preservation of brainstem structures. Decerebrate posturing (extension of all extremities) is observed in bilateral cerebral cortical disease extending to upper pons. Decerebrate rigidity can result from increased ICP originating in the posterior fossa, metabolic disease, cerebral hypoxia, hypoglycemia and liver dysfunction.

Flaccidity occurs when a lesion has abolished cortical and brainstem function.

Investigations

Laboratory studies should be carried out to exclude hypo or hyperglycemia, uremia, hepatic dysfunction, dys-

electrolytemia and other metabolic abnormalities. Blood ammonia, lactate, acid-base disturbances, toxins and poisoning should be investigated on suspicion by preserving appropriate samples. Ferric chloride test shows purple color with ketones and aspirin poisoning. It gives green color with phenothiazine and isoniazid intoxication. Inflammatory causes of the CNS should be excluded by a lumbar puncture and blood/CSF culture and a sepsis screen. In febrile coma, peripheral smear should be examined for malarial parasite. Computerized tomography helps to identify intracranial bleeds, infarct, raised ICP, meningeal enhancement and hydrocephalus.

Treatment

Airway should be kept patent and tongue prevented from falling back. Dyselectrolytemia and fluid imbalance should be corrected. Hyper and hypothermia should be managed. Bladder/bowel care and care of the eyes and back to avoid bed sores is imperative. Raised intracranial pressure should be treated.

Fever with acute onset coma of uncertain origin with no evidence of meningitis merits treatment as cerebral malaria in endemic areas.

Specific treatment should be given for hypoglycemia (IV glucose), diabetic coma, inflammatory disease of brain or meninges, metabolic causes or organ failure. Raised intracranial pressure is treated with IV infusion of mannitol, at a dose of 0.5 g/kg every 6–8 hr for 6 doses. Hypertonic saline also may be used. In some cases especially TBM, dexamethasone (0.15 mg /kg every 6 hr) may be used. Specific therapy is instituted for hepatic coma. Exchange transfusion, plasmapheresis and peritoneal dialysis are indicated in specific situations. Corticosteroids have been used in certain metabolic encephalopathies and postviral encephalopathies, they are contraindicated in cerebral malaria. Metabolic coma due to inborn metabolic errors requires specific treatment.

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ACUTE BACTERIAL MENINGITIS

Acute bacterial meningitis, a major cause of morbidity and mortality in young children, occurs both in epidemic and sporadic pattern.

Epidemiology

Age. Acute bacterial meningitis is commoner in neonates and infants than in older children because of poorer immunity and phagocytic functions. The common organisms in neonates are *Escherichia coli, Streptococcus pneumoniae, Salmonella* species, *Pseudomonas aeruginosa, Streptococcus fecalis* and *Staphylococcus aureus.* Three months to 3 yr, the infection is most often due to *Haemophilus influenzae, S. pneumoniae* and meningococci (*Neisseria meningitidis*). Beyond 3 yr, the two most common organisms are *S. pneumoniae* and *N. meningitidis.*

Host. Patients with diminished host resistance (complement, immunoglobulin or neutrophil function defects), malignancies, on immunosuppressive drugs are more susceptible to develop meningitis, by fungi, *Listeria* and *Mycoplasma.*

Pathogenesis

The infection spreads hematogenously to meninges from distant foci, e.g. pneumonia, empyema, pyoderma and osteomyelitis. Purulent meningitis may follow head injury. Rarely, the infection may extend from contiguous septic foci, e.g. infected paranasal sinuses, mastoiditis, osteomyelitis and fracture of the base of skull.

Recurrent meningitis may be associated with pilonidal sinus, CSF rhinorrhea, traumatic lesions of the cribriform plate and ethmoidal sinus or congenital fistulae, besides immune deficiency disorders.

Pathology

The leptomeninges are infiltrated with inflammatory cells. The cortex of the brain shows edema, exudate and proliferation of microglia. Ependymal cells are destroyed and purulent exudate collects at the base of the brain, most marked in interpeduncular and chiasmatic cisterns. Exudates may block the foramina of Luschka and Magendie resulting in internal hydrocephalus. Thrombophlebitis of the cerebral vessels may occur leading to infarction and neurological sequelae. In cases of meningococcal meningitis, the illness may be fulminating and death may occur within a few hours because of endotoxic shock.

Subcellular pathogenetic mechanisms. Bacterial pathogens on destruction liberate cell wall and membrane active components (teichoic acids, endotoxins and peptidoglycans). In response the host cells and capillary endothelia produce tumor necrosis factor, cytokines and platelet activating factors. Their interaction with the blood brain barrier and neurons results in extensive host damage. Cerebral edema (vasogenic) results due to endothelial cell injury or cytotoxins, leukocyte products and toxic radicals. The role of dexamethasone in reducing host damage due to blockage of the above mechanisms has been demonstrated in both experimental and clinical settings.

Clinical Features

The onset is usually acute and febrile. The child becomes irritable, resents light, has bursting headache either diffuse or in the frontal region, spreading to the neck and eyeballs.

The infant may have projectile vomiting, shrill cry and a bulging fontanel.

Seizures are a common symptom and may occur at the onset or during the course of the illness. Varying grades of alterations in sensorium may occur. Photophobia is marked. There is generalized hypertonia and marked neck rigidity. Flexion of the neck is painful and limited. *Kernig sign* is present, i.e. extension of knee is limited to less than 135 degrees. In *Brudzinski sign*, the knees show flexion as neck of the child is passively flexed. The fundus is either normal or shows congestion and papilledema. If skin of the abdomen is lightly scratched, flushing may be seen (*tache cérébrale*). The muscle power in the limbs is preserved. Reflexes are normal, diminished or exaggerated. Neurological deficits like hemiparesis, cranial nerve palsies and hemianopsia may develop. Respiration may become periodic or Cheyne-Stokes type often with shock in the late stages of illness.

Meningitis in neonates and young infants. Neck rigidity and Kernig sign are seldom prominent. Symptoms and signs, which arouse suspicion of bacterial meningitis are: (i) sepsis; (ii) vacant stare; (iii) alternating irritability and drowsiness; (iv) persistent vomiting with fever; (v) refusal to suck; (vi) poor tone; (vii) poor cry; (viii) shock, circulatory collapse; (ix) fever or hypothermia; (x) tremor or convulsions; and (xi) neurological deficits of varying types.

The following are risk factors for neonatal meningitis: Prematurity, low birthweight, complicated labor, prolonged rupture of membranes, maternal sepsis and babies given artificial respiration or intensive care.

Special Features

Meningococcal meningitis. Epidemics of meningococcal meningitis are generally caused by serotype A and less commonly by type C. Type B generally cause sporadic disease. Children living in overcrowded houses are specially predisposed. Carrier state is common in children.

Besides features of meningitis, children show petechial hemorrhages on the skin or mucosa. Meningococcemia may be associated with acute fulminant illness with adrenal insufficiency, hypotension, shock and coma. This is called *Waterhouse Friderichsen syndrome* and occurs due to hemorrhage and necrosis in the adrenal glands.

Chronic meningococcemia may occur with intermittent fever, chills, joint pains and maculopapular hemorrhagic rash lasting for several days. Meningococci are very fragile organisms and are destroyed very easily if there is delay in CSF culture.

Pneumococcal meningitis. While pneumococcal meningitis occurs at all ages, it is uncommon in the first few months of life. Usually follows otitis media, sinusitis, pneumonia or head injury. Exudates are common on the cortex and subdural effusion is a usual complication.

Staphylococcal meningitis. Neonatal staphylococcal meningitis is often associated with umbilical sepsis, pyoderma or septicemia. In older children it follows otitis media, mastoiditis, sinus thrombosis, pneumonia, arthritis and septic lesions of the scalp or skin.

Haemophilus influenzae type B meningitis. Is frequent between the ages of 3 and 12 months. Subdural effusion should be suspected in infants in whom focal neurological signs and fever persist even after the CSF clears biochemically and microbiologically. Convulsions are common. Residual auditory deficit is a common complication. HiB vaccine is recommended to reduce the community prevalence of this infection.

Complications

CNS complications include subdural effusion or empyema, ventriculitis, arachnoiditis, brain abscess and hydrocephalus. CNS complications should be suspected if infants and children fail to respond to treatment, or if fever, focal neurological signs and constitutional symptoms recur after a lapse of few days. Longterm neurological deficits include hemiplegia, aphasia, ocular palsies, hemianopsia, blindness, deafness, sensorineural auditory impairment (deafness) and mental retardation. Systemic complications include shock, myocarditis, status epilepticus and syndrome of inappropriate ADH secretion (SIADH).

Diagnosis

Acute bacterial meningitis should be suspected in children presenting with a brief history of fever, irritability, photophobia, headache, vomiting, convulsions and altered sensorium. Diagnosis should be substantiated by examination of the cerebrospinal fluid. The CSF should be examined promptly for cellular response and sent for culture for bacteria and stained to identify morphology. The CSF has elevated pressure, is turbid with an elevated cell count, often >1,000/mm^3 with mostly polymorphonuclear leukocytes. Proteins are elevated above 100 mg/dl and sugar is reduced below 50% of blood sugar or below 40 mg/dl. Microscopic examination of the sediment stained with gram stain helps to identify organisms. Collect the CSF for culture on a transport medium.

In partially treated meningitis, CSF may be clear with predominant lymphocytes; culture is usually sterile. Biochemistry may be variably altered.

CT scan is not necessary for diagnosis, but is useful to exclude the presence of subdural effusion, brain abscess, hydrocephalus, exudates and vascular complications. It is also useful to distinguish partially treated pyogenic meningitis from tuberculous meningitis.

Rapid diagnostic tests may be used to distinguish between viral, bacterial and tuberculous meningitis based on antigen or antibody demonstration, e.g. countercurrent immunoelectrophoresis, latex particle agglutination, coagglutination, ELISA and other techniques. Besides being rapid, they are unaltered by previous antibiotic

usage. Latex agglutination and ELISA have sensitivity and specificity of almost 80%. Polymerase chain reaction is used for diagnosis of infection with herpes simplex, enteroviruses, meningococci and tuberculosis.

Differential Diagnosis

Meningism. This may occur in inflammatory cervical lesions, apical pneumonia and in toxemia due to typhoid, influenza. There are no neurological signs and the cerebrospinal fluid is normal.

Partially treated bacterial meningitis. If the child has received prior antibiotics, the cerebrospinal fluid becomes sterile. Biochemistry may be altered and pleocytosis persists, though type of cellular response changes. It poses a difficult problem in the differential diagnosis from tuberculous meningitis and aseptic meningitis. The onset, clinical course, rapid diagnostic tests and other ancillary investigations may be useful.

Aseptic meningitis. The clinical and laboratory profile is similar to pyogenic meningitis. The CSF pressure is elevated, shows mild pleocytosis and moderate increase in protein with near normal sugar. The CSF lactic acid is not elevated. No organisms are cultured.

Tuberculous meningitis. The onset is insidious with lethargy, low-grade fever, irritability, vomiting and weight loss. Features of meningeal irritation are less prominent and course of the illness is prolonged. Neurological features include seizures, gradually progressive unconsciousness, cranial nerve deficits, motor deficits and visual involvement. Features of hydrocephalus and decerebration are relatively common. Evidence of systemic tuberculosis and family contact should be looked for. Mantoux test may be positive and there may be evidence of tuberculosis elsewhere. CSF shows 100–500 cells, with majority of lymphocytes; sugar is less reduced than in pyogenic meningitis and protein is elevated.

Cryptococcal meningitis. It usually occurs in an immunocompromised host. There is low-grade fever, mild cough and pulmonary infiltration. Meningeal involvement has a gradual onset with a protracted course. The clinical features are not specific. The CSF shows the fungus as thick walled budding yeast cells, surrounded by a large gelatinous capsule in India ink preparation. The organism grows well on Sabouraud medium.

Viral encephalitis. Acute onset with early disturbances of sensorium, raised intracranial pressure and variable neurological deficit. The CSF is clear, may show mild pleocytosis, mild elevation of protein and normal sugar. PCR for viral antigens and rising CSF antibody titers are useful diagnostic clues.

Subarachnoid hemorrhage. Sudden headache and sensorial alteration occur without preceding fever. The course of illness is rapid and signs of meningeal irritation are marked. CT scan is diagnostic. CSF reveals crenated RBCs.

Lyme disease. It is an infection of central nervous system with *Borrelia burgdorferi*, a tick-borne spirochete. Patients develop encephalopathy, polyneuropathy, leukoencephalitis and hearing loss.

Treatment

Initial Empiric Therapy

Initial therapy recommended is a third generation cephalosporin such as ceftriaxone or cefotaxime. A combination of ampicillin (200 mg/kg) and chloramphenicol (100 mg/kg/24 hr) for 10–14 days is also effective as initial empiric choice. If fever or meningeal signs persist after 48 hr of therapy, a lumbar puncture should be repeated and the choice of antibiotics reviewed. All antibiotics are administered intravenously.

Specific Antimicrobial Therapy

Meningococcal or pneumococcal meningitis. Penicillin 400–500,000 units/kg/day q 4 hr. Cefotaxime (150–200 mg/kg/day q 8 hr IV) or ceftriaxone (100–150 mg/kg/day q 12 hr IV) are also effective.

H. influenzae meningitis. Ceftriaxone or cefotaxime IV is used as a single agent. The combination of ampicillin (300 mg/kg/day IV q 6 hr) and chloramphenicol (100 mg/kg/day) is less preferred.

Staphylococcal meningitis. Vancomycin is the treatment of choice if methicillin or penicillin resistance is suspected. Addition of rifampicin to the regime increases CSF penetrance and efficacy of these drugs.

Listeria. Ampicillin (300 mg/kg/day IV q 6 hr) and aminoglycoside (gentamicin, amikacin or netilmicin) are preferred.

Gram-negative bacilli. Cefotaxime, ceftazidime or ceftriaxone, or a combination of ampicillin and aminoglycoside may be used.

Pseudomonas. A combination of ceftazidime and an aminoglycoside is used. Ceftazidime may also be replaced with ticarcillin. Meropenem or cefepime are effective agents, if the above drugs fail.

Duration of Therapy

Generally, patients with bacterial meningitis show quick improvement within days. The treatment is for 10–14 days. except for staphylococcal meningitis and Gram-negative infection, where it is extended to 3 weeks. Routine lumbar puncture at the end of therapy is not recommended. In delayed or partial clinical response, a repeat CSF examination is indicated. Therapy is stopped if child is afebrile, cerebrospinal fluid protein and sugar become normal, and the cell count in the cerebrospinal fluid is less than $30/mm^3$.

Steroid Therapy

Dexamethasone at a dose of 0.15 mg/kg IV q 6 hr for 2–4 days is recommended. The first dose of corticosteroids is best given shortly before or simultaneously with the first dose of antibiotic. This helps to reduce the incidence of residual neurological complications, such as sensorineural deafness, hydrocephalus and behavioral disturbances. This is especially useful in *Haemophilus* meningitis. There is no role of dexamethasone in neonatal meningitis.

Symptomatic Therapy

Increased intracranial pressure. Lumbar puncture should be done very carefully in the presence of increased intracranial pressure. Osmotic diuresis with 0.5 g/kg of mannitol as a 20% solution is administered intravenously every 4–6 hr for a maximum of 6 doses.

Convulsions. These are treated using diazepam 0.3 mg/kg (maximum 5 mg) IV, followed by phenytoin 15–20 mg/kg as initial treatment and continued at a dose of 5 mg/kg/day PO or IV. Antiepileptic drugs can be stopped after 3 months.

Fluid and electrolyte homeostasis. Maintenance fluids are given, hypotonic fluids should be avoided. ADH secretion occurs in some patients. If unconscious, child may be fed through the nasogastric tube.

Hypotension. The patients are treated with intravenous fluids and vasopressors such as dopamine and dobutamine.

Nursing care. The oral cavity, eyes, bladder and bowel should be taken care of. Management of constipation prevents atony of the rectum. Retention of the urine is managed by gentle suprapubic pressure or a hot water bottle. Bedsores are prevented by repeated change of posture in the bed and application of methylated spirit. Soft foam rubber mattress or air cushion is used to prevent pressure on the bony points.

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Complications

Subdural empyema is managed by drainage of the subdural space along with intensive antibiotic therapy; subdural effusions generally resolve spontaneously.

Hydrocephalus may occur in the acute phase and generally regresses. Ventriculoatrial or ventriculoperitoneal shunt is rarely required.

Followup and Rehabilitation

Followup for early detection of residual neurological handicaps ensures appropriate rehabilitation. Auditory evaluation should be carried out at the time of discharge and 6 weeks later.

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TUBERCULOUS MENINGITIS

Meningitis is a serious complication of childhood tuberculosis. It may occur at any age, but is most common between 6 and 24 months of age. There is usually a focus of primary infection or miliary tuberculosis. Mortality rate has reduced but serious disabling neurological sequelae may occur.

Pathogenesis

The tuberculous infection usually reaches the meninges by hematogenous route, less commonly through the lymphatics. Tubercle bacilli affect end arteries and form submeningeal tubercular foci. The tubercle bacilli discharge into the subarachnoid space intermittently, proliferate and cause perivascular exudation followed by caseation, gliosis and giant cell formation. Tuberculous meningitis may occur as a part of the generalized miliary tuberculosis, with tubercles in the choroid plexus directly infecting the meninges.

Pathology

The meningeal surface and ependyma are inflamed, covered with yellow grayish exudates and tubercles. These are most severe at the base, in the region of the temporal lobes and along the course of the middle cerebral artery. The subarachnoid space and the arachnoid villi are obliterated resulting in poor reabsorption of cerebrospinal fluid and dilation of the ventricles, resulting in hydrocephalus. Cerebral edema may be present.

The choroid plexus is congested, edematous and studded with tubercles. There may be infarcts in the brain due to vascular occlusion. Necrotizing or hemorrhagic leukoencephalopathy may occur in some cases.

Clinical Manifestations

The clinical course of tuberculous meningitis is described in three stages. This differentiation is arbitrary as one-stage merges into the other.

Prodromal stage or stage of invasion. The onset is insidious and vague with low grade fever, loss of appetite and disturbed sleep. The child who was active and playful earlier becomes peevish, irritable and restless. Vomiting is frequent and the older children may complain of headache. Child may exhibit head banging and resents exposure to sunlight (photophobia).

Stage of meningitis. During this stage, neck rigidity may be present and Kernig sign may be positive. Fever may be remittent or intermittent, pulse is slow but regular. Breathing may be disturbed. The patient may be drowsy or delirious. Muscle tone may be increased. As the disease progresses, convulsions and neurological deficits may occur; sphincter control is usually lost.

Stage of coma. This stage is characterized by loss of consciousness, rise of temperature and altered respiratory pattern. Pupils are dilated, often unequal, with nystagmus and squint. Ptosis and ophthalmoplegia are frequent. With the progression of the disease, coma deepens; episodic decerebration is observed which progresses in severity. The respiration becomes Cheyne-Stokes or Biot type, bradycardia is common. Untreated illness is lethal in about four weeks.

Hemiplegia, quadriplegia, cranial nerve palsies and decerebrate rigidity are common findings. Some patients show monoplegia, hemiballismus, tremors, cerebellar sings and decorticate rigidity.

Diagnosis

Lumbar puncture. Lumbar puncture should always be done in children with low grade pyrexia, unexplained recurrent vomiting, unusual irritability and lassitude. The cerebrospinal fluid pressure is elevated to 30–40 cm H_2O (normal 3–4 cm H_2O). The CSF may be clear or xanthochromic. On standing, a pellicle or a cobweb coagulum is formed in the center of the tube. It is composed of cells and tubercle bacilli enmeshed in fibrin. CSF show lymphocytic pleocytosis (100–500 cells/mm^3), elevated protein (more than 40 mg/dl), mild hypoglycorrhachia and low chloride values (less than 600 mg/dl). Cerebrospinal fluid does not confirm the etiological diagnosis, but provides adequate evidence for starting antitubercular therapy. Demonstration of acid fast bacilli by direct smear and culture yields variable results.

CT scan. Computerized tomography is useful in tubercular meningitis and may reveal basal exudates, inflammatory granulomas, hypodense lesions or infarcts, hydrocephalus both communicating and less commonly obstructive type (Fig. 18.7). X-ray of the chest may provide supportive evidence for tuberculosis. Negative Mantoux test does not exclude the diagnosis.

Serological tests for the diagnosis of tuberculous meningitis are not very sensitive. *Bactec* and *PCR* for tuberculosis carry better sensitivity and specificity. Tests for HIV should be performed on all suspected subjects.

Differential Diagnosis

Purulent meningitis. The onset is acute with rapid progression. The cerebrospinal fluid is turbid or purulent with a significant increase in the number of polymorphonuclear leukocytes in the CSF. CSF protein content is

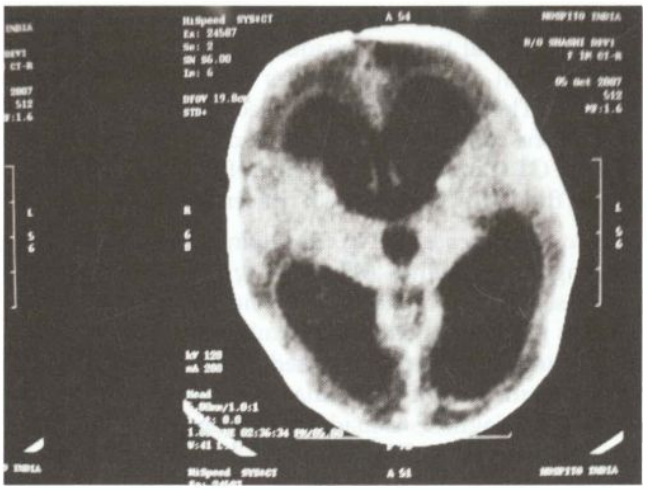

Fig. 18.7: Contrast enhanced CT of brain showing communicating hydrocephalus and periventricular ooze in a child with tubercular meningitis (*Courtesy:* Dr Atin Kumar, Deptt. of Radiodiagnosis, AIIMS, New Delhi)

elevated and sugar level is markedly decreased. The etiological agent is demonstrated by the examination of smear, culture or serology.

Partially treated purulent meningitis. The clinical features and cerebrospinal fluid changes are often indistinguishable from tuberculous meningitis. Rapid diagnostic tests to rule out specific bacterial antigens should be performed PCR and Bactec provide supportive evidence for tuberculosis. MRI brain with gadolinium contrast often provides clue to the underlying etiology.

Encephalitis. The onset is acute with fever, seizures, disturbances of sensorium, drowsiness and diffuse or focal neurological signs. The cerebrospinal fluid reveals mild pleocytosis, normal or mildly elevated proteins and normal sugar. MRI brain may be normal or may show signal changes in basi frontal and temporal lobes (Herpes encephalitis); thalamic and midbrain involvement occur in Japanese B encephalitis.

Typhoid encephalopathy. Typhoid presents with severe toxemia, drowsiness without meningeal signs. Cerebrospinal fluid is normal. Blood culture for *S. typhi* and Widal test is positive.

Brain abscess. Presents with irregular low grade fever, localized neurological symptoms and features of raised intracranial pressure. A prior history of congenital cyanotic heart disease or pyogenic lesions (suppurative otitis media, mastoiditis, lung abscess or osteomyelitis) should be asked for. The cerebrospinal fluid is normal except when the abscess communicates with the subarachnoid space; CT scan is diagnostic.

Brain tumor. The onset is slow with history of headache, recurrent vomiting, disturbances of vision and localizing neurological signs. The patients are usually afebrile. CT or MRI helps in diagnosis.

Chronic subdural hematoma. There may be a history of head injury or trivial trauma, headache, vomiting, localizing neurological signs and features of raised intracranial pressure. The fundus shows papilledema or choked discs. The sutures may be separated. The cerebrospinal fluid is normal. CT scan or ultrasound is useful. The subdural tap shows fluid with high protein concentration.

Amebic meningoencephalitis. Free living amebae can cause meningoencephalitis. While *Naegleria* meningoencephalitis presents acutely, *Acanthamoeba* meningoencephalitis presents as chronic granulomatous encephalitis, chiefly in immunocompromised hosts. Nonresponse to antipyogenic or antitubercular therapy should arouse suspicion. Diagnosis is made by demonstration of motile amebae in fresh CSF preparation. Culture is confirmatory.

Prognosis

The prognosis is poorer in younger children. Early diagnosis, adequate and prolonged therapy improves the prognosis. Untreated cases die within 4 to 8 weeks.

Recovery is a rule in stage 1 disease. The mortality in stage 2 is 20–25% and of the survivors, 25% have neurological deficits. Stage 3 disease has 50% mortality and almost all survivors have neurological sequelae. Longterm complications include intellectual disability, seizures, motor and cranial nerve deficits, hydrocephalus, optic atrophy, arachnoiditis and spinal block.

Treatment

Antitubercular therapy. The treatment of tuberculous meningitis should be prompt, adequate and prolonged for at least 12 months. Short course chemotherapy is not recommended. At least 4 antitubercular drugs should be used for initial 2 months comprising (i) isoniazid (5 mg/kg/day, maximum 300 mg per day); (ii) rifampicin (10 mg/kg/orally, once empty stomach in the morning, maximum dose 600 mg/day); (iii) ethambutol (15–20 mg/kg/day); and (iv) pyrazinamide (30 mg/kg/day PO). Streptomycin (30–40 mg/kg/day IM) may be used initially for 2–3 weeks. The first two drugs are continued to complete one year of therapy.

Steroids. Parenteral dexamethasone (0.15 mg/kg/dose q 6 hr) is preferred in acute phase of illness and switched over to oral prednisolone. Oral corticosteroids may be continued for 6 weeks and tapered over next two weeks. Steroids reduce the intensity of cerebral edema, risk of development of arachnoiditis, fibrosis and spinal block.

Symptomatic therapy of raised intracranial pressure, seizures, dyselectrolytemia should be done. The patient should be kept under observation for development of papilledema, optic atrophy or increasing head circumference. Decerebration is common in advanced cases in the acute phase. Ventriculocaval shunt may be required in cases with increasing hydrocephalus and persistent decerebration.

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ENCEPHALITIS AND ENCEPHALOPATHIES

Encephalitis is defined as an inflammatory process of the brain parenchyma. The term encephalopathy implies cerebral dysfunction due to circulating toxins, poisons, abnormal metabolites or intrinsic biochemical disorders affecting neurons but without inflammatory response.

Etiopathology

Various causes of encephalitis and encephalopathies are listed in Table 18.7.

The pathological changes are nonspecific except in herpes simplex encephalitis and rabies. Gross examination of the brain usually shows diffuse edema, congestion and hemorrhages. Microscopically, there may be perivascular cuffing with lymphocytes and neutrophils. The neurons show necrosis and degeneration, associated with neuronophagocytosis.

Clinical Manifestations

The clinical manifestations depend on: (i) severity of infection; (ii) susceptibility of the host; (iii) localization of the agent; and (iv) presence of raised intracranial pressure. Clinical spectrum may range from inapparent/abortive ilness to severe encephalomyelitis.

Onset. The onset of illness is generally sudden but may at times be gradual.

Initial symptoms. The initial symptoms are high fever, mental confusion, headache, vomiting, irritability, apathy or loss of consciousness, often associated with seizures. Raised intracranial pressure may result in decerebration, cardiorespiratory insufficiency, hyperventilation and autonomic dysfunction. Child may develop ocular palsies, hemiplegia, involuntary movements speech dysfunction and cerebellar symptoms. Extrapyramidal symptoms are common in Japanese B encephalitis and lateralization to one side with temporal or frontal involvement is common in herpes encephalitis.

Typical features. Include increased intracranial pressure and evidence of brainstem dysfunction. Unchecked brain swelling may lead to herniation at tentorial hiatus,

Table 18.7: Etiology of encephalitis and encephalopathies

Encephalitis
RNA viruses (mumps, measles, rubella, enteroviruses)
DNA viruses (herpes simplex, cytomegalovirus, Epstein-Barr)
Arthropod borne viruses (Japanese B, West Nile, Russian spring summer, equine viruses)
HIV, rabies, lymphocytic choriomeningitis, dengue virus
Slow virus infections, prion infections
Rickettsia; fungi (cryptococcus); protozoa (*T. gondii*)
Bacteria (tuberculous meningitis, listeria)
Encephalopathies
Acute disseminated encephalomyelitis
Postinfectious: Typhoid, shigella, Reye syndrome
Hypoxic encephalopathy, heat hyperpyrexia
Metabolic: Diabetic acidosis, uremic coma, hepatic coma, neonatal hyperbilirubinemia, lactic acidosis, mitochondrial disorders, inborn errors of metabolism
Fluid and electrolyte disturbances. Water intoxication, hypernatremia, hyponatremia, alkalosis, acidosis
Toxic: Heavy metals (lead, mercury, arsenic), insecticides, *Cannabis indica*, carbon monoxide
Post-vaccination

compression of the midbrain causing deterioration in consciousness, pupillary abnormalities, ptosis, sixth nerve palsy, ophthalmoplegia, paralysis of upward gaze, Cheyne-Stoke breathing, hyperventilation and bradycardia.

Prognosis

Recovery depends on the severity of illness. Mild illness usually has a complete recovery and substantial morbidity occurs in severe forms. Metabolic encephalopathies may have an intermittent or progressive course despite treatment. Inborn metabolic errors may have an intermittent course.

Diagnosis

Every effort should be made to arrive at a precise etiological diagnosis by a careful history, systemic examination, account of recent illnesses or exposure to toxins. Lumbar puncture must always be done after excluding papilledema. CSF cytology, biochemistry, serology and cultures are mandatory. Serum electrolytes, blood sugar, urea, blood ammonia, metabolic screening, ABG, serum lactate, urinary ketones and urinalysis should be done. Toxicologic studies should be undertaken in suspected patients. One should exclude treatable causes such as enteric encephalopathy, malaria, shigella, toxins, poisoning, diabetes mellitus and renal disease. Serum lead levels should be estimated if there is a possible exposure of the child to lead contaminated environment.

Acute disseminated encephalomyelitis (ADEM). Acute demyelination of brain and spinal cord may occur with insults to oligodendroglia following an infection or vaccination. Damage is perivenular in location, commonly at the gray-white zone. Usually a monophasic illness, permanent deficits after the initial severe manifestation occasionally. Acute stage is characterized by seizures, altered sensorium, multifocal neurological signs, raised intracranial pressure, visual disturbances, etc. Cerebrospinal fluid may be normal, or shows mild pleocytosis, mildly elevated protein and normal glucose. MRI brain generally reveals multiple hyperintensities in white matter, which enhance with contrast. MRI may also show spinal cord, basal ganglia lesions in addition to white matter involvement. Therapy with pulse corticosteroids is useful.

Management

Treatment aims to save life, prevent neurological residua and relieve symptoms.

Emergency treatment. Airway should be kept patent and assisted respiration given if necessary. Hyperpyrexia should be managed with water sponging and anti-pyretics. Shock is managed by infusion of appropriate fluid, or vasopressors. Dopamine or dobutamine are used to maintain blood pressure. Seizures are controlled by intravenous diazepam and phenytoin. Raised intracranial pressure is managed by IV infusion of 20% mannitol solution and corticosteroids. The role of corticosteroids in most encephalitides is not proven except in acute disseminated encephalomyelitis and autoimmune encephalitis.

Herpes simplex encephalitis. Herpes simplex type I virus is the causative organism. Type II virus causes perinatal herpes infections. Clinical features includes fever of sudden onset, mental confusion, vomiting, meningeal irritation, headache and papilledema. In localizing signs (focal seizures, focal neurological deficit and EEG changes), presence of red cells in the CSF and focal involvement of the temporal lobe on CT scan are important diagnostic clues. Diagnosis can be established by CSF culture or PCR. The drug of choice is acyclovir (20 mg/kg/dose every 8 hourly) for 21 days. Early therapy is crucial for recovery. Prognosis is variable; about half the patients recover after timely therapy.

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Reye Syndrome

The first description of this syndrome was probably made by Najib Khan in Jamshedpur, in 1956 (Jamshedpur fever).

Reye and colleagues described an entity with diffuse fatty infiltration of the liver, to a lesser extent of the kidney and cerebral edema with diffuse mitochondrial injury.

Pathogenesis

It is an acute self limiting metabolic insult of diverse etiology resulting in generalized mitochondrial dysfunction. Drugs (salicylates), toxins (aflatoxins), viral infections (varicella, influenza) and certain inborn errors of metabolism (single enzyme defects of β-oxidation) can precipitate Reye syndrome. Neuroglucopenia and hyperammonemia result from mitochondrial and sodium pump failure. Encephalopathy is secondary to the liver damage.

Clinical Features

A mild prodromal illness is followed by acute onset of the disease. The child has vomiting for one or two days along with anorexia, listlessness, followed by altered sensorium, irregular breathing, decerebration, pupillary changes and rapidly developing coma. Seizures occur in more than 80% patients. There are few focal neurological or meningeal signs. Hepatomegaly is present in half the cases; jaundice is infrequent. The clinical features are described in four stages:

Stage I. Vomiting, anorexia, mild confusion, listlessness, apathy

Stage II. Delirium, restlessness, irritability, lack of orientation, frightened, agitated states

Stage III. Coma, decorticate posture which later becomes decerebrate.

Stage IV. Flaccidity, areflexia, apnea, dilated pupils not reacting to light, severe hypotension

18

Laboratory Investigations

There may be some degree of hypoglycemia with low levels of glucose in the cerebrospinal fluid. Serum ammonia levels are elevated. Prothrombin time is prolonged and hepatic enzymes are increased. Liver biopsy shows fatty change and glycogen depletion but no necrosis of the liver cells. EEG shows generalized slow waves.

Prognosis

Prognosis is poor with 25–70% mortality. Survivors may have neurological sequelae.

Management

Hepatic failure needs appropriate management. The patient is given low protein diet with adequate calories. Intravenous infusion of mannitol (20% solution; 0.5 g/kg/IV q 6 hr) and dexamethasone are used to reduce the brain edema. Hypoglycemia should be corrected by IV 10–25% glucose. Acidosis, hypoxia and dyselectrolytemia should be corrected. Double volume exchange transfusion has been used in stage III. Vitamin K and fresh frozen plasma may be required. Surgical decompression of raised intracranial pressure may be required to save life.

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INTRACRANIAL SPACE OCCUPYING LESIONS

Intracranial space occupying lesions include brain tumors, masses of congenital origin and inflammatory disorders such as brain abscess, neurocysticercosis, tuberculoma and subdural fluid collection. Brain edema may also simulate space occupying lesions. Clinical features of space occupying lesion in brain are detailed below:

Increased Intracranial Tension (ICT)

The intracranial space and its contents (brain, CSF and blood) are in a state of delicate equilibrium. After closure of sutures and fontanel the adaptive mechanisms to raised pressure in the brain are through the displacement of CSF from the intracranial cavity and compensatory hemodynamic changes. Heart rate slows, respiratory rate is altered and blood pressure rises to maintain the cerebral circulation.

The signs of raised ICT appear early in infratentorial tumors and are relatively late in supratentorial neoplasms. Common clinical features of raised ICT include either one or a combination of the following clinical features.

Increased head size and/or papilledema. In infants, there is separation of the cranial sutures, wide fontanels and increased head circumference. The fontanel should be examined with the baby relaxed and placed in the upright position. A delayed fontanel closure or a tense and non-pulsatile fontanel is significant. Separation of the sutures compensates for increase in the intracranial pressure.

The *MacEwen or crackpot sign* indicates raised intracranial pressure after sutures have closed. Papilledema is unusual in infancy unless intracranial pressure is very high. The changes include loss of cupping of the disc, absent venous pulsations and raised disc margins. In severe cases, hemorrhages may be observed.

Vomiting. Unexplained projectile vomiting with or without headache should arouse suspicion of raised pressure. It is attributed to direct pressure on the medullary centers.

Headache. Persistent headache in young children, prominent in early morning is highly suspicious.

Diplopia and sixth nerve palsy. Increased pressure displaces the brainstem downwards, thus stretching the sixth nerve and resulting in paralysis of the lateral gaze and diplopia.

Localizing Signs

These signs help to detect the anatomical site of the lesion.

Cranial nerve palsies. Multiple cranial nerve palsies occur in brainstem lesions along with involvement of pyramidal tract and cerebellar pathways. Sixth nerve palsy usually has no localizing value. Combined sixth and seventh nerve involvement may suggest a pontine lesion. Pseudobulbar palsy may suggest 1X and X cranial nerves involvement.

In supranuclear hypoglossal paralysis, tongue is tilted to contralateral side. Nasopharyngeal masses, rhabdomyosarcoma, lymphosarcoma and inflammatory masses may involve cranial nerves in their course.

Head tilt. Head tilt is seen in superior oblique paralysis, cerebellar lesions and posterior fossa tumors.

Ataxia. Ataxia occurs in cerebellar, spinocerebellar tract, frontal lobe or thalamic lesions.

Motor deficit. This may occur in cerebral, brainstem and spinal cord lesions.

Seizures. These indicate cortical or subcortical lesion. Intermittent decerebrate posturing may be due to infratentorial pathology.

Nystagmus. Both irritative and destructive lesions in any part of cerebellovestibular system may cause nystagmus with fast and slow components in opposite direction. Unilateral cerebellar lesion may produce bilateral manifestations because of compression across the midline. Brainstem lesions cause vertical nystagmus. The site of lesion is towards the side of the coarse nystagmus.

Vision. It is difficult to evaluate visual acuity and field of vision in children. Impaired vision with normal refraction should arouse suspicion of lesion near optic nerve, chiasma, optic radiations or cortical blindness. Bitemporal hemianopsia may indicate compression over chiasma.

Personality disturbances. Infants may become irritable, lethargic and show disturbances of behavior or speech. Loss of cortical sensation as described in supratentorial tumors of adults is difficult to interpret in children. There may be a decline in intellectual function.

Personality disturbances, inappropriate sphincter control and grasp response suggest localization of tumor near the frontal lobe. There may be optic atrophy in the fundus of the same side and papilledema in the opposite eye (*Foster Kennedy syndrome*).

Brain Tumors

Tumors arising from the brain are common in children. Certain genetic syndromes and familial factors increase risk of occurrence of brain tumors. Primary brain tumors may be malignant or benign. Benign tumors located near the vital areas of brain may be life-threatening.

Over two-thirds of brain tumors in children are infratentorial. *About one-third to half of these are medulloblastomas and one-third are astrocytomas of cerebellum.* Brainstem gliomas and ependymomas account for the rest. Most of these tumors occur near the midline. Therefore they commonly obstruct CSF circulation and cause hydrocephalus early in disease. In adults, infratentorial tumors account for less than 10% of brain neoplasms. Common supratentorial tumors are astrocytomas, ependymomas, craniopharyngioma and malignant gliomas. Papillomas of choroid plexus and pineal body tumors are less common. Meningiomas, acoustic neuromas and pituitary adenomas are rare in childhood. Ataxia telangiectasia and neurocutaneous syndromes are associated with a higher incidence of brain tumors. CT gives adequate information about ventricular size, tumor and surrounding edema. It is useful for followup. MRI provides better information regarding mass size, infratentorial and spinal cord extension and tumor detail.

Cerebellar Tumors

Medulloblastoma. These are midline cerebellar tumors and occur in infancy. They are fast growing and malignant. Craniospinal spread along neuraxis is common and death occurs early. They cause truncal ataxia, early papilledema, unsteadiness in sitting position and a tendency to walk with a broad base. Radiation, chemotherapy and a ventriculoperitoneal shunt are generally required.

Astrocytoma. These are common in the cerebellar hemisphere. Ataxia and incoordination are common on the side of the lesion. Nystagmus is observed on lateral gaze of the child to the affected side. Areflexia and hypotonia are present. The head is tilted to the side of lesion to relieve the increased intracranial pressure caused by herniation of tumor or cerebellar tonsils through the foramen magnum. Complete surgical excision of the tumor is often feasible. Chemotherapy with tomustin, vincristine and cisplatin is advised. Brachytherapy is now used in a variety of brain tumors to limit radiation necrosis and provide local irradiation to improve prognosis.

Brainstem Tumors

Signs of increased intracranial tension are minimal, yet vomiting occurs due to infiltration of medullary vomiting center. Hemiparesis, cranial nerve deficits and personality changes are common; reflexes in the lower limbs are exaggerated. The pontine tumors affect the 6th and 7th cranial nerves.

Glioma of the brainstem causes bilateral involvement of the cranial nerves and long tracts. Cerebellar dysfunction is often present. The usual age of onset is in the later half of the first decade. Brainstem gliomas carry the worst prognosis. Most children die within 18 months. Surgical excision is difficult and not very promising. Hyperfractionation radiotherapy is being evaluated. Chemotherapy does not have significant role.

Ependymoma of the fourth ventricle. It occurs in the first decade of life. The flow of cerebrospinal fluid is obstructed, causing an early rise in the intracranial pressure. These patients may present with subarachnoid hemorrhage. The tumors metastasize along the neuraxis. Surgical excision is rarely possible, patients may be treated with radiotherapy. Survival of the child for a long period is unusual.

Supratentorial Tumors

Craniopharyngioma. These can present at anytime during childhood. The tumor is congenital and arises from squamous epithelial cell rests of the embryonic Rathke pouch. The neoplasm is usually cystic and benign. Clinical features include: (i) growth failure; (ii) bitemporal hemianopsia, asymmetric or unilateral visual field defects; (iii) signs of increased intracranial pressure; and (iv) endocrine abnormalities such as diabetes insipidus and delayed puberty (in less than 10% of cases). X-ray films may show calcification. Cranial imaging reveals the extent of mass and its nature. Bone age is retarded. Surgical excision is possible but difficult. The tumor cyst may be aspirated or malignant ones are treated with radiotherapy or implants.

Glioma of the cerebral hemispheres. These usually occur during the first and second decade of the life. The patient presents with seizures and hemiparesis. Rarely, involvement of frontopontine cerebellar fibers may cause ataxia. Vomiting, headache and papilledema are relatively late features of supratentorial tumors. Incidence of gliomas is higher in children with neurocutaneous syndromes. The histological types include astrocytoma, oligodendroglioma and glioblastoma.

Hypothalamic glioma. These rare tumors cause diencephalic syndrome in infants. The children fail to thrive, the subcutaneous fat is lost and have sleep and respiratory disturbances. Older children may present with precocious puberty. Histological types observed are glioma, pinealoma, teratomas and hamartomas.

Glioma of optic nerve. Visual disturbances, squint, proptosis, exophthalmos and optic atrophy are the usual presenting features. MRI of the orbit is diagnostic. Progression of tumor is relatively slow. Surgery is possible if the lesion is limited to one side.

Inflammatory Granulomas

Inflammatory granulomas are an important cause of raised intracranial pressure and partial seizures in childhood. These may be tubercular, parasitic, fungal or bacterial in origin. Neurocysticercosis and tuberculomas are the commonest granulomas.

Neurocysticercosis

It is caused by larval stage of *Taenia solium*.

Pathogenesis. Evolution occurs from a nonattenuating cyst, to a ring with perilesional edema, to a disc lesion; which may disappear, persist or even calcify. Neurocysticercosis can be classified as parenchymal, intraventricular, meningeal, spinal or ocular depending on the site of involvement.

Clinical features. Parenchymal neurocysticercosis –seizures are the commonest manifestations (80%), followed by raised intracranial pressure, focal deficits and rarely meningeal signs. Seizures may be generalized or partial. Intraventricular neurocysticercosis may present with features of raised intracranial pressure, focal neurological deficits and hydrocephalus. Visual symptoms or blindness results from cysts within the eye. *Spinal neurocysticercosis* presents with features of spinal cord compression or transverse myelitis.

Diagnosis. Neurocysticercosis is the most common cause of a cranial ring enhancing lesion (Fig. 18.8). The lesion is disc or ring like image with a hypodense center. Lesion may be single or multiple. A scolex is often present within the ring. There is often considerable edema surrounding the lesion. The midline shift is not significant. Lesion is usually supratentorial but may occur in infratentorial regions. MRI is more useful than a CT scan in doubtful cases.

ELISA for cysticercosis is positive in almost half the patients with single lesion. Cerebrospinal fluid may be examined for cells, cysticercal antigens and PCR, though its diagnostic utility is variable.

Therapy. Cysticidal therapy is not necessary for inactive and calcified lesions. There may be benefit to treat single active and multiple lesions. Cysticidal drugs commonly used include albendazole and praziquantel. Albendazole is the preferred drug because of efficacy, and is less expensive. The dose (15 mg/kg/day) may be given for varying periods from 5 to 28 days. Corticosteroids

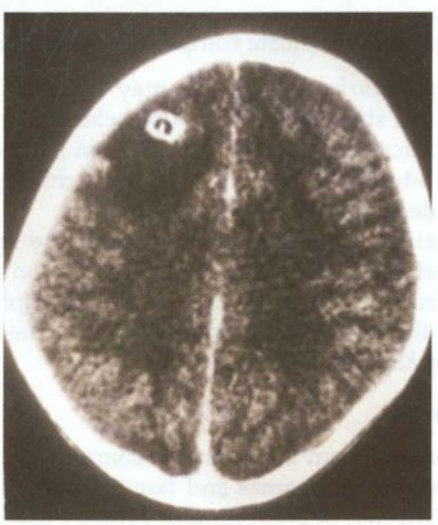

Fig. 18.8: Contrast enhanced CT of brain showing a degenerating ring enhancing cyst with eccentric scolex and perilesional edema in right frontal lobe (*Courtesy:* Dr Atin Kumar, Deptt. of Radiodiagnosis, AIIMS, New Delhi)

(prednisolone 1–2 mg/kg/day) are started 2–3 days before initiating therapy and continued for a total of 5 days during cysticidal therapy. Symptomatic treatment includes anticonvulsants for 6–9 months or until resolution of the lesions. Calcified lesions require anticonvulsant therapy for 2–3 yr.

Tuberculoma

The clinical presentation is similar to neurocysticercosis. On CT scan, there is a single or multiple ring enhancing lesions. Tuberculoma rings are usually larger. The lesion often has a thick (≥20 mm) irregular wall and may be associated with a midline shift and severe perilesional edema (Fig. 18.9). Focal deficits are more frequent in tuberculomas. Presence of basal exudates should arouse suspicion of tuberculoma. The diagnosis is often suspected based on family history of contact, positive tuberculin reaction, other evidences of tuberculosis and subacute course of the illness.

Antituberculous therapy is recommended for 1 yr (2 HRZE + 10 HR) as for tubercular meningitis along with corticosteroids for initial 6–8 weeks.

Brain Abscess

Brain abscess is an important differential diagnosis among children with unexplained fever, altered sensorium, elevated intracranial pressure, localized neurological findings and headache.

Predisposing factors include cyanotic heart disease, immunosuppressed status, otitis media, sinusitis, mastoiditis, systemic sepsis and post-traumatic.

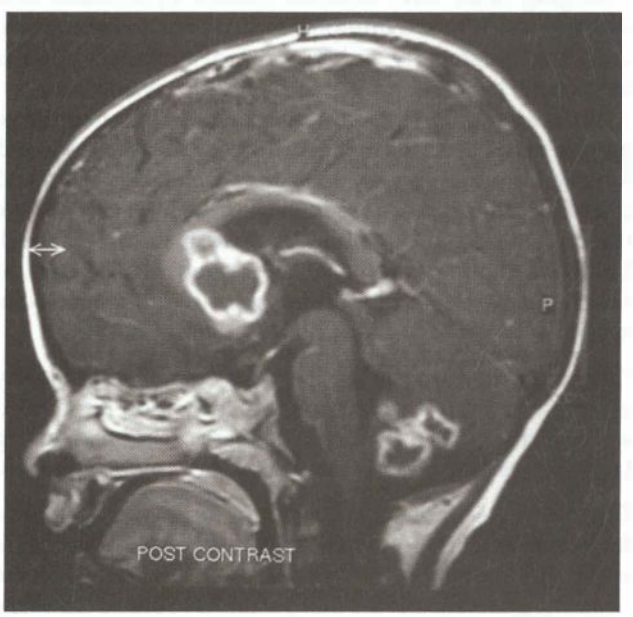

Fig. 18.9: Contrast enhanced MRI (sagittal view) of brain showing enhancing irregular ring like multiple tuberculomas (*Courtesy:* Dr Atin Kumar, Deptt. of Radiodiagnosis, AIIMS, New Delhi)

Etiology. Anaerobic organisms, streptococci, *Staphylococcus aureus*, pneumococci, *Proteus* and *Haemophilus influenzae* are common infecting organisms. The abscesses are observed more often in the cerebrum compared to infratentorial compartment.

Clinical features of brain abscess may be described under 4 broad headings: (i) features of raised intracranial pressure; (ii) manifestations of intracranial suppuration such as irritability, drowsiness, stupor and meningeal irritation; (iii) features suggesting toxemia, e.g. fever, chills and leukocytosis; and (iv) focal neurological signs such as focal convulsions, cranial nerve palsies, aphasia, ataxia, visual field defects and neurological deficit.

Diagnosis is established by CT scan or MRI. Lumbar puncture is avoided as the procedure may precipitate herniation of the brainstem.

Management includes investigation for source of infection, treatment of precipitating cause, management of raised intracranial pressure and symptoms. Empirical therapy should begin with a third generation cephalosporin, vancomycin and metronidazole and continued for 4–8 weeks. Surgical drainage or excision of the abscess should be done in case of abscesses of >2.5 cm, located in posterior fossa, fungal abscess or if gas is identified inside the abscess.

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SUBDURAL EFFUSION

Subdural effusion may be acute or chronic. In infancy, subdural effusions are often associated with bacterial meningitis. These are generally acute, small and regress spontaneously. Rarely a large effusion may result in increased intracranial pressure and focal neurological signs. Chronic subdural effusion presents as raised intracranial pressure. The protein content of this fluid is high and vascular membrane forms around the subdural effusion. This may require surgical intervention.

Clinical features are nonspecific. Convulsions, vomiting, irritability and drowsiness are present. There is persistent fever, anterior fontanel bulges and head size increases. In the newborn period, the skull may show increased transillumination. CT/MRI or subdural tap establishes the diagnosis.

Treatment. Small collections are absorbed spontaneously. Large effusions may need to be aspirated every 24 to 48 hr until these become small. Surgical irrigation with indwelling drains may be considered if the effusion persists for more than 2 weeks. Surgical excision of the subdural membrane is difficult and results are not encouraging.

HYDROCEPHALUS

The CSF is secreted by the choroid plexus within the ventricles by ultrafiltration and active secretion. It passes from the lateral ventricles to the third and fourth ventricles and exits from foramen of Luschka and Magendie into the basal cisterns and then the cerebral and spinal subarachnoid spaces where it is absorbed via the arachnoid villi (granulations) into the venous channels and sinuses. About 20 ml of CSF is secreted in an hour and its turnover is 3 or 4 times in a day.

Etiology Hydrocephalus results from an imbalance between production and absorption of cerebrospinal fluid. It may be communicating or noncommunicating.

Communicating hydrocephalus. There is no blockage in the CSF pathway but reabsorption may be affected. Excess CSF may be produced in papilloma of choroid plexus.

Obstructive or noncommunicating hydrocephalus. The block is at any level in the ventricular system, commonly at the level of aqueduct or foramina of Luschka and Magendie (Fig. 18.10).

In obstructive hydrocephalus, the ventricles are dilated above the block. In cerebral atrophy, ventricles are dilated but pressure is not raised (*hydrocephalus ex vacuo*). Presence of periventricular ooze on CT or MR imaging helps to identify the former. Hydrocephalus may be congenital or acquired (Table 18.8).

Table 18.8: Causes of hydrocephalus

Congenital hydrocephalus
Intrauterine infections: Rubella, cytomegalovirus, toxoplasmosis, intracranial bleeds, intraventricular hemorrhage
Congenital malformations: Aqueduct stenosis, Dandy-Walker syndrome (posterior fossa cyst continuous with fourth ventricle), Arnold-Chiari syndrome (portions of cerebellum and brainstem herniating into cervical spinal canal, blocking the flow of CSF to the posterior fossa)
Midline tumors obstructing CSF flow
Acquired hydrocephalus
Tuberculosis, chronic and pyogenic meningitis
Post-intraventricular hemorrhage
Posterior fossa tumors: Medulloblastoma, astrocytoma, ependymoma
Arteriovenous malformation, intracranial hemorrhage, ruptured aneurysm
Hydrocephalus *ex vacuo*

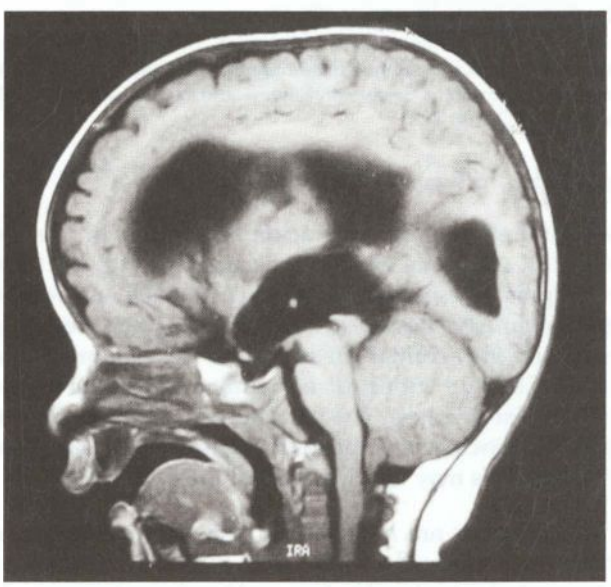

Fig. 18.10: Arnold-Chiari II malformation: MRI T1W sagittal view showing obstructive hydrocephalus stretched brainstem and tonsillar herniation (patient also had a meningomyelocele) (*Courtesy:* Dr Atin Kumar, Deptt. of Radiodiagnosis, AIIMS, New Delhi)

Pathology Ventricles are dilated, at times unevenly. Ependymal lining of ventricles is disrupted resulting in periventricular ooze and hence periventricular white matter is compressed. Cortex is generally preserved until late but cortical atrophy may occur. The process may be reversible if the treatment is initiated early.

Clinical features Hydrocephalus may manifest with enlarging head size, delayed closure of fontanel and sutures. Associated symptoms include headache, nausea, vomiting, personality and behavior disturbances such as irritability, head banging, apathy and drowsiness.

Papilledema, pyramidal tract signs and cranial nerve palsies may occur. Skull contour becomes abnormal and forehead is prominent. Scalp veins become prominent and dilated. A sunset sign is seen in the eyes, i.e. sclera above the cornea becomes visible. Upward gaze is impaired. Limbs become spastic because of stretching of cortical fibers. Distortion of the brainstem may lead to bradycardia, systemic hypertension and altered respiration rate.

Congenital hydrocephalus starts in fetal life and may manifest or even develop subsequently. The large head size at birth causes difficulty in delivery of the head during labor. There may be associated congenital malformations.

Diagnosis Accurate serial recording of the head circumference is essential for early diagnosis of hydrocephalus and should be supported by serial USG. An increase in the head circumference in the first 3 months of life >1 cm every fortnight should arouse suspicion of hydrocephalus. Brain grows very rapidly in the first few weeks of life and therefore sagittal and coronal sutures may be separated up

to 0.5 cm. This physiological separation disappears after the first fortnight of life. Persistent widening of squamoparietal sutures is not physiological and should arouse suspicion of hydrocephalus.

Cranial ultrasound and computed tomography help to evaluate serial ventricular size while the latter gives information about cortical mantle, periventricular ooze and etiology of hydrocephalus. MRI may be necessary to determine the site of obstruction and in congenital hydrocephalus to identify associated malformations. Arnold-Chiari malformation has downward displacement of cerebellum and medulla, obstruction of CSF pathway or migration defects. Dandy-Walker malformation reveals a cystic malformation, atresia of outlet foramina or any brain malformations.

Differential diagnosis

Megalencephaly refers to the increase in volume of brain parenchyma. There are no signs of increased intracranial pressure. The ventricles are neither large, nor under increased pressure. Causes include Hurler syndrome, metachromatic leukodystrophy and Tay-Sachs disease.

Chronic subdural hematoma causes large head, mostly located in the parietal region without prominent scalp veins or sunset sign. Large head size is also observed in hydranencephaly, rickets, achondroplasia, hemolytic anemia and familial macrocephaly.

Treatment Management includes making a precise etiological diagnosis and identification of associated malformations, clinical course and severity of hydrocephalus.

If hydrocephalus is arrested spontaneously, surgical intervention may not be necessary. Medical management should be instituted if surgery is not indicated. Acetazolamide at a dose of 25–100 mg/kg/day diminishes CSF production in mild, slowly progressive hydrocephalus. Oral glycerol has also been used for similar purpose. A conservative approach is better in most cases.

If the head size enlarges rapidly, or is associated with progressive symptoms, where vision or life is endangered it is desirable to treat surgically before irreparable damage occurs. In congenital obstructive hydrocephalus, acquired hydrocephalus, periventricular ooze with hydrocephalus a ventriculoatrial or preferably a ventriculoperitoneal shunt should be done to drain the CSF directly into the circulation or into the peritoneal cavity. Third ventriculotomy by endoscopic approach is another option particularly in children with obstructive hydrocephalus. In cases of bacterial meningitis, an acute hydrocephalus may set in which is self limited. Patients with tuberculous meningitis and progressive hydrocephalus require a shunt, specially if it is obstructive.

A variety of shunts are now available. It is usually necessary to keep the shunt for the entire life. As the child grows in size it may be necessary to revise the shunt, using a longer tube. Blockage and infection are the two most common shunt complications. Shunt revision may also be necessary if there is bacterial colonization of the shunt.

Prognosis Even with the best of treatment, prognosis is guarded. Almost two-thirds patients have variable mental and developmental disabilities. Prognosis of hydrocephalus associated with spina bifida is not satisfactory.

Pseudotumor Cerebri

It is a benign self limiting disorder with generally a favorable outcome. Intracranial pressure is elevated and ventricular system is either normal or small. Generally, there are no focal neurological signs. Onset of symptoms of raised intracranial pressure may be sudden or gradual extending over a week. Visual field shows enlargement of blind spot.

Pseudotumor cerebri may follow use of outdated tetracycline, high doses of vitamin A, quinolones, lateral sinus thrombosis (following otitis media, mastoiditis especially on the right side) and obstruction of venous outflow due to pressure on superior vena cava. It may occur during withdrawal of corticosteroid therapy, Addison disease, hypoparathyroidism and systemic lupus erythematosus. EEG shows excessive slow wave activity. Isotope brain scan, CT or MRI are normal. The patient improves spontaneously after a few months. Acetazolamide or oral glycerol helps in symptomatic relief. Dexamethasone may be required. Cerebral decompression is rarely necessary.

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NEURAL TUBE DEFECTS

Neural tube defects (NTD) are one of the most common congenital anomalies due to failure of proper closure of neural tube and covering mesoderm and ectoderm. These defects occur in about 1.5 per 1,000 live births; the risk in second sibling is 5 per 100 births. The incidence in North India is as high as 3.9–9/1,000 live births.

Etiology

Primary neural tube defects have multifactorial inheritance. Maternal risk factors include zinc and folate deficiency, alcohol, radiation exposure, insulin dependent diabetes mellitus (IDDM), and use of valproate and carbamazepine during pregnancy. Patients with trisomy 13 and 15 shows these defects.

Maternal folate deficiency is an important risk factor for development of NTD. Periconceptional folic acid supplementation with 4 mg folate supplementation 1 month before conception and through first trimester decreases the occurrence and recurrence of NTD. The exact mechanism for this protective effect remains unknown.

Clinical Features

The defect is obvious at birth or through fetal sonography. It varies in severity from an occult anomaly to severe life-

threatening problem. Lumbosacral region is the commonest site, but any part of the spine may be affected. The defect may extend over a variable length of the spinal cord.

The spectrum includes spina bifida (meningocele, meningomyelocele, spina bifida occulta), anencephaly (absence of brain calvaria, total or partial), encephalocele (herniation of brain and meninges through defect in calvaria), craniorhachischisis (anencephaly associated with continuous bony defect of spine and exposure of neural tissue) and iniencephaly (dysraphism of occipital region accompanied by retroflexion of neck and trunk).

Neural tube defects may be associated with other congenital anomalies and dysfunction of organ systems. Affected children may have lower body paralysis, bladder and bowel dysfunction, learning disabilities, hydrocephalus due to Arnold-Chiari type 2 malformation and endocrine abnormalities. Anencephaly is an important cause of fetal and infant mortality. Severe cases die *in utero*, or in the early neonatal period. Longterm sequelae include neurological, motor, physical disability, psychosocial maladjustments and increased financial burden on family.

Spina bifida occulta constitutes about 5% cases and is asymptomatic. Meningocele or myelomeningocele, presents clinically as a raw red fleshy plaque, consists of meninges, CSF, nerve roots and dysplastic spinal cord. In *meningocele*, the sac is covered only by skin and generally there is no neurologic deficit.

In *meningomyelocele* the neurologic deficit includes varying degrees of flaccid paraparesis and sensory deficit in the trunk and legs corresponding to involved segments of the dysplastic cord. The cord distal to the site of the lesion is severely affected. Involvement of bowel and bladder results in fecal and urinary incontinence. Hydrocephalus is usually present in varying degrees. Arnold-Chiari malformation may cause facial weakness and swallowing difficulty. Tongue movements may be impaired and there may be laryngeal stridor.

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Management

Prenatal diagnosis of myelodysplasia is possible by elevated alpha-fetoprotein level in the maternal blood between 14 and 16 weeks of gestation, or in the amniotic fluid in early pregnancy where the test is more specific. Additional test in amniotic fluid includes acetyl cholinesterase estimation. Ultrasound detection is around 100%; raised maternal blood alphafetoprotein has accuracy of 60–70%, amniocentesis for alpha-fetoprotein and acetylcholinesterase has accuracy of 97%.

Investigations include ultrasound of head, meningocele and the abdomen and chest and spine X-rays.

Treatment

Management of NTD requires a team approach with the cooperation of pediatrician, neurologist, neurosurgeon, urologist and orthopedic surgeon with assistance from physiotherapist, social worker and psychiatrist. The degree of paralysis, presence of hydrocephalus, kyphosis, congenital malformation, evidence of infection of nervous system influences decisions.

Surgery includes closure of the defect and a VP shunt (if associated with hydrocephalus). Early closure prevents neurological deterioration. Open lesions draining CSF should be closed within 24 hr. Closed lesions should be operated within 48 hr.

Lorber's criteria for selective surgery. Surgery is not recommended if there is severe paraplegia at or below L3 level, kyphosis or scoliosis, gross hydrocephalus, associated gross congenital anomalies, intracerebral birth injuries and neonatal ventriculitis before closure of back.

Prognosis

Delay in intervention causes increase in complications like worsening of neurologic deficit, infection (local or ventriculitis) and progressive hydrocephalus. Late complications include: hydrocephalus in 80–90% because of Chiari II malformation, urinary tract infections, enuresis, fecal incontinence or constipation, sexual dysfunction, intellectual deterioration, delayed neurological problems (tethered cord, intradural mass lesions), epilepsy in 10–30%, ocular problems (30%), shunt infection (25%), psychosocial problems and motor deficits. 2% die during initial hospitalization and 15% die by ten years of age.

Prevention

Primary prevention includes periconceptional folate supplementation to all prospective mothers. Food fortification is another possible approach. Counseling of family with a previous child with NTD is essential. The risk of recurrence is 3.5% with 1 affected child, 10% with 2 affected children and 25% with 3 affected children. *MTHFR* polymorphisms should be studied in case of recurrence of births with NTD. Periconceptional folate and prenatal diagnosis is advised in subsequent pregnancy. Folate supplementation reduces recurrence risk by 70%. Zinc and vitamin A supplementation is also advised.

Dose for primary prevention is 0.4 mg per day. A mother who has previously delivered a child with NTD should receive 4 mg per day of folic acid in subsequent pregnancies. Secondary prevention is imperative after an index case. Duration of supplementation is 2 months before and 3 months after conception.

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ACUTE HEMIPLEGIA OF CHILDHOOD

Acute hemiplegia of childhood is most often due to cerebrovascular disorders. The exact cause often remains obscure despite extensive biochemical and radiological investigations.

Causes

Cerebral venous sinus thrombosis. Inherited prothrombotic conditions (deficiency of antithrombin III, protein C or protein S; factor V Leiden mutation; homocysteinemia); acquired prothrombotic condition (nephrotic syndrome, antiphospholipid antibodies); infections (otitis media, mastoiditis, sinusitis, meningitis); systemic lupus erythematosus; polycythemia, thrombocytosis; head trauma; neurosurgery dehydration

Arterial thrombosis or embolism. Cyanotic congenital heart disease; infective endocarditis; paradoxical emboli through patent foramen ovale; arrhythmia; sickle cell SS or SC disease; polycythemia; thrombocytopenia; thrombocytosis antiphospholipid antibodies; inherited prothrombotic conditions (as listed above); disseminated intravascular coagulation; paroxysmal nocturnal hemoglobinuria; infections (meningitis, bacteremia, local head and neck infections); systemic lupus erythematosus; head trauma

Intracranial hemorrhage. Arteriovenous malformation; cerebral aneurysm; coagulopathy; inherited or acquired thrombocytopenia; thrombasthenia

Infections. Cerebral abscess, meningitis, encephalitis

Intracranial space occupying lesion. Cerebral tumor (primary or metastatic); inflammatory granuloma

Focal postviral encephalitis. Herpes virus, varicella

Moyamoya syndrome

Transient cerebral arteriopathy. Vascular spasm; drug induced (amphetamine, cocaine), metabolic disease with stroke like episodes (MELAS, Leigh disease, homocystinuria, pyruvate dehydrogenase deficiency, ornithine transcarbamoyl transferase deficiency); intracranial vascular dissection

Todd paralysis

Porencephaly

Clinical Features

Mode of onset. The rapidity of onset varies with the cause. Emboli occur abruptly with maximum neurological signs at onset and improves with time. Although intracranial hemorrhage occurs acutely, it manifests usually after a brief lapse with headache and nuchal rigidity. Cerebrovascular thrombosis is relatively less rapid in onset.

History and physical examination. History of ear, throat mastoid infection, intraoral or neck trauma, associated cardiac disease or hematological disorders may be helpful in determining the cause.

In mild hemiparesis, one should observe for circumduction of involved leg, asymmetric movements of upper extremities and cortical fisting of involved hands. If the child is pushed from sitting position the child extends his arm to protect himself from a fall, called lateral propping reaction. In spastic hemiplegia, this reaction is asymmetric. Absent propping reaction in infants after the age 8–9 months is always abnormal.

Benign intracranial hypertension occurs in lateral sinus thrombosis. Seizures, raised intracranial pressure and vomiting are common in superior sagittal sinus thrombosis. Arterial occlusions generally occur in the first two years of life. These may be associated with hemiparesis and seizures, which are difficult to control with medication. Hemiparesis, cerebral hemiatrophy and cerebral porencephaly may result.

Localization

Cortical lesions. Cortical lesions are characterized by the specific pattern of motor deficit, depending on the vascular distribution of the artery involved. Seizures and cortical sensory loss are usual.

In the left-sided lesion, aphasia is a dominant clinical feature. The child has difficulty in reading, writing and comprehension. Organization of space and body image are affected. In right parietal lesions, the child exhibits lack of attention for objects on his left side. He may ignore the left side of a picture placed before him or may not even recognize his left hand. He has difficulty in copying simple figures, (indicating constructional apraxia). He gets lost easily and confuses directions given to him because of spatial disorganization.

Corona radiata. The hemiplegia is generally complete and seizures are absent.

Internal capsule. Hemiplegia is complete, often with sensory loss.

Midbrain. Hemiplegia affects the contralateral side and paralysis of 3rd and 4th cranial nerves on the same side (Weber syndrome).

Pons. Hemiplegia affects the opposite side and involves paralytic of 6th and 7th cranial nerves on the same side (Millard-Gubler syndrome).

Medulla oblongata. Contralateral hemiplegia with ipsilateral involvement of lower cranial nerves is noted.

Management

Investigations for the predisposing illness should include platelet count, hemoglobin, MCV, MCH, serum iron and iron binding capacity, nitroprusside reaction for homocystinuria, sickle cell preparation of blood, antinuclear antibody tests, protein C and S estimation, Factor V Leiden, testing for *MTHFR* mutations, antiphospholipid antibodies, serum and CSF lactate and pyruvate, chest X-ray and echocardiography. Metabolic tests are done if indicated. Investigations should include CT scan, electroencephalogram and MR angiography. Lumbar puncture is indicated if an inflammatory CNS disease is suspected.

Treatment. Specific treatment depends on the etiology of hemiplegia. The role of tissue plasminogen activator in childhood stroke is not established. In thrombotic stroke, low molecular weight heparin may be indicated followed by oral warfarin pending evaluation for underlying prothrombotic state. Seizures should be controlled and hydration should be maintained. Physiotherapy and speech therapy should be started early.

Treatment of acute cerebral thrombosis is directed towards increasing cerebral perfusion, limiting brain edema, and preventing recurrences. Aspirin may be indicated to prevent recurrence. Calcium channel blockers have been found useful in some. Seizures often persist and anticonvulsants may be required.

Prognosis

Prognosis with regard to seizures and mental retardation is worse in acute idiopathic hemiplegia below 3 yr of age. Hemiplegic side may be atrophied and athetosis may be seen on the same side. Cerebral hemiatrophy with flattening of the skull and porencephaly secondary to parenchymal damage may occur.

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PARAPLEGIA AND QUADRIPLEGIA

Paraplegia refers to motor weakness of both lower limbs. Quadriplegia is the nomenclature used for neurological weakness of all four limbs; the involvement is more in the upper limbs as compared to the lower extremities. Neurological weakness may be (i) *spastic* with spasticity, exaggerated tendon reflexes and extensor plantars; or (ii) *flaccid* with flaccidity, diminished tendon reflexes, flexor plantar response and muscle wasting. It may be acute or insidious in onset and have a variable course. Vascular, traumatic and postinfective lesions are usually acute in onset with variable gradual recovery. Compressive or neoplastic lesions have insidious onset with gradually progressive deficit. Degenerative disorders have an insidious onset with slowly progressive course.

Flaccid weakness may result from involvement of anterior horn cell, nerve roots, nerves and myopathies. Acute onset follows demyelinating polyneuropathy, polio, vascular and traumatic spinal cord insults. Chronic causes include spinal muscular atrophy, peripheral neuropathies and myopathies. Table 18.9 enlists the common causes of paraplegia and quadriplegia.

Table 18.9: Causes of paraplegia or quadriplegia

Spastic
Compressive
Tuberculosis of spine with or without paraspinal abscess
Extradural, e.g. metastasis from neuroblastoma, leukemia, lymphoma; inflammatory process, such as epidural abscess (usually posterior to the spinal cord), bony abnormalities such as achondroplasia, Morquio disease, hemivertebrae and occipitalization of atlas vertebra, atlantoaxial dislocation
Intradural. Neurofibroma and dermoid cyst
Intramedullary. Glioma, ependymoma, hemato- or hydromyelia
Noncompressive myelopathies
Vascular anomalies of the spinal cord: Arteriovenous malformations, hemangiomas and telengiectasia
Trauma or transection of cord
Transverse myelitis/myelopathy. Viral, neuromyelitis optica, segmental necrosis due to vascular occlusion, e.g. of anterior spinal artery
Familial spastic paraplegia
Lathyrism due to consumption of Lathyrus sativum
Degenerative spinal cord disease
Supra-cord lesions
Cerebral palsy
Hydrocephalus
Bilateral cortical disease
Bilateral white matter disease
Flaccid weakness
Spinal shock in the initial stages of spinal cord damage, e.g. after trauma, vascular, inflammatory, neoplastic lesions, or transverse myelopathy
Guillain-Barré syndrome
Acute poliomyelitis
Spinal muscular atrophies
Peripheral neuropathies
Botulism, Riley Day syndrome
Pseudoparalysis
Surgery, osteomyelitis, fractures, myositis, metabolic myopathy

It should be remembered that symmetrically brisk tendon reflexes with flexor plantar response may be normal in children and do not necessarily indicate any pathological process. In case of doubt between plantar reflex and withdrawal response, the dorsilateral aspect of the foot should be stroked (Chaddock maneuver) to obtain the plantar response. In lesions above the level of midbrain, jaw reflex becomes brisk. Abdominal reflexes should be elicited by stroking the skin over the abdomen close to the umbilicus. The patient should be examined carefully for sensory involvement, sensory level, wasting at the segments of the lesion, posterior column involvement and bladder bowel involvement.

Management

In acute myelitis, dexamethasone in high dose (5 mg/kg/day) or IV methylprednisolone pulse (30 mg/kg/day) for 3–5 days may be useful. Tuberculosis is managed with antitubercular drugs, corticosteroids and local management. In acute trauma and paraplegia due to neoplasia, the treatment may be surgical.

Paraplegia is initially flaccid but later becomes spastic with development of painful flexor spasms due to the stimulation of pain fibers. Nursing on foam mattress and frequent change of position on bed would prevent decubitus ulcers. Physiotherapy should be done. Bladder must be emptied regularly by compression or repeated catheterization to prevent it being distended and becoming atonic. Later, the bladder may become spastic with frequent but partial reflex emptying. Urinary tract infection may supervene due to inadequate drainage of the bladder. It should be appropriately treated. In severe spasticity, drugs that reduce tone provide relief.

Guillain-Barré Syndrome

See Chapter 19

SYDENHAM CHOREA (RHEUMATIC CHOREA)

Choreiform movements are irregular, nonrepetitive, quasi-purposive and involuntary movements that are usually proximal but may affect fingers, hands, extremities and face. Chorea may precede or follow manifestations of rheumatic fever. There is a significant epidemiological association of chorea with rheumatic fever. Nearly one-third of these patients develop rheumatic valvular heart disease. Concurrent association of chorea with rheumatic polyarthritis is rare because chorea generally supervenes later in the course of rheumatic activity. Chorea is a major criterion for the diagnosis of rheumatic activity.

Clinical Features

Sydenham chorea is more common in girls than in boys. The usual age of onset is 5 to 15 yr. The clinical picture may be variable depending on the severity of the illness. The child may appear clumsy, and develop deterioration in handwriting. Movements may be limited to one side of the body as in hemiballismus. The movements are aggravated by attention, stress or excitement, but disappear during sleep. Emotional lability, hypotonia and a jerky speech are common associations.

The following clinical maneuvers are helpful in arriving at the diagnosis:

i. When the hand is outstretched above the head, forearms tend to pronate
ii. When hands are stretched forwards, wrist flexes and fingers hyperextend
iii. The child relaxes hand grip on and off as if he is milking a cow (*Milkmaid grip*)
iv. The child cannot maintain tongue protrusion (*darting tongue*)
v. During speech an audible click is heard
vi. The knee reflex may show a sustained contraction resulting in a hung up reflex.

Investigations. The neurological investigations are generally unrewarding. Antistreptolysin O titer may not be elevated because the onset of chorea is late.

Prognosis. The disorder is generally self limiting and may last from a few weeks to few months (up to 2 yr). Relapses or recurrences can occur.

Treatment. The child should be protected from injury; bedding should be well padded. These children may be treated with chlorpromazine, haloperidol, sodium valproate or carbamazepine. Drugs are maintained at minimum doses required for symptom suppression. Antistreptococcal prophylaxis with penicillin G should be given to prevent recurrence of rheumatic activity.

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ATAXIA

Ataxia is not unusual in childhood. Movements of the limbs are uncoordinated even in absence of weakness. The child is unsteady and tends to sway while standing with feet together. Nystagmus, dysarthria, posterior column signs and evidence of labyrinthine or cerebellar disease or raised intracranial pressure should be looked for. A history of drug, toxins and recent infections is important.

Acute Cerebellar Ataxia

Acute cerebellar ataxia may result from many causes: the common being postinfectious cerebellitis (varicella), drugs; brainstem encephalitis and paraneoplastic states.

Other causes include Miller Fisher syndrome, trauma, migraine, kawasaki disease and inherited episodic ataxia.

The usual age of onset is between 1 and 5 yr. Ataxia may develop within a few hr following a febrile illness. The patient has hypotonia, dysarthria, significant ataxia of gait and some incoordination in extremities. The tendon jerks are often pendular and nystagmus is common. The cerebrospinal fluid shows mild pleocytosis. Prognosis is good. Corticosteroids are useful and a quick response is observed. Recurrence is uncommon. Postviral ataxia is an diagnosis of exclusion; other diagnoses should be entertained if ataxia recurs or does not respond.

Ataxia-Telangiectasia

This is an autosomal recessive disorder localized to long arm of chromosome 11, characterized by progressive cerebellar ataxia starting at 1–3 yr. A few years later, telangiectasia over the conjunctivae and skin may be observed. These children may have IgA deficiency or impaired cell mediated immunity, frequent sinopulmonary infections and increased predisposition to lymphoreticular malignancies. They have elevated alpha-fetoprotein levels and defects in DNA repair.

Friedreich Ataxia

This autosomal recessive disorder presents in adolescence or second decade. The classical changes include degeneration of the dorsal, pyramidal and spinocerebellar spinal tracts.

There is loss of position and vibration sense, ataxia nystagmus, dysarthria and areflexia. Plantar response is usually extensor because of pyramidal involvement. Intellect is not affected. In addition, these children show skeletal abnormalities such as pes cavus and kyphoscoliosis. Cardiac lesions may include hypertrophic cardiomyopathy. Optic atrophy is usually present. There is a higher incidence of diabetes mellitus.

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Occult Neuroblastoma

A child with acute cerebellar ataxia, hyperkinetic spontaneous movement of eyes in many directions (opsoclonus) and myoclonic jerks of face and body should always be investigated for occult malignancy, especially neuroblastoma.

Refsum Disease

It is due to disturbances in phytanic acid metabolism. Clinical features include ataxia, atypical retinitis pigmentosa with night blindness, deafness, ichthyosis and conduction defects in the heart. Protein level in CSF is high. These patients should be treated by excluding green vegetables (rich in phytanic acid) from the diet.

Demyelinating and Storage Diseases

Ataxia is an important component of disorders of demyelination. Visual involvement, pyramidal tract involvement and a waxing and waning course may be observed. Lipidoses can also present with cerebellar features.

Developmental Disorders

Cerebellar ataxia may also occur due to rudimentary development of cerebellar folia. It may be associated with diplegia, both spastic and flaccid, congenital chorea and mental defect. These are nonprogressive and may appear to improve with physiotherapy.

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INFANTILE TREMOR SYNDROME

Infantile tremor syndrome, as reported from Indian subcontinent, is a self limiting clinical disorder in infants and young children. It has an acute or gradual onset with mental and pychomotor changes, pigmentary disturbances of hair and skin, pallor and tremors. The disease is now encountered less frequently.

Etiopathogenesis

The clinical features suggest a disorder of the extrapyramidal system. Etiologic possibilities are malnutrition, vitamin B12 deficiency and viral infections but none have been conclusively proven.

Malnutrition. Due to its close resemblance with Kahn's nutritional recovery syndrome, malnutrition was postulated as a possible etiology. However, the majority of children are not malnourished, look chubby and their serum proteins are within normal range.

Vitamin B12 deficiency. Low vitamin B12 levels, megaloblastic bone marrow and a prompt response to vitamin B12 therapy is described but not substantiated.

Magnesium deficiency. Low magnesium levels in the serum and cerebrospinal fluid are reported in some cases.

Infections. Seasonal incidence and cortical biopsy suggest that it might be a form of meningoencephalitis. The failure to isolate any viral antigen, consistently normal CSF, presence of pigmentary changes and pallor do not support this hypothesis.

Toxin. Epidemiological evidence does not support the view that infantile tremor syndrome is due to a toxin.

Enzyme defect. A transient tyrosine metabolism defect might lead to interference in melanin pigment production. Depigmentation of substantia nigra may explain the tremor. This needs further confirmation.

Clinical Features

Infantile tremor syndrome occurs in apparently plump, normal or underweight and exclusively breastfed children of age 5 months to 3 yr. Boys are twice as commonly affected as girls. Most cases occur in summer months in children belonging to the low socioeconomic group.

The prodromal phase lasts for 2 weeks to 2 months. In a typical case, the onset is heralded by mental or motor regression characterized by apathy, vacant look, inability to recognize the mother, lack of interest in surroundings, lethargy and poor response to bright and colored objects. There is hyperpigmentation, especially over the dorsum of hands, feet, knees, ankles, wrists and terminal phalanges. Hair become light brown, sparse, thin, silky and lusterless. There is mild to moderate pallor. At times there may be fever, upper respiratory tract infections, diarrhea, edema, hepatomegaly and a tremulous cry.

The next phase is characterized by abrupt onset of tremors, which are usually generalized. Tremors are coarse, fast, 6–12 cycles per second, of low amplitude, initially intermittent but become continuous later on. Rate of tremors may vary from one limb to the other. Head is tossed from side-to-side and trunk may show twisting or wriggling dystonic movements. Tremors disappear during sleep and are aggravated during crying, playing or feeding. Tone is variable. Consciousness is retained. Average duration of this phase is 2–5 weeks. The condition remains static for some time before disappearing altogether.

During the recovery phase, pallor and pigmentation become less, the child becomes more alert. Improvement in psychomotor function is relatively slow. This phase usually lasts for one to six months but the course may be unduly prolonged with associated infections. Mortality is never directly related to the disease but may be attributed to concurrent infections. Subnormal intelligence is the only longterm sequelae.

Investigations

Laboratory investigations are not pathognomonic. There is mild to moderate anemia with hemoglobin between 6–11 g/dl. Morphology of red cells is variable (normocytic, microcytic, macrocytic or dimorphic). Bone marrow shows normoblastic, dimorphic or megaloblastic changes. Cerebrospinal fluid is normal. Histological evaluation of liver, skin, muscle, rectum and nerve are noncontributory. Cortical biopsies reveal mild inflammatory changes. CT scan shows no abnormalities or mild atrophy. EEG may show epileptiform activity. Virological studies are negative.

Differential Diagnosis

Kahn nutritional recovery syndrome, infection of the central nervous system, chronic liver diseases, hypoglycemia, hypomagnesemia, heredofamilial degenerative diseases, phenothiazine toxicity, hyperthyroidism and megaloblastic anemia may be considered in the differential diagnosis.

Treatment

Treatment is largely empirical, and supportive. Iron, calcium, magnesium, vitamin B6 supplements and injectable vitamin B12 therapy is reported to help some patients. Tremors may diminish considerably after administration of propranolol. Phenobarbitone, phenytoin and antiparkinsonism drugs do not shorten the duration of tremors. Nutrition should be maintained with dietary supplementation. Parents should be reassured. Associated infections and secondary complications must be treated.

Suggested Reading

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CEREBRAL PALSY

Cerebral palsy (CP) is defined as a nonprogressive neuromotor disorder of cerebral origin. It includes heterogeneous clinical states of variable etiology and severity ranging from minor incapacitation to total handicap. Most of the cases have multiple neurological deficits and variable mental handicap. The term does not include progressive, degenerative or metabolic disorders of the nervous system.

It is difficult to estimate the precise magnitude of the problem since mild cases are likely to be missed. Approximately 1–2 per 100 live births is a reasonable estimate of the incidence.

Etiopathogenesis

Factors may operate prenatally, during delivery or in the postnatal period. Cerebral malformations, perinatal hypoxia, birth trauma, chorioamnionitis, prothrombotic factors, acid base imbalance, indirect hyperbilirubinemia, metabolic disturbances and intrauterine or acquired infections may operate. Most infants have multiple risk factors. Prematurity is an important risk factor for spastic diplegia while term weight babies get quadriparesis or hemiparesis. The mechanism of CP in a large proportion of cases remains unclear and primary neurological aberrations may be unfolded in future. The importance of role of birth asphyxia has been questioned by recent data and asphyxia may be manifestation of the brain damage rather than the primary etiology.

A variety of pathological lesions such as cerebral atrophy, porencephaly, periventricular, leukomalacia, basal ganglia thalamic and cerebellar lesions may be observed.

Types of Cerebral Palsy

Cerebral palsy is classified on basis of topographic distribution, neurologic findings and etiology.

Spastic Cerebral Palsy

This is the commonest form (65%) and is topographically classified into spastic quadriparesis, diplegia or hemiparesis. Early diagnostic features of neural damage include abnormally persistent neonatal reflexes, feeding difficulties, persistent cortical thumb after 3 months age and a firm grasp. On vertical suspension, the infant goes into scissoring due to adductor spasm with an extensor posture and does not flex his knees or thigh. The stretch tendon reflexes are always brisk. They have variable degrees of mental and visual handicaps, seizures and behavioral problems.

Spastic quadriparesis is more common in term babies and exhibits signs including opisthotonic posture, pseudobulbar palsy, feeding difficulties, restricted voluntary movements and motor deficits.

Spastic diplegia is commoner in preterm babies and is associated with periventricular leukomalacia. The lower limbs are more severely affected with extension and adduction posturing, brisk tendon jerks and contractures.

Spastic hemiplegia is usually recognized after 4–6 months age. Early hand preference, abnormal persistent fisting, abnormal posture or gait disturbance may be the presenting complaint. Vascular insults, porencephaly or cerebral anomalies may be associated.

A thorough screen for associated handicaps and developmental assessment is warranted.

Hypotonic (Atonic) Cerebral Palsy

Despite pyramidal involvement, these patients are atonic or hypotonic. Tendon reflexes are normal or brisk and Babinski response is positive. They are often severely mentally retarded. In cerebellar involvement, hypotonia is not associated with exaggerated reflexes. Muscles may show fiber disproportion and delayed CNS maturation is common.

Extrapyramidal CP

This form accounts for 30% of cases. The clinical manifestations include athetosis, choreiform movements, dystonia, tremors and rigidity. Arms, leg, neck and trunk may be involved. Mental retardation and hearing deficits may be present. High tone audiometry should be performed. Cerebral damage following bilirubin ence-phalopathy is one of the causes.

Cerebellar Involvement

This form is seen in less than 5% of the patients. There is hypotonia and hyporeflexia. Ataxia and intention tremors appear by the age of 2 yr. Nystagmus is unusual; mental status may be near normal in some of these patients.

Mixed Type

A proportion of the patients have features of diffuse neurological involvement of the mixed type.

Severity of Lesion

Mild cases of cerebral palsy are ambulatory; these account for only 20% of patients. Moderately involved patients achieve ambulation by help, may be treated at outpatient level and include 50% of the patients. Severely affected children and those with multiple deficits account for the remainder.

Evaluation

Eyes. Nearly half of the patients have strabismus, paralysis of gaze, cataracts, coloboma, retrolental fibroplasia, perceptual and refractive errors.

Ears. Partial or complete loss of hearing is usual in kernicterus. Brain damage due to rubella may be followed by receptive auditory aphasia.

Speech. Aphasia, dysarthria and dyslalia are common among dyskinetic individuals.

Sensory defects. Astereognosis and spatial disorientation are seen in one-third of the patients.

Seizures. Spastic patients usually have generalized or focal tonic seizures. Seizures are more common in disorders acquired postnatally. These patients respond poorly to antiepileptic agents. Electroencephalograms show gross abnormalities.

Intelligence. About a quarter of the children may have borderline intelligence (IQ 80–100); and about half of them are severely mentally retarded.

Miscellaneous. Inadequate thermoregulation and problems of social and emotional adjustment are present in many cases. These children may have associated dental defects and are more susceptible to infections.

Diagnosis

The diagnosis of cerebral palsy should be suspected in a child with low birthweight and perinatal insult; clinically has an increased tone, feeding difficulties and global development delay. Abnormalities of tone posture, involuntary movements and neurological deficits should be recorded. Evaluation includes perinatal history, detailed neurological and developmental examination and assessment of language and learning disabilities. Inborn errors of metabolism may need to be excluded by screening of the plasma aminoacids and urine organic acid, reducing substance. CT and MRI help delineate the extent of cerebral damage in a case of cerebral palsy.

Differential Diagnosis

Neurodegenerative disorders. Progressively increasing symptoms, familial pattern of disease, consanguinity, specific constellation of symptoms and signs are usual clues for neurometabolic disorders. Failure to thrive, vomiting, seizures are significant symptoms. Laboratory investigations are necessary.

Hydrocephalus and subdural effusion. Head size is large, fontanel may bulge and sutures may separate.

Brain tumors or space occupying lesions. Lesion is progressive and features of increased intracranial pressure are evident.

Muscle disorders. Congenital myopathies and muscular dystrophies can mimic cerebral palsy. Distribution of muscle weakness and other features is characteristic, hypotonia is associated with diminished reflexes. The enzyme creatine phosphokinase may be elevated. EMG and muscle biopsy are diagnostic.

Ataxia-telangiectasia. Ataxia may appear before the ocular telangiectasia are evident.

Prevention

Prevention of maternal infection, fetal or perinatal insults, good maternal and neonatal care reduces prevalence. Early diagnosis, prompt adequate management plans can reduce the residual neurological and psychosocial emotional handicaps for the child and his family.

Management

The management plan should be holistic, involve the family and be directed to severity, type of neurological deficits and associated problems. Stress on improving posture, reducing tone, preventing contractures and early stimulation is necessary. Identification of associated deficits is important for appropriate physiotherapy and occupational therapy. Symptomatic treatment is prescribed for seizures. Tranquilizers are administered for behavior disturbances and muscle relaxants may be used for improving muscle function. Baclofen and tizanidine help to reduce spasticity. Diazepam may ameliorate spasticity and athetosis. Dantrolene sodium helps in relaxation of skeletal muscles. Dynamic contractures can be managed with botulinum toxin injection or alternatively nerve block with phenol. Plastic orthoses may help to prevent contractures, surgical procedures for spasticity and contractures may be required in selected patients.

Occupational therapy. The beginning is made with simple movements of self-help in feeding and dressing with progressive development of more intricate activities like typing.

Educational. The defects of vision, perception, speech and learning are managed by adequate special education experiences.

Orthopedic support. Tendon, muscle and bony surgeries may be required. Light weight splints may be required for tight tendo-Achilles and cortical thumb.

Social. The family should be given social and emotional support to help it to live with the child's handicap.

Rehabilitation and vocational guidance. Parents should help the child to adjust in the society and if possible to become independent by proper vocational guidance and rehabilitation. Severe handicapped children may need to be institutionalized.

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DEGENERATIVE BRAIN DISORDERS

A wide variety of hereditary and acquired disorders cause progressive degeneration of the central nervous system. In these disorders, new developmental skills are not achieved. As the disease advances, skills already acquired may also be lost. The degeneration may primarily involve the gray or white matter, resulting in corresponding clinical profile.

Late cases may have common features. A fluctuant course with recurrent seizures, mental deterioration, failure to thrive, infections, abnormal urine odor, skin and hair changes may point to inborn errors of metabolism. Some common causes of neurodegeneration are described below.

Infantile Gaucher Disease (Type II)

It is a metabolic disorder with autosomal recessive inheritance. The lysosomal enzyme glucocerebroside beta-glucosidase is deficient. Glucocerebroside accumulates in various tissues. Foamy reticulum cells are present in the bone marrow. Acid phosphatase is raised in the blood and tissues. The deficient enzyme can be identified in leukocytes/fibroblasts. Mortality occurs within first 3 yr of age. Clinically, these children show a characteristic triad of retroflexed head, trismus and squint. They may show hypertonia, marked feeding problems, vomiting and dysphagia. Splenomegaly and hepatomegaly are observed later. Enzyme replacement has been tried for juvenile and adult forms of this disease.

Tay-Sachs Disease (GM2 Gangliosidosis)

Inheritance is autosomal recessive. A history of consanguinity is usually obtained. It was earlier reported in Ashkenazi Jews but has been reported in other racial groups also. Low serum beta-hexosaminidase level is the characteristic metabolic defect. As a result GM2 ganglioside accumulates in the neurons. Initially, milestones are delayed. Later, there is regression of development and death occurs by 2 to 4 yr. The baby has an abnormal startle response to noise. Convulsions, rigidity of the extensor

group of muscles and blindness supervene after the first year.

A cherry-red spot is seen over the macular region of the retina. The head size increases. Liver and spleen are not enlarged. Sandhoff disease is described in non-Jewish people. It resembles Tay-Sachs disease clinically except for later onset, mild visceromegaly and progressive ataxia. Both hexosominidase A and B are deficient. These cases may show congestive heart failure and enlarged liver.

Metachromatic Leukodystrophy

Inheritance is autosomal recessive and the gene is located on chromosome 22. The characteristic metabolic defect is decreased urinary or leukocyte aryl sulphatase A activity. Clinically, the illness manifests as ataxia, stiffness starting in the second year of life. A little later, signs of bulbar involvement and intellectual deterioration are observed. Initially there is hypotonia, but later spasticity supervenes. Characteristically, distal tendon reflexes are lost due to associated peripheral neuropathy. Progressive intellectual impairment, optic atrophy and loss of speech develop in the course of illness. Convulsions may occur in some cases. CT scan and MRI reveal abnormal white matter finger like projections, sural nerve biopsy may reveal metachromatic granules and the enzyme arylsulfatase A is low.

Mucopolysaccharidoses

Group of disorders with autosomal recessive inheritance, Hurler syndrome is most common and is characterized by deficiency of L-iduronidase. Heparan and dermatan sulphate excretion in the urine is increased. Delayed milestones become apparent by the age of 1 yr. The facies is coarse. The child appears a dwarf with gibbus at the level of L1 vertebra. Liver and spleen are enlarged. Hands are short and stubby. Deafness, haziness of cornea and valvar heart disease may be there.

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Subacute Sclerosing Panencephalitis

This condition is believed to follow several months to years after an attack of measles. The usual age of onset is between 5 and 15 yr. In the early stages, minor personality changes may be observed and school performance deteriorates. Later, slow myoclonic jerks in the limbs and trunk are observed. Progressive neurologic deterioration occurs. Electroencephalogram shows stereotyped periodic slow waves with high voltage and a burst suppression pattern. Diagnosis is established by raised measles antibody titer in serum (≥1:256) and/or cerebrospinal fluid (≥1:4).

MENTAL RETARDATION

Mental retardation is defined as subaverage general intelligence, manifesting during early developmental period. The child has diminished learning capacity and does not adjust well socially.

Grades of Mental Handicap

Intellect comprises perception, memory, recognition, conceptualization, convergent and divergent reasoning verbal facility and motor competence. Intelligence tests devised to measure different parameters of intelligence in the different age groups include the following:

Gesell's developmental schedules, Bayley Infant Scales, Griffith's Mental Development Scale, Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), Stanford-Binet Tests (Terman-Merrill revision), Raven's Matrices, Denver II Development Screening Test, Good enough Draw-a-man Test, Adaptive Behavior Scale, DEPI and II.

Indian adaptations of some of these are: Kulshrestha or Kamath adaptations of the Stanford-Binet test, Phatak adaptation of the Bayley Scales, Malin's adaptation of the WISC, Vineland Social Maturity Scale and Bhatia's Battery of Performance Tests.

The *intelligence quotient (IQ)* is calculated according to the formula: mental age divided by chronological age, multiplied by 100.

The degree of mental handicap is designated *mild, moderate, severe and profound*, for IQ levels of 51–70, 36–50, 21–35 and 0–20, respectively. An IQ level of 71 to 90 is designated *borderline intelligence* and is not included in mental handicap. The terms *educable* and *trainable* are used for mild and moderate mental handicap, respectively, while the severe and profoundly handicapped are designated *custodian*. However, all levels of mentally retarded children are educable and trainable to some extent.

Prevalence

In the general population, 2 to 3% of children have an IQ below 70. Nearly three-fourths of such cases are mildly handicapped. About 4 per 1,000 (or 0.4%) of the general population are more severely handicapped with an IQ below 50.

Etiology

It is difficult to incriminate a single factor in etiology of mild mental retardation. Majority of cases are idiopathic. In moderate to severe mental retardation the cause is easier to identify (Table 18.10).

Predisposing Factors

Low socioeconomic strata. These children are exposed to several environmental causes of mental handicap, such as inadequate nutrition of mother and child, poor antenatal and obstetric care, lack of immunization, delayed and inappropriate treatment of infections, and unsatisfactory environmental stimulation.

Low birthweight. The small for gestational age infant has a poorer longterm prognosis for postnatal development than preterm infants of equal weight, who are appropriate for gestational age. However, even the preterm infant is

Table 18.10: Etiology of mental retardation

Chromosomal disorders: Trisomies 21, 18, 13; Klinefelter syndrome
Genetic syndromes: Fragile X, Prader-Willi syndrome, tuberous sclerosis
Inborn errors of metabolism: Phenylketonuria, Tay-Sachs disease, mucopolysaccharidoses, galactosemia, organic acidemias
Congenital infections: HIV, toxoplasmosis, rubella, CMV, syphilis, herpes simplex
Perinatal causes: Hypoxic ischemic encephalopathy, intraventricular hemorrhage, periventricular leukomalacia, fetal alcohol syndrome
Postnatal causes: Trauma, meningitis, hypoglycemia, kernicterus, thrombosis of cerebral vessels
Iodine deficiency
Developmental defects: Microcephaly, craniostenosis, porencephaly, cerebral migration defects

at risk for cerebral hemorrhage, anoxia and infections. The small for gestational age infant is subjected to adverse genetic or prenatal environmental influences, which may occasionally result in brain damage.

Advanced maternal age. Chromosomal anomalies such as Down syndrome as well as intrauterine factors, such as fetal deprivation and hypoxia are commoner in offspring of older mothers. Birth trauma is frequent in the infant of the older primipara.

Consanguinity of parents is associated with a high incidence of genetically transmitted mental handicap.

Clinical Features

The mental age is below the chronological age. Most of them present with the behavior syndrome of cerebral dysfunction, such as hyperactivity, short span of attention, distractibility, poor concentration, poor memory, impulsiveness, awkward clumsy movements, disturbed sleep, emotional instability, frustration, low tolerance and wide scatter in intellectual function.

Associated defects of the musculoskeletal system, of vision, or speech and hearing are often found in mentally handicapped children. Congenital anomalies of other systems, apart from the neurological system, may be associated. Convulsions are common in the mentally handicapped.

History should include developmental and family history. A complete physical examination will usually help in the diagnosis. It should include an examination of the fundus and a developmental assessment.

Additional investigations are necessary in some cases, depending on the probable diagnosis. These include urine tests (chromatography and screening for phenylketonuria, homocystinuria and galactosemia) and chromosomal studies, where indicated. Appropriate tests are required to diagnose hypothyroidism, storage disorders and intrauterine infections. Computerized tomography and MRI helps define hydrocephalus, porencephaly, absence of corpus callum, tuberous sclerosis and migration defects.

Prevention

Genetic counseling. The risk of disorders with autosomal recessive inheritance is high in consanguineous marriages. Parents should be counseled about the risk of recurrence in inherited neurometabolic disorders. Mothers older than 35 yr should be screened for Down syndrome during pregnancy.

Vaccination of girls with rubella vaccine should be encouraged to prevent fetal rubella syndrome. During pregnancy, good antenatal care and avoidance of teratogens should be emphasized. Mothers should be protected from contact with patients suffering from viral diseases. When indicated, amniocentesis may be done for study of amniotic fluid for tissue culture, chromosome studies, alpha-fetoprotein and enzyme for prenatal diagnosis. During labor, *good obstetric and postnatal supervision* is essential to prevent occurrence of birth asphyxia, injuries, jaundice and sepsis.

Postnatally, neonatal infections should be diagnosed and treated promptly. Hyperbilirubinemia should be managed with phototherapy and/or exchange transfusion. Cretinism and galactosemia, if diagnosed and treated in early infancy, have a satisfactory prognosis. Screening of newborn infants by tandem mass spectroscopy helps to diagnose metabolic disorders such as phenylketonuria, biotinidase deficiency, organic aciduria, hypothyroidism and homocystinuria, permits early treatment thereby averting irreversible brain damage.

Management

The parents should be counseled together. The diagnosis, principles of early stimulation and management should be explained, emphasizing the prognosis. Parental guilt and the home situation should be discussed. Minimal criticism and high appreciation, short-term goals and structured learning results in less withdrawal, aggressive and hostile reactions.

Associated diseases and dysfunctions, e.g. of musculoskeletal system, vision, hearing, locomotion and feeding should be appropriately managed. Anticonvulsive medications such as phenobarbitone should be avoided. Patients with hyperactivity often respond to amphetamines including methylphenidate.

Institutionalization should be avoided. Day care centers and schools, integrated schools, vocational training centers, sheltered farms and workshops are useful. Classes should be taken to educate mothers and families in caring for the handicapped and in trying to develop their potential to the maximum, in an effort to make these children as independent as possible.

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NEUROCUTANEOUS SYNDROMES

There are five major neurocutaneous syndromes, viz. (i) neurofibromatosis; (ii) tuberous sclerosis; (iii) von Hippel-Landau disease; (iv) Sturge-Weber syndrome; and (v) ataxia telangiectasia. All of these are inherited disorders except for Sturge-Weber syndrome. Clinical profile of these syndromes is diverse, varying from the mild abortive forms to severe potentially fatal disorders.

Neurofibromatosis

Inheritance is autosomal dominant. There are two types: type NF1 (von Recklinghausen disease or peripheral NF1) and type NF2 (central neurofibromatosis). Deletion or inactivation of the NF gene on chromosome 17 is responsible for NF1. Gene for NF2 is located on chromosome 22.

NF1. Two or more of the following are present: (i) six or more café au lait spots, each over 5 mm in diameter before puberty or over 15 mm diameter in older persons; (ii) two or more neurofibromas or one plexiform neuroma; (iii) freckling in axillary or inguinal regions; (iv) optic glioma; (v) two or more Lisch nodules; dysplasia of the sphenoid bone or thinning of the cortex of long bones with or without pseudoarthrosis; and (vi) a first degree relative with NF1.

NF2. Presence of bilateral auditory neuroma; unilateral auditory neuroma along with a first degree relative with meningioma, schwannoma or juvenile posterior subcapsular lenticular opacity.

Management. Management comprises supportive care, surveillance for and treatment of new manifestations and surgical management of spinal deformities. Genetic counseling is necessary.

Tuberous Sclerosis Complex

Tuberous sclerosis is an autosomal dominantly neurocutaneous disorder. The presenting features vary with age.

Cardinal features are skin lesions, convulsion and mental retardation. Early skin lesions are hypopigmented, ash leaf shaped macules (Fig. 18.11), red or pink papules (angiofibromas) called adenoma sebaceum on face. These enlarge with age. Other lesions are shagreen patches, subungual fibromas and gingival fibromas. Retinal hamartoma may be present. In early life tumors in heart and kidneys may be detected on ultrasonography. Myoclonic jerks often lead to detection of this entity and are an important cause of West syndrome. Vigabatrin is a useful medication.

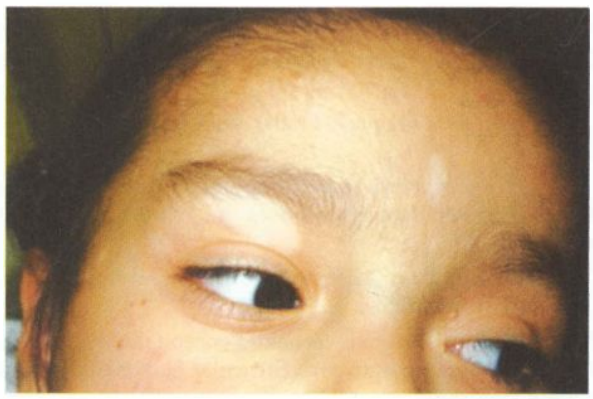

Fig. 18.11: Facial skin showing multiple ash leaf spots in a child with tuberous sclerosis

Sturge-Weber Syndrome

Sturge-Weber syndrome is characterized by facial nevus flammens (usually in the distribution of first branch of trigeminal nerve but not limited to it), contralateral focal seizures, calcification of the cortex and subcortical structures and glaucoma on the same side as the skin lesions. Early surgery is recommended in symptomatic cases.

von Hippel-Lindau Disease

In this disorder, there are retinal and cerebellar hemangioblastomas besides spinal cord angiomas and cystic tumors of pancreas, kidneys and epididymis. Patients may show nystagmus, ataxia and increased intracranial pressure.

Ataxia-Telangiectasia

It is an autosomal recessively inherited disease that has been mapped to chromosome 11q. The syndrome manifests with progressive cerebellar ataxia, oculocutaneous telangiectasia, choreoathetosis, pulmonary and sinus infections, immune deficiency and lymphoreticular malignancies. Telangiectasia appears by 2–7 yr on bulbar conjunctiva and even skin. Increased incidence of abnormal movements, vitiligo, abnormal glucose tolerance are observed. Investigations reveal decreased serum IgA in three-fourths of the patients. Alpha-fetoprotein is almost universally elevated. Treatment is symptomatic.

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Neuromuscular Disorders 19

Sheffali Gulati

A motor unit comprises one anterior horn cell and all the muscle fibers that it innervates. Neuromuscular disorders may be due to lesions anywhere along the motor unit. These include neuronopathies (primary disorders of anterior horn cell), neuropathies (primary disorders of axon or its myelin), neuromuscular junction disorders and myopathies (primary disorders of muscle). A careful history and physical examination help in localizing the disorder within the motor unit.

APPROACH TO EVALUATION

The predominant presenting complaint of a patient with a neuromuscular disorder is weakness. Weakness may also result from disorders of the upper motor neuron, e.g. cerebral palsy. Weakness due to an upper motor neuron lesion is associated with increased tone, brisk reflexes and extensor plantar responses. Additional features that suggest central nervous system involvement include seizures and cognitive impairment.

Lower motor neuron lesions are associated with significant weakness, hypotonia, depressed reflexes and flexor plantar responses. Anterior horn cell involvement (e.g. spinal muscular atrophy) is associated with wasting, fasciculations and hyporeflexia. Peripheral nerve involvement (e.g. hereditary sensory and motor neuropathies) is associated with predominantly distal weakness, distal wasting, hyporeflexia and sensory involvement. Neuromuscular junction involvement (e.g. myasthenia gravis) classically leads to fatigable and fluctuating weakness. Muscle diseases (e.g. muscular dystrophies) are associated with proximal weakness and relatively preserved bulk and reflexes. The mode of inheritance is variable, e.g. X-linked recessive in Duchenne muscular dystrophy and Becker muscular dystrophy; autosomal dominant in facioscapulohumeral dystrophy; and autosomal recessive in sarcoglycanopathies and congenital muscular dystrophies.

The presentation and pattern of disease over time allows definition of possible conditions. For example, muscular dystrophy is associated with inexorable weakness. Metabolic disease and ion channelopathies (periodic paralysis) are associated with episodic course. Inflammatory disorders such as dermatomyositis are associated with waxing and waning course and pain. Cardiac disease often accompanies Duchenne muscular dystrophy and myotonic dystrophy. Skin rash is seen in dermatomyositis, while eye involvement is noted in myotonic dystrophy, congenital muscular dystrophies and mitochondrial diseases. Liver involvement may be seen with mitochondrial disorders, acid maltase deficiency and carnitine deficiency.

Laboratory Evaluation

Creatine phosphokinase (CPK), a muscle enzyme, is elevated in most muscular dystrophies. Muscle biopsy is a frequently performed test that enables diagnosis based on specific morphological features, immunohistochemistry (absent or reduced staining for specific protein) and enzyme histochemistry (absent or reduced enzyme function). Electrophysiological tests, including nerve conduction studies and electromyography, help localize the lesion and assess its severity.

Other diagnostic tests include nerve biopsy, antibody testing (e.g. acetylcholine receptor antibodies in myasthenia gravis). Molecular genetic testing is now available for many neuromuscular disorders (spinal muscular atrophy and Duchenne muscular dystrophy).

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Hypotonia

Hypotonia is a common sign of neuromuscular disorders. Any lesion along the motor unit can result in *peripheral hypotonia*, characterized by depressed muscle stretch reflexes and loss of muscle power. The common causes of floppiness in infancy are shown in Fig. 19.1. Hypotonia *in utero* may result in hip dislocation or multiple contractures (*arthrogryposis*). The mother may give a history of reduced fetal movements or polyhydramnios.

An alert hypotonic infant with absent deep tendon reflexes, predominantly distal movements and fasciculations is the typical phenotype of spinal muscular atrophy. Neuropathies usually present later in childhood. Atrophy out of proportion to weakness, depressed or absent reflexes and predominantly distal weakness suggests a nerve disorder. Fatigability, ptosis, proximal muscle weakness and history of myasthenia gravis in the mother may indicate an underlying neuromuscular junction disorder. Predominantly proximal muscle weakness, normal or depressed tendon reflexes and static or improving course may indicate a muscle disease. Deep tendon reflexes are preserved in muscle disease or if reduced, are in proportion to the degree of muscle wasting and weakness. Atrophy is less prominent in muscle disorders.

Central hypotonia is characterized by preserved muscle power and normal or brisk deep tendon reflexes. Sometimes a child may display features of both central and peripheral hypotonia; common causes of *mixed hypotonia* include hypothyroidism, motor unit disorders with superimposed hypoxia, acid maltase deficiency, mitochondrial disorders and infantile neuronal degeneration.

Muscle Weakness in Older Children

Distal weakness is predominantly seen in neuropathies and some muscle disorders like myotonic dystrophy. Proximal weakness has broad differential diagnosis. The child may complain of difficulty in rising from the chair, going up and down the stairs or reaching with their arms. A clinical approach to a child to proximal weakness is summarized in Fig. 19.2. Some disorders such as chronic inflammatory demyelinating polyneuropathy (CIDP) and certain muscular dystrophies show both proximal and distal weakness.

DISORDERS AFFECTING ANTERIOR HORN CELLS

Spinal muscular atrophy and poliomyelitis are the two most common anterior horn cell disorders encountered in children. Besides these, other enteroviruses (e.g. coxsackievirus and echovirus), juvenile form of amyotrophic lateral sclerosis and neurometabolic disorders like Tay-Sach disease, neuronal ceroid lipofuscinosis and Pompe disease may also involve anterior horn cells.

Spinal Muscular Atrophy

This is an autosomal recessive disease caused by mutational in the *SMN* 1 gene, encoding the SMN protein essential for survival of anterior motor horn cells. Three clinical types are recognized. Patients with type *1 disease*

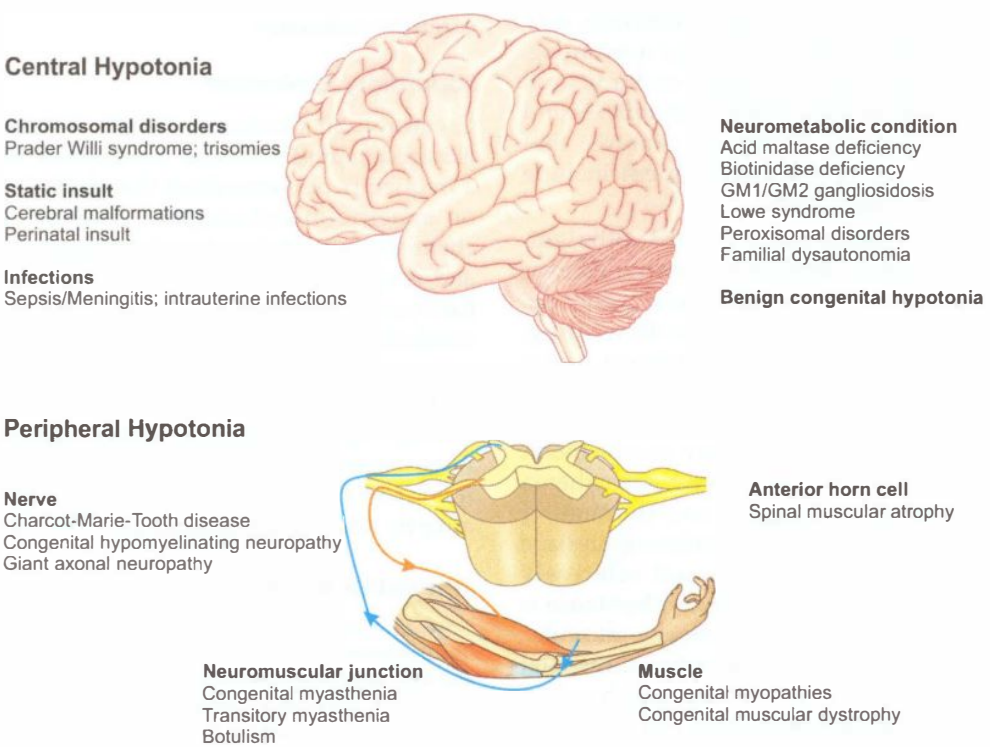

Fig. 19.1: Common etiologies of 'floppy infant'. Maintenance of normal tone requires an intact central and peripheral nervous system

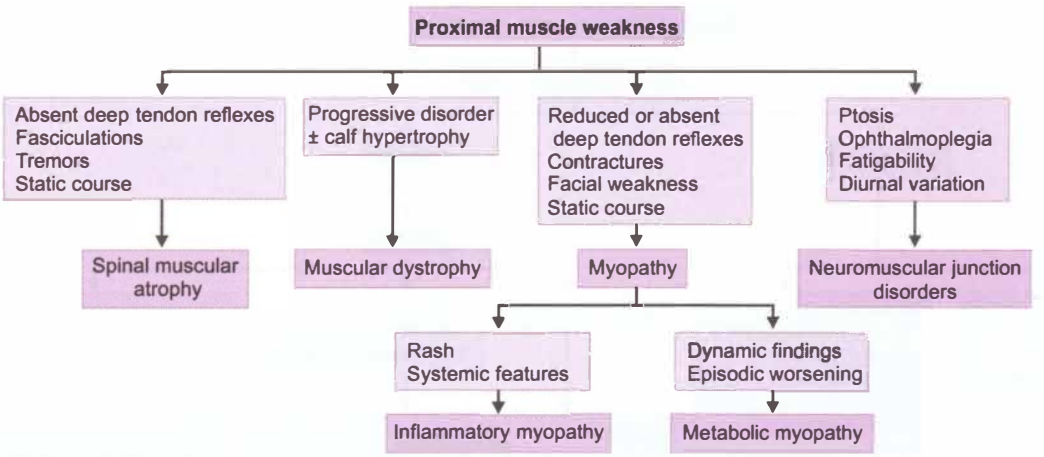

Fig. 19.2: Clinical approach to a child with proximal muscle weakness

(Werdnig-Hoffmann disease) present with profound hypotonia, flaccid weakness and global areflexia (Fig. 19.3). Respiratory weakness, poor swallowing and tongue fasciculations are common. These children usually never learn to sit. Aspiration pneumonia is an important cause of morbidity and mortality. Patients with type *2 disease* (Dubowitz disease) have onset of illness at 6–18 months of age and are usually able to sit unaided. They may develop kyphoscoliosis, tremors (polyminimyoclonus), poor swallowing and respiratory insufficiency. Patients with type *3 disease* (Kugelberg-Welander disease) present later in childhood (>18 months) and are usually able to walk. These children are often misdiagnosed as limb girdle muscular dystrophy or myopathy. Global areflexia, fasciculations, tremors and electrophysiology may give a clue towards underlying anterior horn cell pathology.

Treatment is usually supportive and includes respiratory care, management of problems in feeding and swallowing, ensuring adequate nutrition, treatment for gastroesophageal reflux, orthopedic care and rehabilitation, appropriate immunization and family education and counseling. Therapeutic agents undergoing evaluation include valproate, gabapentin, aminoglycosides and riluzole.

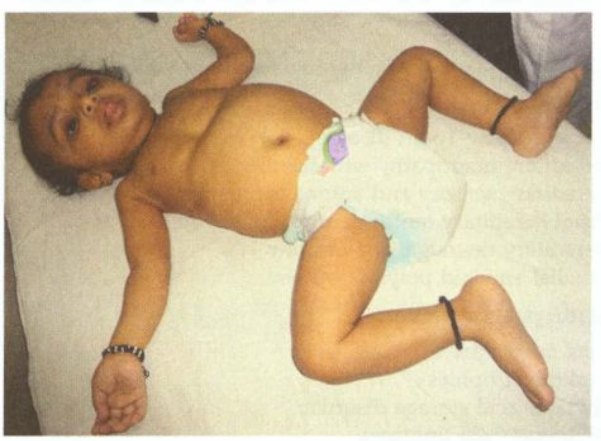

Fig. 19.3: A 5-month-old boy presented with motor delay and repeated chest infections. Examination revealed generalized hypotonia, absent deep tendon reflexes, poor muscle power and tongue fasciculations. Note the 'frog-like' posture and subcostal retractions due to respiratory muscle weakness. A diagnosis of spinal muscular atrophy type 1 was made

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PERIPHERAL NEUROPATHIES

Most neuropathies are chronic. Guillain-Barré syndrome is the most common cause of acute neuropathy. A clinical approach to a child with suspected peripheral neuropathy is shown in Fig. 19.4. The clinical presentation, electrophysiological characteristics and ancillary laboratory studies may help narrow down the differential diagnosis in a child with suspected peripheral neuropathy, as discussed below.

Type of neuropathy. Most neuropathies are primarily axonal. Finding a demyelinating pattern narrows the differential diagnosis. Clinical pointers to a demyelinating process include: (i) presence of global areflexia; (ii) moderate to severe muscle weakness with relative preservation of bulk; (iii) predominantly motor symptoms; and (iv) hypertrophy of nerves. The differentiation between the two types of neuropathy is mainly electrophysiological. Electrophysiologically, demyelination is suggested by: (i) decreased conduction velocity; (ii) prolonged distal latencies and late responses; (iii) asymmetry; (iv) presence of conduction block; and (v) abnormal temporal dispersion (suggesting an acquired process). Axonal disorders show decreased compound muscle action potentials with preserved conduction velocity and distal latencies.

Pattern of neuropathy. Most polyneuropathies show distal-to-proximal gradient of symptoms and signs ('length

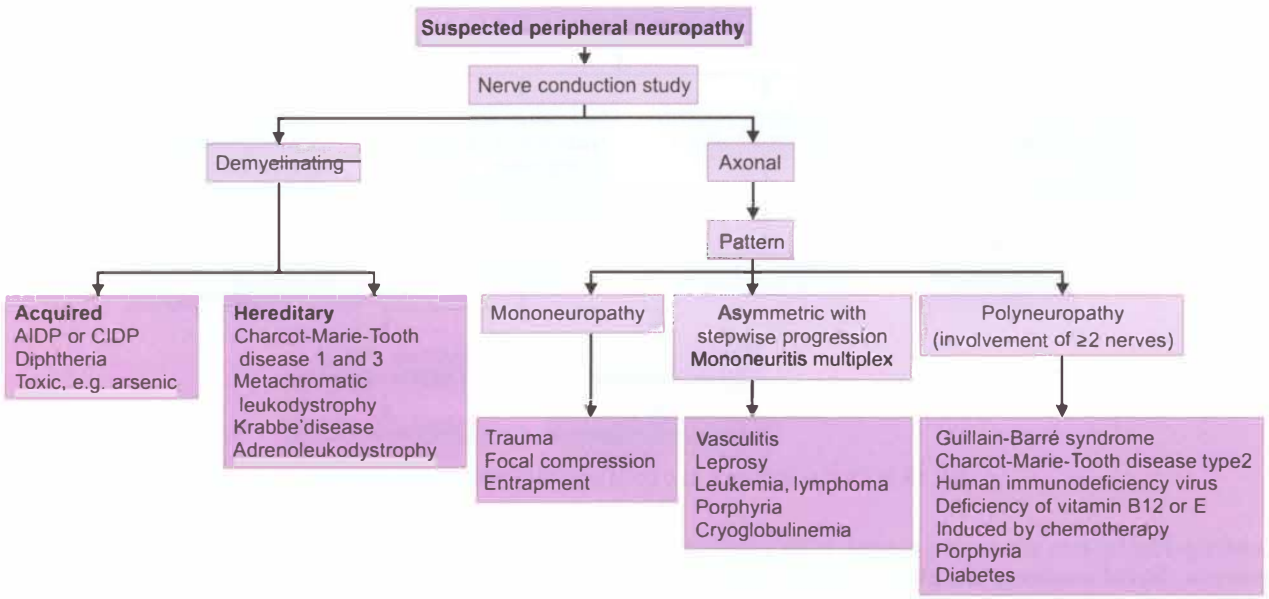


Fig. 19.4: Approach to peripheral neuropathies in childhood. Mononeuritis multiplex refers to the involvement of multiple separate non-contiguous peripheral nerves, either simultaneously or serially. AIDP acute inflammatory demyelinating polyneuropathy; CIDP chronic inflammatory demyelinating polyneuropathy

dependent' or 'dying back' pattern). More proximal nerves may be involved rarely, e.g. inflammatory demyelinating polyneuropathy and porphyria. The presence of asymmetry and a stepwise progression may point towards mononeuritis multiplex. Mononeuropathies are rarely encountered in pediatric practice and are usually due to trauma, focal compression or entrapment.

Type of nerve fiber involved. Neuropathies that predominantly affect large fibers result in sensory deficits (impaired touch or vibration), weakness and loss of deep tendon reflexes. Small fiber neuropathies present with distal sensory deficit, painful burning dysesthesias and autonomic dysfunction. Pure sensory neuropathies are unusual.

Hereditary Neuropathy

A slowly progressive course, prominent sensory signs in absence of sensory symptoms, foot deformities and a family history point towards an inherited neuropathy. The hereditary neuropathies encountered in children are listed in Table 19.1. Charcot-Marie-Tooth disease is the most common hereditary neuropathy, and the most common peripheral neuropathy in children.

The phenotype of a child with Charcot-Marie-Tooth disease consists of distal weakness and wasting, especially of the peroneal compartment ('stork leg' appearance; Fig. 19.5), some distal sensory impairment, skeletal deformities, contractures and diminished or absent deep tendon reflexes. The clinical features, electrophysiological characteristics, inheritance pattern and, occasionally, features on nerve biopsy, suggest a specific hereditary neuropathy and guide further evaluation.

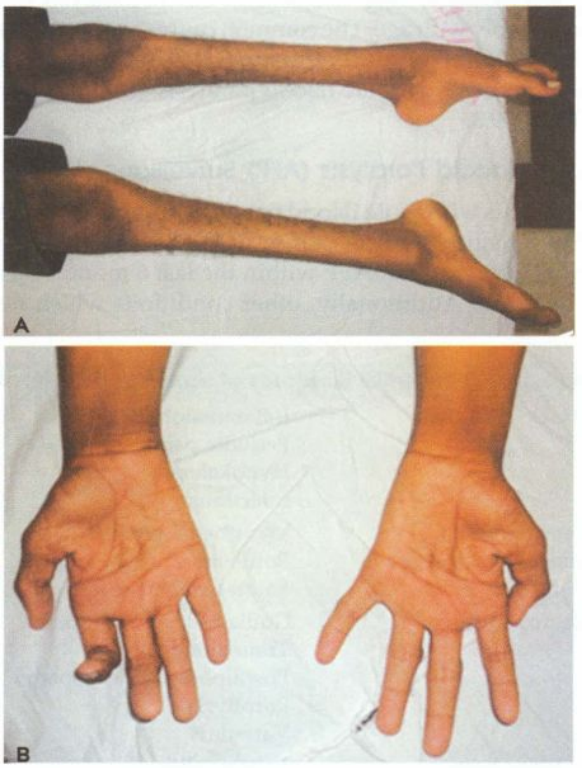
Guillain-Barré Syndrome

This is a common cause of acute flaccid paralysis (AFP) in children. It is an immune-mediated, rapidly progressive, predominantly motor, symmetric polyradiculoneuropathy that often leads to bulbar and respiratory compromise. Many subtypes are described and include acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, acute motor and sensory neuropathy, acute sensory neuropathy, acute pandysautonomia and the Miller Fisher syndrome.

The condition can occur at any age. About two-thirds patients have an antecedent infection within 6 weeks prior

Table 19.1: Hereditary neuropathies

Primary disease
Charcot-Marie-Tooth disease
Hereditary neuropathy with liability to pressure palsies
Hereditary sensory and autonomic neuropathies
Distal hereditary motor neuropathies
Hereditary neuralgic amyotrophy
Familial amyloid polyneuropathy
Multisystem disorder
Lipid metabolism
Leukodystrophies
Phytanic acid storage disorder
Sphingomyelin lipidoses
Porphyria
Defective DNA repair: Ataxia-telangiectasia, xeroderma pigmentosa
Hereditary ataxias: Friedrich ataxia, spinocerebellar ataxia
Miscellaneous: Neuroacanthocytosis, mitochondrial disorders



Figs 19.5A and B: A 7-yr-old boy presented with progressive gait difficulties, frequent twisting of ankles, foot deformities and progressive thinning of legs. Examination revealed distal weakness and wasting, absent ankle reflexes and enlarged common peroneal nerves. (A) Note the 'stork leg' appearance of legs with foot deformities; and (B) hand deformities. A diagnosis of Charcot-Marie-Tooth disease was made

to symptom onset, generally an upper respiratory tract infection or gastroenteritis. The clinical manifestations include acute onset of symmetrical ascending weakness that is both proximal and distal. Facial weakness is frequent, and involvement of respiratory muscles occurs in one-fourth cases. Dysautonomia is common and is suggested by tachycardia, arrhythmia, ileus, bladder dysfunction, labile blood pressure and impaired thermoregulation. The weakness usually reaches a nadir 2–4 weeks after onset of symptoms and is followed by gradual recovery over weeks to months. The illness is usually monophasic but 7–16% patients may suffer from recurrent episodes of worsening after an initial improvement. As compared to demyelinating forms, the axonal form of Guillain-Barré syndrome exhibits a more rapid and severe course, with frequent involvement of respiratory muscles and cranial nerves and infrequent and mild involvement of the autonomic nervous system. The Miller Fisher syndrome is characterized by the triad of ophthalmological abnormalities, ataxia and areflexia.

Diagnosis depends on clinical features, electrophysiological findings and cerebrospinal fluid examination. Electrophysiology may reveal absent F-responses or H-reflexes and reduced compound muscle action potential or sensory nerve action potential in axonal forms of the illness. Prolonged distal latencies, reduced conduction velocities, abnormal temporal dispersion and conduction blocks are noted in demyelinating types. The cerebrospinal fluid protein concentration is raised in 80% cases, while mononuclear cell count is either normal (albuminocytologic dissociation) or below 50 cells/mm^3. Electrophysiological studies and cerebrospinal fluid analysis may be normal during the first week of the illness.

Immunotherapy is the mainstay of treatment. Intravenous immunoglobulin (IVIG, 2 g/kg over 2–5 days) should be administered or plasma exchanges performed if the child presents within 2–4 weeks of onset of symptoms. Such treatment is indicated in nonambulatory patients, but their role in mildly affected patients who are mobile is unclear. Plasma exchanges may hasten recovery compared to supportive treatment alone in adult patients. In patients with severe disease, therapy with IVIG (if initiated within two weeks from onset) hastens recovery as much as plasma exchange and is more likely to be completed than plasma exchange. Further, giving IVIG after plasma exchange did not confer significant extra benefit. Low quality evidence suggests that IVIG probably hastens recovery in children compared with supportive care alone. Information on appropriate therapy is limited for patients with mild disease and in those where treatment starts more than two weeks after onset. Patients who do not respond to initial treatment with IVIG may benefit from a second course of therapy. General supportive care includes cardiorespiratory care, physical therapy, nutritional management, management of neuropathic pain, care of bladder and bowel and prevention of deep vein thrombosis.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

This uncommon condition is slowly progressive (>4 weeks) or relapsing and has symmetric proximal and distal weakness in the upper and lower extremities with concomitant sensory loss. Asymmetric forms, distal predominant forms and sensory predominant forms also occur. The minimum duration of symptoms to reach the trough in patients with chronic inflammatory demyelinating polyradiculoneuropathy is 2 months. This helps to distinguish this condition from Guillain-Barré syndrome, which usually evolves in less than 4 weeks. Electrophysiology and nerve biopsy help in diagnosis. Treatment modalities for chronic inflammatory demyelinating polyradiculoneuropathy include IVIG, plasma exchange and prednisolone. Spontaneous remission of chronic inflammatory demyelinating polyradiculoneuropathy is rare, and most patients require longterm immunomodulating therapy.

Suggested Reading

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Vavra MW, Rubin DI. The peripheral neuropathy evaluation in an office based neurlogy setting. Semin Neurol 2011;31:102–4

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ACUTE FLACCID PARALYSIS

Acute flaccid paralysis (AFP) is a clinical syndrome characterized by rapid onset of weakness, progressing to maximum severity within several days to weeks. The term 'flaccid' refers to the absence of spasticity or other upper motor neuron signs. At the 41st World Health Assembly in May 1988, the resolution to eradicate polio was passed. In the Global Polio Eradication Initiative, acute flaccid paralysis is defined as any case of AFP in a child aged <15 yr, or any case of paralytic illness in a person of any age when polio is suspected. It can result from involvement at any point in the motor unit. Common causes of acute flaccid paralysis include Guillain-Barré syndrome, poliomyelitis, transverse myelitis, traumatic neuritis, postdiphtheric neuropathy and nonpolio enteroviral illnesses.

Over the last few years the number of cases of poliomyelitis has been going down. In 2009, there were 741 cases of poliomyelitis and in 2010, there were 42 cases. The last case of confirmed wild poliovirus (P1 type) was reported from West Bengal in 2011.

The differential diagnosis of acute flaccid paralysis varies considerably with age. The common causes are enumerated in Table 19.2. The differentiating features between the common causes of acute flaccid paralysis are summarized in Table 19.3.

Acute Flaccid Paralysis (AFP) Surveillance

All patients with acute flaccid paralysis should be reported to Surveillance Medical Officer of World Health Organization. Every case of AFP within the last 6 months has to be reported. Additionally, other conditions which need

Table 19.2: Differential diagnoses of acute flaccid paralysis

Muscle disorders	Inflammatory myopathy Periodic paralysis Hypokalemia Infections
Neuromuscular junction disorders	Myasthenia gravis Botulism Eaton-Lambert syndrome
Neuropathies	Guillain-Barré syndrome Traumatic neuritis Postdiphtheric neuropathy Porphyria Vasculitis
Anterior horn cell disorders	Poliomyelitis Nonpolio enteroviruses
Spinal cord disease	Transverse myelitis Spinal cord compression Trauma

Table 19.3: Differentiating among common causes of acute flaccid paralysis

	Poliomyelitis	*Guillain-Barré syndrome*	*Transverse myelitis*	*Traumatic neuritis*
Fever	Present; may be biphasic	May have a prodromal illness	May have a prodromal illness	Absent
Symmetry	Asymmetric	Symmetrical	Symmetrical	Asymmetric
Sensations	Intact; may have diffuse myalgias	Variable	Impaired below the level of the lesion	May be impaired in distribution of the affected nerve
Respiratory insufficiency	May be present	May be present	May be present	Absent
Cranial nerves	Affected in bulbar and bulbospinal variants	Usually affected	Absent	Absent
Radicular signs	May be present	Present	Absent	Absent
Bladder, bowel complaints	Absent	Transient; due to autonomic dysfunction	Present	Absent
Nerve conduction	May be abnormal	Abnormal	Normal	Abnormal
Cerebrospinal fluid	Lymphocytic pleocytosis; normal or increased protein	Albumino-cytologic dissociation	Variable	Normal
MRI spine	Usually normal	Usually normal	Characteristic*	Normal

* Local enlargement of the spinal cord and increased signal intensity over several spinal segments

notification include: (i) isolated facial palsy; (ii) isolated bulbar palsy; (iii) unproved hypokalemia; (iv) neck flop; (v) floppy baby; (vi) flaccid hemiplegia; (vii) encephalitis; (viii) postictal weakness (Todd's paralysis); and (ix) post-diphtheric polyneuritis.

These cases are immediately investigated, usually within 48 hr of notification, by a trained medical officer. After confirming the case as AFP, the investigator takes a detailed medical history, examines the child and proceeds with the other aspects of case investigation including collection and transportation of stool specimens for laboratory testing, search for additional cases and outbreak response investigation in the affected community, 60 days followup examination, analysis of laboratory results and case classification. Collection of stool specimens from every AFP case is an important aspect of the polio eradication strategy. From every case of AFP, two stool specimens are collected, ideally within 14 days of onset of paralysis and at least 24 hr apart. Although the optimal time period for detection of poliovirus in the stool is within 14 days of paralysis onset, stool specimens should be collected from any late-reported AFP case up to 60 days from the date of paralysis onset. Beyond 60 days after paralysis onset, the likelihood of detecting poliovirus is very low. Voided stool sample is preferred. But in cases where it is not possible other methods include digital extraction (when child is constipated or dies), postmortem stool collection (contents of large intestine) and use of rectal tube. Enema or purgatives are not recommended. Each specimen should be 8 g each (about the size of one adult thumb), collected in a clean, dry, screw-capped container. The specimens are collected, labeled and then transported in the 'cold chain'.

Two types of cell lines are used for poliovirus isolation from the stools. The RD cell lines (derived from human rhabdomyosarcoma) which favor growth of all enteroviruses and L20B cell lines which favor the growth of only polioviruses. If cytopathic effects appears in L20B cell line, the isolate then goes for neutralization test to determine the serotype (type 1, 2, or 3) of the poliovirus by using appropriate antisera. An intratypic differentiation test is done to determine whether the particular isolate is wild poliovirus or vaccine poliovirus. All wild poliovirus isolates also undergo genetic sequencing.

A case is classified as *polio* if wild poliovirus is isolated from the stool specimen. Cases with inadequate stool specimens and having residual weakness, who have died or are lost to followup undergo additional investigation and are presented for review by the National Expert Review Committee. This committee classifies the case as *compatible with polio* or *discarded as nonpolio AFP*.

Experience in other parts of the world indicates that at least 1 case of nonpolio AFP occurs for every 1,00,000 children aged <15 yr per year ('background' AFP rate). As per National Polio Surveillance Project, the nonpolio AFP rate, an indicator of surveillance sensitivity, should be equal or to more than 1:100,000.

Suggested Reading

Field Guide. Surveillance of acute flaccid paralysis. 3rd edn. New Delhi: Ministry of Health and Family Welfare, Government of India;2005

Francis PT. Surveillance of acute flaccid paralysis in India. The Lancet 2007;369:1322–3

NEUROMUSCULAR JUNCTION DISORDERS

Disorders affecting the neuromuscular junction can be acquired or inherited (Table 19.4). They are usually pure motor syndromes affecting proximal, bulbar or extra-ocular muscles.

Table 19.4: Neuromuscular junction disorders in children

Immune mediated	**Metabolic causes**
Myasthenia gravis	Botulism
Lambert-Eaton myasthenic syndrome	Organophosphate poisoning
Congenital myasthenic syndromes	Snake envenomation
Choline acetyltransferase deficiency	Tick paralysis
Paucity of synaptic vesicles	Hypermagnesemia
Endplate acetyl-cholinesterase deficiency	**Drugs**
Acetylcholine receptor defects	Aminoglycosides
Mutations in rapsyn or plectin	Erythromycin
Dok-7 deficiency	Tetracycline
	Fluoroquinolones
	Neuromuscular blocking agents
	Phenytoin
	D-penicillamine
	Lithium
	Interferon α

Myasthenia Gravis

About 20% of all patients with myasthenia gravis have onset in childhood or adolescence. Fatigable weakness is the hallmark. Most patients have ptosis or ophthalmoplegia which may be asymmetric and variable over time. Pupillary reactions are normal. Children may develop diplopia especially on sustained gaze or continuous activity like reading. On attempting to tightly close the eyes, after few minutes, the cornea may get exposed due to inability to sustain contraction of orbicularis oculi ('peep' sign).

About half of the children with ocular findings may develop bulbar or limb girdle weakness within 2 yr. Bulbar weakness may manifest in form of difficulty in swallowing and chewing and nasal and slurred speech. Limb weakness is usually symmetric and proximal. Deep tendon reflexes are either normal or reduced in proportion to the degree of muscle weakness. Respiratory muscles may also get involved and may lead to *myasthenic crises*.

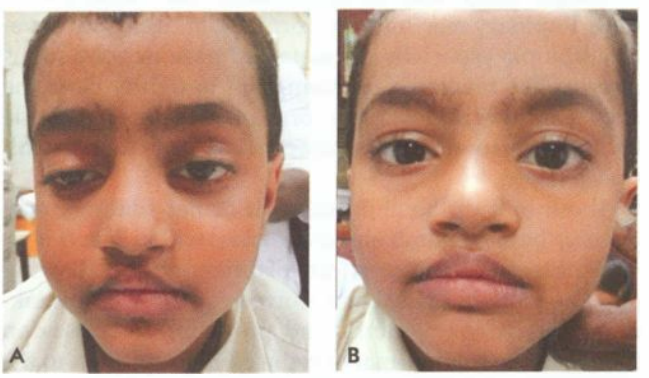
Myasthenia gravis may be associated with thyroid disorders, systemic lupus erythematosus, diabetes mellitus and rheumatoid arthritis. Thymomas are found mainly in adolescent onset myasthenia gravis and are rare (<5%) in early childhood.

Transitory neonatal myasthenia may occur in about 15% of babies born to myasthenic mothers. Symptoms usually start within few hours afterbirth but may be delayed till the third day. These include difficulty in feeding, weak cry, hypotonia, lack of facial expression and respiratory insufficiency. Supportive care suffices in majority of the cases. Oral or intramuscular pyridostigmine, usually for 4–6 weeks, may be warranted in severe cases.

Edrophonium testing is usually the first test performed in a suspected case of myasthenia gravis. The dose used is 0.1-0.2 mg/kg [may be repeated every minute to a total maximum dose of 5 mg (weight <34 kg) or 10 mg (weight >34 kg)]. Effects are seen within 10 seconds and persist till 120 seconds. A positive result consists of transient resolution of the clinical sign (ptosis/ophthalmoplegia/dysarthria) under observation. Edrophonium is not recommended for use in infants due to high risk of arrhythmias and short duration of action which precludes objective assessment. *Neostigmine* can be used as a diagnostic test by intramuscular injection. The dose used is 0.125 mg/kg in an infant and 0.04 mg/kg in an older child. It is slower in action, with anticipated response in 10–15 min and maximum in 30 min (Fig. 19.6). If the result is equivocal or negative, the dose may be repeated in 4 hr.

Repetitive nerve stimulation studies are abnormal in 50–70% cases with generalized myasthenia gravis. A decrement of >10% is characteristic. Electromyography may be normal or may show unstable or myopathic muscle unit action potentials. Single fiber electromyography is more sensitive and may show increased jitter or blocking.

Acetylcholine receptor (AChR) antibodies may be positive in children with myasthenia gravis. The positivity rates are lower in peri- and prepubertal children (50–60%). Antibodies to muscle specific kinase (Anti-MuSK) antibodies may be demonstrable in 40% seronegative myasthenia gravis patients. X-ray chest or CT of ante mediastinum may show thymoma or thymic hyperpl



Figs 19.6A and B: A 9-yr-old boy presented with drooping of eyelids, more in the evening than morning, and restricted eye movements. Examination revealed asymmetric ptosis, external ophthalmoplegia, normal pupils and normal motor examination. Neostigmine challenge test was performed. Note the improvement in ptosis between (A) before and (B) after administration of neostigmine. A diagnosis of juvenile myasthenia gravis was made

Congenital Myasthenia Syndromes

The congenital myasthenia syndromes are exceptiona rare. They should be suspected in seronegative myasthe gravis, floppy infant with underdeveloped muscles anc adults with childhood history of difficulties affecti cranial, respiratory, truncal or limb muscles. Common fe tures include hypotonia, limb weakness, feedir difficulties, respiratory difficulties, arthrogryposis, ptosi ophthalmoparesis, dysphagia and dysarthria. The clinic presentation, electrophysiological features and geneti studies help to differentiate between these subtypes. The do not respond to steroids and other immunosuppres sants. Conditions like endplate acetylcholinesterase deficiency and slow channel congenital myasthenia may worsen with pyridostigmine.

Treatment

Cholinesterase inhibitors are usually the initial treatment for myasthenia gravis. Pyridostigmine is commonly used at doses of 1–7 mg/kg/day in 4 divided doses. Oral steroids may also be used in a nonacute setting. Prednisolone is started at low doses (0.5 mg/kg/day) and titrated according to clinical response. Azathioprine, cyclosporine, cyclophosphamide and mycophenolate mofetil have been used as steroid sparing drugs or for refractory cases. Drugs that interfere with neuromuscular transmission (Table 19.4) should be used with caution. Thymectomy in seropositive patients may be beneficial.

A myasthenic crisis necessitates cardiorespiratory monitoring and support. It should be differentiated from cholinergic crises due to overdosage of acetylcholine esterase inhibitors. Antecedent events, predominance of cholinergic symptoms, ice pack test and edrophonium challenge test may help to differentiate between the two entities. IVIG or plasmapheresis may be required.

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MUSCLE DISORDERS

Congenital Myopathies

The congenital myopathies are a diverse group of muscle disorders caused by genetic defects in the contractile apparatus of the muscle and defined by distinctive histochemical or ultrastructural changes on muscle biopsy. Majority of these disorders present as 'floppy infant'

syndrome. The common presenting features include hypotonia, static or non-progressive muscle weakness and normal or decreased deep tendon reflexes. Respiratory insufficiency, feeding difficulties, contractures and skeletal deformities may be present. They may also present in late childhood or adulthood.

The serum creatine kinase is either normal or mildly raised. Electromyography reveals myopathic pattern. Clinically these disorders may be indistinguishable from one another, they are typically distinguished by characteristic morphological features observed on skeletal muscle biopsy with new immunohistochemical techniques and electron microscopy. Advances in molecular genetics has also improved our understanding of congenital myopathies. Table 19.5 summarizes the key features of commonly recognized congenital myopathies.

Suggested Reading

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Sharma MC, Jain D, Sarkar C, Goebel HH. Congenital myopathies– a comprehensive update of recent advancements. Acta Neurol Scand 2009; 119:281–92

Muscle Dystrophies

The muscular dystrophies are diseases of muscle membrane or supporting proteins which are generally characterized by pathological evidence of ongoing muscle degeneration and regeneration. Diagnosis of these disorders is based on clinical presentation, genetic testing, muscle biopsy and muscle imaging.

Dystrophinopathies

Dystrophinopathies are a group of disorders resulting from mutations in the dystrophin gene (located on the short arm of X chromosome in the Xp21 region). Duchenne muscular dystrophy is the most common dystrophinopathy with an incidence of 1 in 3500 live male births. Its allelic variant, Becker muscular dystrophy, differs from Duchenne muscular dystrophy by its later age of onset (usually >6 yr of age), later age of wheelchair confinement (>15 yr), more incidence of myalgias, occasional rhabdomyolysis following exercise and early cardiomyopathy.

Over 4700 mutations have been reported in the Leiden Duchenne muscular dystrophy mutation database. Deletion of ≥1 exons is the most common mutation seen (~65%). In dystrophinopathies, 65% of the pathogenic changes are large partial deletions. Mutations in the dystrophin gene can cause Duchenne muscular dystrophy or Becker muscular dystrophy. This is explained by the reading frame hypothesis, which states that mutations that disrupt the reading frame (frame-shift) eventually leads to dystrophin deficiency and usually cause Duchenne muscular dystrophy. In Becker muscular dystrophy, however, mutations maintain the reading frame (inframe mutations) and generally result in abnormal but partly functional dystrophin. The reading frame rule holds true for over 92% of all dystrophinopathies.

Children with Duchenne muscular dystrophy usually become symptomatic before age of 5 yr and may even have history of delayed walking. Gait disturbances often become apparent at 3–4 yr of age. Waddling gait, Gower sign and calf muscle pseudohypertrophy (Fig. 19.7) are classical findings at this stage. Neck flexor muscle weakness is early. Other muscles to show hypertrophy may be vastus lateralis, infraspinatus, deltoid, gluteus maximus, triceps and masseter. The progression of weakness may plateau between 3 and 6 yr of age. Subsequently there is increasing gait difficulty, development of contractures (initially dynamic and then fixed) and increased lumbar lordosis. Natural history studies have shown the age at loss of independent ambulation in untreated Duchenne muscular dystrophy to be between 8.8 and 10.5 yr. After loss of ambulation, there is worsening kyphoscoliosis, increasing upper limb weakness and bulbar dysfunction.

Weakness of intercostal and diaphragmatic muscles with spinal deformity affects the respiratory function. Dropping of vital capacity <20% of normal leads to nocturnal hypoventilation. Cardiomyopathy and arrhythmias are the major cardiac manifestations in Duchenne muscular dystrophy. Children with deletions of exons 48 to 53 are especially prone for cardiac complications. The cause of death in Duchenne muscular dystrophy patients is usually a combination of respiratory insufficiency and

Table 19.5: Classification of congenital myopathies

Congenital myopathy	*Inheritance*	*Histopathology*
Structured congenital myopathy		
Central core disease	AD, AR*, sporadic	Cores in type I muscle fibers
Multi-mini-core disease	AD, AR	Both fiber types are poorly defined and with short cores
Nemaline myopathy	AD, AR, sporadic	Nemaline bodies on trichrome stain
Centronuclear or myotubular	X-linked, AD, sporadic	Central nuclei in all muscle fibers
Desminopathies	AD, AR	Desmin positive myofibrillar aggregates
Myosin myopathies	AD, AR	Variable, type I fiber predominance, hyaline bodies
Unstructured congenital myopathy		
Congenital fiber type disproportion	AD, AR, X-linked	Type I fiber predominance, small type I fibers

* Autosomal recessive (AR); Autosomal dominant (AD)

cardiomyopathy. Other clinical features of Duchenne muscular dystrophy include variable degree of intellectual disability and impaired gastric motility.

Around 10% of female carriers may show variable degree of weakness with elevated creatine kinase levels, calf hypertrophy, myalgias and cramps and increased risk of dilated cardiomyopathy. Full Duchenne muscular dystrophy phenotype may be present in case of complete inactivation of normal X chromosome.

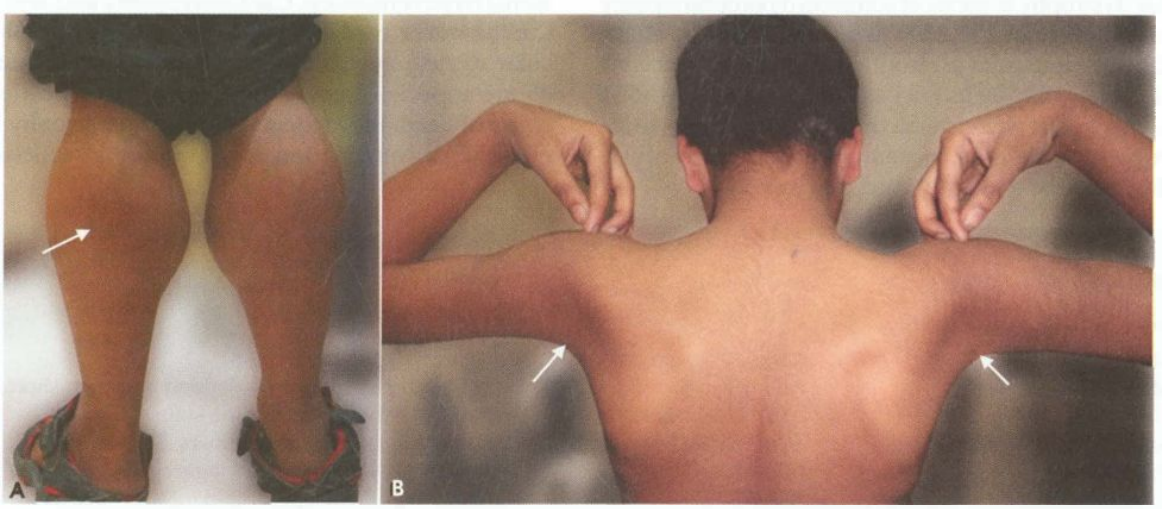
The serum *creatine kinase* levels are greatly elevated (>10 times upper limit of normal). It has no correlation with severity of the disease or response to treatment. Multiplex PCR and the more sensitive multiplex ligation-dependent probe amplification (MLPA) are commonly employed genetic techniques for detection of mutations. *Muscle biopsy* may be required in mutation negative cases and also to differentiate between these two dystrophinopathies. The muscle biopsy shows features of muscular dystrophy which include necrosis and attempted regeneration of individual muscle fibers, increased variability of muscle fiber diameter with both hypertrophic and small fibers, and central nuclei. In an end-stage biopsy, almost the entire muscle is replaced by fibrofatty tissue. To confirm the clinical diagnosis immunohistochemical analysis of the muscle biopsy is usually performed. Absence of dystrophin (1, 2 and 3) staining is seen in Duchenne muscular dystrophy whereas it is reduced and patchy in Becker muscular dystrophy.

Management Management of a child with Duchenne muscular dystrophy requires a multidisciplinary team. The mainstays of management are maintenance of strength and joint range of motion by exercise, physiotherapy and avoidance of prolonged immobility. Corticosteroids (prednisone and deflazacort) are the only therapies proven to improve strength and prolong ambulation in children with Duchenne muscular dystrophy. Low dose prednisolone may be started with aim of preserving upper limb strength, reducing progression of scoliosis and delaying the decline in respiratory and cardiac function. Other supportive management includes pulmonary and cardiac care, nutrition, calcium homeostasis, appropriate immunization and orthopedic care. Table 19.6 summarizes the management in a child with Duchenne muscular dystrophy.

Myotonic Dystrophy Type 1

It is the most common muscular dystrophy encountered in adults. It is a multisystem disorder transmitted by autosomal dominant inheritance and is caused by an abnormal expansion (>80) of $[CTG]_n$ repeats in the *DMPK* gene located on chromosome 19. The classic form presents in childhood with myotonia, facial weakness, distal limb weakness, cataracts (iridescent spoke-like posterior capsular cataract), frontal baldness, endocrinopathies (testicular atrophy, hyperinsulinism, adrenal atrophy and growth hormone disturbances), cardiac arrhythmias and disturbed gastrointestinal motility. The *congenital form* may present with respiratory failure, poor feeding, hypotonia, facial diplegia, clubfoot and gastroparesis. Myotonia is absent in neonates and infants. There may be a history of decreased fetal movements and polyhydramnios in the mother. The serum creatine kinase levels are variable. Electromyography may show myopathic pattern along with myotonia ('revving engine' sound). Genetic testing is confirmatory.

Treatment is symptomatic and wide range of drugs have been used. Drugs that block sodium channels (procainamide, disopyramide, phenytoin, quinine, mexiletine); tricyclic antidepressants (clomipramine, imipramine); diuretics



Figs 19.7A and B: A child presented with progressive gait difficulties and lurching gate. Examination revealed proximal muscle weakness, more in the lower limbs, calf hypertrophy and positive Gower sign, leading to a diagnosis of Duchenne muscular dystrophy. (A) Calf pseudohypertrophy is shown; (B) examination in another child shows hypertrophy of deltoid and infraspinatus with wasting of posterior axillary fold muscles ('Valley' sign)

Table 19.6: Management of Duchenne muscular dystrophy

Corticosteroids

Indication. Children >2 yr with static or declining function

Dose. Prednisolone, 0.3–0.75 mg/kg/day (initially 0.3 0.6 mg/kg/day if non-ambulatory)
Deflazacort, 0.9 mg/kg/day (preferred in children with excessive weight gain or behavioral problems)

Ensure immunization against pneumococcus, influenza and varicella before starting steroids

Monitoring

Pulmonary function tests: Every 6 months if non-ambulatory; annually in ambulatory patients

Echocardiography: Once in 2 yr for <10 yr of age; annually if >10 yr)

Serum calcium, phosphate, 25(OH) vitamin D3 (biannually)
EXA scan annually

Physical therapy

Effective stretching and appropriate positioning at various joints, assistive devices to prevent contractures, avoid high resistance strength training

Surgery. For fixed contractures and spinal deformities

Other components

Respiratory and cardiac care
Management of gastrointestinal problems
Psychosocial management
Family education and genetic counseling

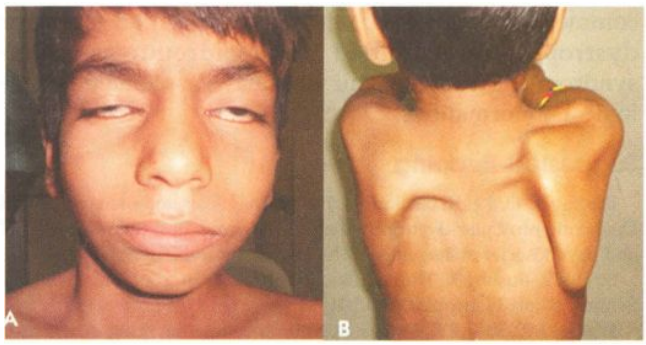
Newer therapies

Exon skipping, gene therapy, cell therapy, pharmacological approaches (utrophin upregulation, read through compounds, myostatin inhibitors)

(acetazolamide, thiazides) and other drugs (taurine, nifedipine, diazepam, carbamazepine, prednisone and beta-agonist such as albuterol) have been used. A Cochrane review concluded that it was not possible to determine whether drug treatment was safe and effective for myotonia. Larger, well-designed randomized controlled trials are needed to assess the efficacy and tolerability of drug treatment for myotonia.

Facioscapulohumeral Muscular Dystrophy

It is inherited in an autosomal dominant fashion. The clinical spectrum is wide ranging from aymptomatic children to wheelchair bound patients. Age at onset is also variable. The disease may start with asymptomatic facial weakness followed sequentially by scapular fixator, humeral, truncal and lower extremity weakness. Biceps and triceps are typically involved with sparing of deltoid and forearm muscles resulting in the "popeye" arm appearance. Lower abdominal muscles are weaker than the upper abdominal muscles resulting in Beevor sign. The progression of weakness is typically slow. Extraocular and bulbar muscles are spared and contractures are rare. Side-to-side asymmetry of muscle weakness is very typical (Fig. 19.8). Extramuscular manifestations include high frequency hearing loss, Coats' disease (retinal telangiectasia with exudation and



Figs 19.8A and B: A child with facioscapulohumeral dystrophy. (A) Note the facial weakness and inability to close the eyes completely; (B) asymmetric scapular winging

detachment), atrial arrhythmias and restrictive respiratory disease. Serum creatine kinase levels are variable. EMG and muscle biopsy are nonspecific. Diagnosis is clinical and confirmed by demonstrating the presence of contraction of the D4Z4 repeats in one copy of 4q 35. Treatment is mainly supportive.

Emery-Dreifuss Muscular Dystrophy

It is characterized by slowly progressive muscle wasting and weakness in humeroperoneal distribution, early contractures especially of elbows, Achilles tendon and postcervical muscles and cardiac conduction defects. Cardiac involvement is the most serious aspect of the disease and may even occur before any significant muscle weakness. X-linked forms, autosomal dominant or recessive forms may be seen. There is no specific treatment available currently.

Limb Girdle Muscular Dystrophy

Limb girdle muscular dystrophy is a group of clinically heterogenous syndromes consisting of different specific disease entities. They may be autosomal dominant or recessive in inheritance. Most childhood onset limb girdle muscular dystrophies are associated with lower extremity predominant weakness. The neck flexors and extensors may be involved. Facial weakness is usually mild. Cardiac or other systemic involvement is variable. Serum creatine kinase is usually modestly elevated but can be very high in the sarcoglycanopathies, dysferlinopathy and caveolinopathy. The autosomal recessive limb girdle muscular dystrophies generally have an earlier onset, more rapid progression and higher creatine kinase values. Treatment is symptomatic.

Congenital Muscular Dystrophy

They usually present at birth or in first year of life. The affected infant shows hypotonia, weakness, arthrogryposis, bulbar dysfunction or respiratory insufficiency. Weakness is static or slowly progressive. Diagnosis is supported by dystrophic myopathic features on muscle biopsy, elevated creatine kinase levels and exclusion of

common myopathies of newborn. Congenital muscular dystrophies are divided into syndromic and non-syndromic. The syndromic ones have associated neurological abnormalities.

Suggested Reading

Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, Part 1: Diagnosis and pharmacological and psychosocial management. The Lancet Neurol 2010;9:77–93

Straub V, Bushby K. The childhood limb-girdle muscular dystrophies. Semin Pediatr Neurol 2006;13:104–14

Wattjes MP, Kley RA, Fischer D. Neuromuscular imaging in inherited muscle diseases. Eur Radiol 2010;20:2447–60

Inflammatory Myopathies

The inflammatory myopathies are a diverse group of disorders in which muscle appears to be injured by the immune system. Dermatomyositis is the most common pediatric inflammatory myopathy. Polymyositis is rare in childhood and inclusion body myositis mainly occurs above 50 yr of age.

Juvenile Dermatomyositis

It is a small vessel vasculitis which typically affects skin and muscle but may involve joints, gut, lung, heart and other internal organs (*see* also Chapter 21). Autoantibodies are commonly seen. The mean age of onset is around 7 yr and is more common in girls. The child can have acute or insidious onset. Fever, malaise, anorexia, weight loss or irritability may be present at the onset. In half of the cases, rash is concomitant with the muscle weakness but may precede the weakness. The dermatologic manifestations include 'heliotrope' rash, confluent macular violaceous erythema over face, neck and anterior chest ('V' sign) and upper back ('shawl' sign). The skin over metacarpal and interphalangeal joints may be discolored and hypertrophic (Gottron papules) (Fig. 19.9). Pruritus may be problematic. Nailfold capillaroscopy may reveal capillary drop-out and terminal bush formation.

The muscle weakness is symmetrical and proximal. Weakness of neck flexors and dysphagia is common. The serum creatine kinase is usually elevated. Electromyography reveals myopathic changes with occasional evidence of denervation. The muscle MRI may reveal multifocal or diffuse hyperintensities on T2-weighted images with fat suppression which is more marked in proximal limb muscles. It may also guide the site for muscle biopsy. The muscle biopsy may reveal perimysial perifascicular atrophy, perivascular inflammatory cells and absence of multiple myofibers surrounded by inflammatory cells.

The primary modality of treatment for juvenile dermatomyositis remains corticosteroids (oral or intravenous pulses). Methotrexate and azathioprine are other first line agents. Physical therapy, photoprotection, topical therapies for skin rash, calcium and vitamin D supplementation are other adjunctive therapies. Other therapies include intravenous immunoglobulin, cyclosporine, cyclophosphamide, mycophenolate mofetil, rituximab and anti-TNF-α agents.

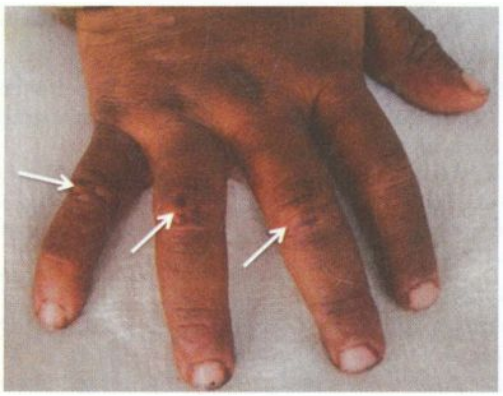


Fig. 19.9: Gottron papules in a child with juvenile dermatomyositis. One needs to examine carefully in a dark-skinned child

Suggested Reading

Wedderburn LR, Rider LG. Juvenile dermatomyositis: new developments in pathogenesis, assessment and treatment. Best Pract Res Clin Rheumatol 2009;23:665–78

Metabolic Myopathy

The metabolic myopathies are a group of muscle disorders resulting from failed energy production related to defects in glycogen, lipid, or mitochondrial metabolism. The symptoms arise due to a mismatch between the rate of ATP utilization and the capacity of the muscle metabolic pathways to regenerate ATP. Affected older children and adults present primarily with exercise intolerance, weakness and myoglobinuria; newborns and infants present with severe multisystem disorders. Most metabolic myopathies have dynamic rather than static findings. Some children may present with progressive proximal muscle weakness mimicking a dystrophy or an inflammatory myopathy.

In patients with glycolytic/glycogenolytic defects, symptoms are induced by either brief isometric exercise, such as lifting heavy weights, or by less intense but sustained dynamic exercise. With disorders of lipid metabolism the abnormalities are usually induced by prolonged exercise and prolonged fasting. Plan of investigations include serum creatine kinase, urine myoglobulin, serum ammonia, tandem mass spectroscopy, gas chromatography mass spectrometry, electrophysiological studies, forearm ischemia exercise test, muscle biopsy and molecular studies.

Suggested Reading

Darras BT, Friedman NR. Metabolic myopathies: A clinical approach; part I. Pediatr Neurol 2000;22:87–97

Darras BT, Friedman NR. Metabolic myopathies: A clinical approach; part II. Pediatr Neurol 2000; 22: 171–81

Childhood Malignancies 20

Sadhna Shankar, Rachna Seth

Childhood cancers are a rare but important cause of morbidity and mortality in children younger than 15 yr of age. Malignancies in children are often difficult to detect because the signs and symptoms are often nonspecific and mimic many common disorders of childhood. Cancers in children, when compared to adult cancers, are clinicobiologically distinct and are considered as potentially curable; pediatric tumors are known to be more aggressive but responsive to chemotherapy when compared to adult cancers. Common childhood malignancies include leukemias (30–40%), brain tumors (20%) and lymphoma (12%) followed by neuroblastoma, retinoblastoma and tumors arising from soft tissues, bones and gonads.

LEUKEMIA

Leukemia is a malignancy that arises from clonal proliferation of abnormal hematopoietic cells leading to disruption of normal marrow function leading to marrow failure. The clinical manifestations of leukemia are the result of the unregulated proliferation of the malignant clone and bone marrow failure. Leukemia is the most common cancer in children. There are two main subtypes, the commoner acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). A small proportion may have chronic myeloid leukemia (CML) and juvenile myelomonocytic leukemia (JMML).

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

ALL is the most common childhood malignancy accounting for one-fourth of all childhood cancers and three-fourths of all newly diagnosed patients with acute leukemia. Its incidence is approximately 3–4 cases per 100,000 children below 15 yr of age. There is a peak in the incidence of childhood ALL, between the ages of 2 and 5 yr, due to ALL associated with a pre-B lineage (referred to as *common* ALL). Boys have higher rates than girls, especially in adolescents with T cell ALL.

The etiology of ALL remains unknown in a majority of cases. However, several genetic syndromes have been associated with an increased risk of leukemia. In particular, there is a 10–20 fold increased risk of leukemia (ALL and AML) in children with Down syndrome. Other genetic syndromes associated with leukemia include Bloom syndrome, Fanconi anemia, neurofibromatosis, Klinefelter syndrome, immunodeficiency and ataxia-telangiectasia. Exposure to ionizing radiation, certain pesticides and parental smoking are associated with a higher incidence of ALL. Patients having received therapeutic irradiation and aggressive chemotherapy (alkylating agents, epipodophyllotoxins) are at higher risk of developing acute leukemia (Table 20.1).

Morphology

The classification of ALL has evolved over the years from one that was primarily morphology based to one which

Table 20.1: Risk factors for childhood leukemia

Genetic	*Environmental*
Down syndrome	Ionizing radiation
Fanconi anemia	Alkylating agents (cyclophosphamide, ifosfamide, carboplatin, procarbazine)
Shwachman-Diamond syndrome	
Bloom syndrome	Epipodophyllotoxins (etoposide, tenoposide)
Ataxia telangiectasia	
Diamond-Blackfan anemia	Nitrosourea (nitrogen mustard)
	Benzene
Kostmann syndrome	
Li-Fraumeni syndrome	
Severe combined immune deficiency	
Paroxysmal nocturnal hemoglobinuria	
Neurofibromatosis type 1	

is currently based on immunophenotyping, karyotyping and molecular biology techniques. ALL cells can be classified using the French-American-British (FAB) criteria into morphologic subtypes (Table 20.2). L1 morphology lymphoblasts, are the most common subtype of childhood ALL (80–85%), have scant cytoplasm and inconspicuous nucleoli; these are associated with a better prognosis. Patients in the L2 category, accounting for 15% cases, show large, pleomorphic blasts with abundant cytoplasm and prominent nucleoli. Only 1–2% patients with ALL show L3 morphology in which cells are large, have deep cytoplasmic basophilia and prominent vacuolation; these cells show surface immunoglobulin and should be treated as Burkitt lymphoma.

Immunophenotype

Immunophenotype classification describes ALL as either B cell derived or T cell derived. Progenitor B cell derived ALL constitutes 80–85% ALL, 15% are derived from T cells and 1–2% from mature B cells (Table 20.3).

Cytogenetics

Genetic abnormalities found in the leukemic clone greatly impact the therapy and prognosis of ALL. Conventional cytogenetics and fluorescence *in situ* hybridization should be performed on the bone marrow specimen to look for common genetic alterations in ALL.

The presence of hyperdiploidy (chromosome number >50, DNA index >1.16) is associated with good prognosis in contrast to the poor prognosis in patients with hypodiploidy. Specific chromosomal translocations in ALL, including t(8;14, associated with Burkitt leukemia) in B cell ALL, t(4;11) in infant leukemia and t(9;22) translocation, that forms the Philadelphia chromosome, are associated with a poor prognosis. Certain chromosomal abnormalities are associated with a favorable prognosis like t(12;21) and simultaneous presence of trisomy 4 and 10. Common genetic alterations and their clinical impact are listed in Table 20.4.

Prognostic Factors and Risk Assessment

The two most important prognostic factors include age at diagnosis and the initial leukocyte count. Children less than 1-yr-old have an unsatisfactory prognosis; infant leukemia is often associated with t(4;11) translocation and high leukocyte counts. Children between the ages of 1 and 9 yr do well. The presence of leukocyte count more than 50,000/mm^3 at diagnosis is associated with a bad prognosis. Relapse rates are higher in boys. While patients with B cell leukemia (L3 morphology) previously had unsatisfactory outcome, the prognosis has improved with specific B cell leukemia directed protocols. The presence of T cell leukemia is not a poor prognostic factor unless associated with other risk factors, including high leukocyte count, mediastinal mass or disease affecting the central nervous system at diagnosis. Patients showing hyperdiploidy have a good prognosis, while presence of hypodiploidy is associated with an unsatisfactory outcome. Philadelphia positive t(9;22) ALL and translocation t(4;11) which is present in infant leukemia are associated with poor prognosis. A lack of response to treatment with prednisone is considered a prognostic

Table 20.2: The French-American-British (FAB) classification for acute lymphoblastic leukemia

Cytologic features	*L1 (80–85%)*	*L2 (15%)*	*L3 (1–2%)*
Cell size	Small cells predominate; homogeneous	Large cells; heterogeneous	Large cells; homogeneous
Cytoplasm	Scanty	Variable; often moderately abundant	Moderately abundant
Nucleoli	Small; inconspicuous	One or more; often large	One or more; prominent
Nuclear chromatin	Homogeneous	Variable; heterogeneous	Stippled; homogeneous
Nuclear shape	Regular; occasional clefts	Irregular clefts; indentation	Regular; oval to round
Cytoplasmic basophilia	Variable	Variable	Intensely basophilic
Cytoplasmic vacuolation	Variable	Variable	Prominent

Table 20.3: Correlation of subtypes of acute lymphoblastic leukemia with surface markers

Type	*Surface markers*	*Comment*
Precursor B cell	CD79a+, CD18+, CD19+, CD20+, HLA DR+	Presence of CD10 (common ALL antigen, CALLA) represents a favorable prognosis; absence of CD10 (pro-B ALL) is associated with translocations of *MLL* gene, particularly t(4;11), and poor outcome
Mature B cell	CD19+, CD20+, CD21+, sIg+	Correlates with L3 leukemia; needs intensified regime
T cell	CD3+, CD7+, CD2+ or CD5+	Affects older children; associated with leukocytosis, mediastinal mass and involvement of central nervous system

sIg surface immunoglobulin

Table 20.4: Genetic abnormalities in acute lymphoblastic leukemia (ALL)

Chromosomal abnormality or translocation; affected gene	*Subtype*	*Frequency (%)*	*Implication*
Hyperdiploidy (>50 chromosomes)	Pre-B	20–30	Excellent prognosis
Hypodiploidy (<44 chromosomes)	Pre-B	1–2	Poor prognosis
Trisomies 4 and 10	Pre-B	20–25	Excellent prognosis
t(12;21)(p13;q22); *ETV6 (TEL)* and *RUNX1 (AML1)* fusion (hybrid gene)	Pre-B	15–25	Excellent prognosis
t(1;19)(q23;p13); *TCF3-PBX1* fusion	Pre-B	2–6	High risk; probable CNS relapse
t(4;11)(q21;q23); *AF4-MLL* fusion	Pre-B	1–2	Infantile ALL; poor prognosis
t(9;22)(q34;q11.2); *ABL1- BCR* fusion (Philadelphia chromosome)	Pre-B	2–4	Improved outcome with use of imatinib and chemotherapy
t(8;14)(q23;q32.3); MYC-IgL fusion	Mature B cell	2	Burkitt leukemia; favorable outcome with Burkitt lymphoma-like protocol
Hox 11 rearrangement	T	7–8	Good prognosis
Early T cell precursor phenotype	T	12	Poor prognosis

factor; patients showing ≥1,000/mm^3 blasts in peripheral blood following 7 days treatment with prednisone and an intrathecal dose of methotrexate are likely to have an adverse outcome.

B cell ALL, age between 1 and 9 yr, total leukocyte count less than 50,000/mm^3 at diagnosis, female sex, absence of mediastinal widening, lymphadenopathy and organomegaly, absence of CNS disease, hyperdiploidy and certain chromosomal abnormalities (trisomy 4 and 10) at diagnosis constitute low risk ALL (Table 20.5). The rapidity with which leukemia cells are eliminated following onset of treatment is associated with longterm outcomes. Treatment response is influenced by the drug sensitivity of leukemic cells and host pharmacodynamics and pharmacogenomics.

Table 20.5: Prognostic features in acute lymphoblastic leukemia

Feature	*Standard risk*	*High-risk*
Age	2–10 yr	Below 1 yr; >10 yr
Sex	Female	Male
Initial white cell count	<50,000/mm^3	>50,000/mm^3
Hepatosplenomegaly	Absent	Massive
Lymphadenopathy	Absent	Massive
Mediastinal mass	Absent	Present
Central nervous system leukemia	Absent	Present
Phenotype	Pre-B (T cell intermediate)	Mature B cell
Ploidy	Hyperdiploidy	Hypodiploidy
Cytogenetics	t(12;21), trisomy 4 and 10	t(9;22); t(4;11); t(8;14)
Response to treatment	Good early response	Poor early response
Minimal residual disease after first induction	Negative	Positive

Clinical Presentation

The duration of symptoms in a child with ALL may vary from days to weeks and in some cases few months. The clinical features of ALL are attributed to bone marrow infiltration with leukemic cells (bone marrow failure) and extramedullary involvement. Common features include pallor and fatigue, petechiae or purpura and infections. Lymphadenopathy, hepatomegaly and splenomegaly are present in more than 60% patients. Bone or joint pain and tenderness may occur due to leukemic involvement of the periosteum of bones or joints. Infants and young children may present with a limp or refusal to walk. Tachypnea and respiratory distress may be present secondary to severe anemia leading to congestive heart failure or secondary to the presence of mediastinal mass leading to tracheal compression (superior mediastinal syndrome). A large mediastinal mass may sometimes cause superior vena cava syndrome with facial edema and plethora, throbbing headache, conjunctival congestion and dilated neck veins. Patients with high tumor burden can occasionally present with very high total white cell count (hyperleukocytosis,TLC >1,00,000/mm^3) or tumor lysis syndrome with decreased urine output and azotemia secondary to uric acid nephropathy.

Few patients (2–5%) show central nervous system involvement at diagnosis; most are asymptomatic but some have features of raised intracranial pressure. The diagnosis of CNS leukemia is made on examination of the cerebrospinal fluid. Overt testicular leukemia may be seen in about 1% of cases. It presents with firm, painless, unilateral or bilateral swelling of the testes; the diagnosis is confirmed by testicular biopsy. Other rare sites of extramedullary involvement include heart, lungs, kidneys, ovaries, skin, eye or the gastrointestinal tract.

Diagnosis and Differential Diagnosis

Clinical presentation and peripheral blood counts and morphology are indicative of the diagnosis of ALL.

Children may present with pancytopenia or hyperleukocytosis. The diagnosis is confirmed by peripheral smear examination and or bone marrow aspirate and biopsy. It is important to do both an aspirate as well as biopsy at time of initial diagnosis. Very rarely leukemic cells may be seen only in the biopsy specimen and not in the aspirate. Higher white blood cell counts are more common with T cell ALL. Bone marrow showing >25% lymphoblasts is diagnostic for ALL (Fig. 20.1). While morphology of the leukemic blasts can give important clues to the diagnosis, it needs to be confirmed by immunophenotyping of the bone marrow. Immunophenotype differentiates the cellular lineages of ALL into pre-B, T cell and mature B cell. This distinction has therapeutic implications. Evaluation of CSF for leukemic blasts to determine CNS involvement is important for staging of leukemia. The first spinal tap must be performed ideally with platelet count close to 1,00,000/mm^3. Children with CNS leukemia require intensive CNS directed therapy (Table 20.6).

The clinical profile of acute lymphoblastic leukemia may mimic many other clinical conditions like infectious mononucleosis, acute infectious lymphocytosis, idiopathic thrombocytopenic purpura, aplastic anemia and viral infections like cytomegalovirus that result in leukemoid reactions and pancytopenia. Idiopathic thrombocytopenic purpura is the most common cause of acute onset of petechiae and purpura in children. Children with ITP have no evidence of anemia and have normal total and differential leukocyte count. Bone marrow smear reveals normal hematopoiesis and normal or increased number of megakaryocytes. ALL must be differentiated from aplastic anemia, which may present with pancytopenia. The condition may also be mistaken for juvenile rheumatoid arthritis in patients presenting with fever, joint symptoms, pallor, splenomegaly and leukocytosis. ALL should be distinguished from other malignancies (neuroblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma, Ewing sarcoma and retinoblastoma) that present with bone marrow involvement. Morphologic, cytochemical, immunophenotypic and cytogenetic characteristics of the malignant cells should be done. Occasionally, patient with ALL may present with hypereosinophilia or as an emergency with very high white cell count (hyperleukocytosis, TLC >1,00,000/mm^3), life-threatening infections, hemorrhage, organ dysfunction secondary to leukostasis or signs and symptoms of superior vena cava or superior mediastinal syndrome.

Table 20.6: Evaluation of a child with suspected leukemia

History and physical examination
Complete blood count and differential count
Peripheral smear examination (morphology of cells and blasts; blast count; platelet count; immunohistochemistry; immunophenotype)
Chest X-ray (include lateral view if mediastinal mass present)
Electrolytes, urea, creatinine uric acid, LDH, calcium, phosphate, bilirubin, SGOT and SGPT
Coagulation profile
Bone marrow aspirate: Morphology, immunophenotype, cytogenetics and FISH
Bone marrow biopsy
CSF cytology (diagnostic and to administer the first intrathecal dose of methotrexate)

FISH Fluorescence *in situ* hybridization; CSF cerebrospinal fluid

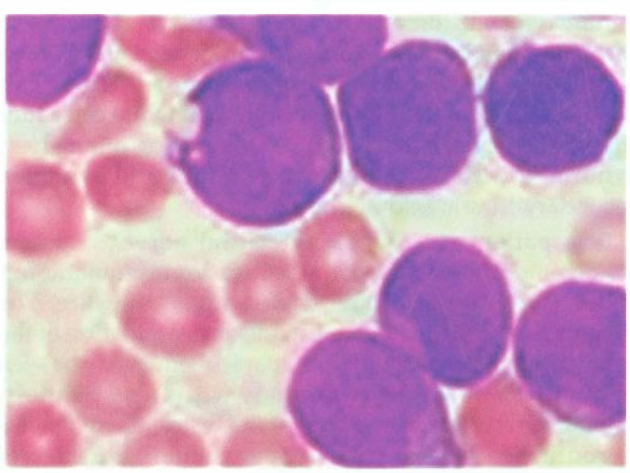


Fig. 20.1: Bone marrow from a child with acute lymphoblastic leukemia shows reduced marrow elements and replacement by lymphoblasts. Neoplastic lymphoblasts are slightly larger than lymphocytes and have scant, faintly basophilic cytoplasm and round or convoluted nuclei with inconspicuous nucleoli and fine chromatin, often in a smudged appearance

Management

The management of acute leukemia needs the combined effort of a number of health professionals. Improvement in survival from ALL with modern therapy is one of the greatest successes in the field of pediatric oncology. Improvement in supportive care and use of combination chemotherapy has led to a survival more than 80% overall and greater than 95% in children with low risk ALL. Treatment is determined by the risk of relapse in each patient.

Risk based approach allows use of modest therapy for children who have historically had very good outcome thereby avoiding the toxic adverse effects of high intensity therapy. Children with historically poor survival are treated with high intensity therapy to increase cure rates. The three most important determinants of this risk are age at presentation, total WBC count at presentation and response to initial therapy. Age 1–9 yr and WBC count <50,000/mm^3 is considered average risk by most study groups. Infants <1 yr of age and children >10 yr are at a higher risk and require more intensive therapy. Infants <6 months of age have extremely poor outcome. Patients with Philadelphia chromosome, t (9;22) and t(4;11) have a high-risk of relapse. Patients with slow initial response

require more intensive therapy to achieve cure than those with early response.

The treatment of ALL requires the control of bone marrow or systemic disease, as well as treatment (or prevention) of extramedullary disease in sanctuary sites, particularly the central nervous system. Different centers use different protocols for childhood ALL (Table 20.7), with 5 yr survival rates above 80–85%.

The treatment on ALL is divided into 4 stages: (i) induction therapy (to attain remission), (ii) CNS prophylaxis or CNS preventive therapy, (iii) intensification (consolidation) and (iv) maintenance therapy (continuation). The intensification (consolidation) phase, following induction of remission, may not be required in low risk patients, though recent studies suggest benefits in longterm survival with intensification therapy in both low risk and high risk patients. The average duration of treatment in ALL ranges between 2 and 2.5 yr; there is no advantage of treatment exceeding 3 yr.

Induction Therapy

The goal of this phase is to eradicate leukemia from the bone marrow such that at end of this phase there are <5% leukemic blasts in bone the bone marrow by morphology. Patients who achieve rapid early remission (<5% blasts in bone marrow) by day 7 or 14 of induction have a better prognosis than slow responders. Failure to achieve this at end of induction is associated with high-risk of relapse. Induction therapy generally consists of 4 weeks of therapy. The drug regimen combining vincristine and prednisone induces remission in 80–95% patients with ALL. Since the remission rate and duration are improved by the addition of a third and fourth drug (L-asparaginase and/or anthracycline), current induction regimens include vincristine, prednisone, L-asparaginase and an anthracycline, with remission achieved in 95–98% of cases. The induction therapy lasts for 4–6 weeks.

CNS Preventive Therapy

Most children with leukemia have subclinical CNS involvement at the time of diagnosis and this acts as a sanctuary site where leukemic cells are protected from systemic chemotherapy because of the blood brain barrier. The early institution of CNS prophylaxis is essential to eradicate leukemic cells which have passed the blood brain barrier. CNS prophylaxis has enabled increased survival rates in leukemia. Most children in the past received a combination of intrathecal methotrexate and cranial irradiation. However, there is considerable concern regarding longterm neurotoxicity and risk of development of brain tumors following this therapy. In order to achieve effective CNS prophylaxis while minimizing neurotoxicity, experts now recommend a lower dose of cranial irradiation with intrathecal methotrexate.

Table 20.7: Chemotherapy protocol for acute lymphoblastic leukemia (MCP 841)

Cycle	*Chemotherapy*	*Dose and schedule*
Induction 1 (I1)	Prednisone	40 mg/m^2 orally on days 1–28
	Vincristine	1.4 mg/m^2 intravenous (IV) on days 1, 8, 15, 22 and 29
	Daunorubicin	30 mg/m^2 IV on days 8, 15 and 29
	L-asparaginase	6000 U/m^2 intramuscular (IM) on alternate days on days 2–20 (10 doses)
	Methotrexate	Intrathecal (IT)* on days 1, 8, 15 and 22
Induction 2 (I2)	6-mercaptopurine	75 mg/m^2 orally on days 1–7 and days 15–21
	Cyclophosphamide	750 mg/m^2 IV on days 1 and 15
	Methotrexate	IT* on days 1, 8, 15 and 22
	Cranial irradiation	200 cGy for 9 days (total 1800 cGy)
Repeat induction 1 (RI1)	Same as induction 1	Doses and schedule as per I1
Consolidation (C)	Cyclophosphamide	750 mg/m^2 IV on days 1 and 15
	Vincristine	1.4 mg/m^2 IV on days 1 and 15
	Cytosine arabinoside	70 mg/m^2 subcutaneously (SC) every 12 hours for 6 doses on days 1–3 and days 15–17
	6-mercaptopurine	75 mg/m^2 orally on days 1–7 and days 15–21
Maintenance (M): 6 cycles	Prednisone	40 mg/m^2 orally on days 1–7
	Vincristine	1.4 mg/m^2 IV on day 1
	Daunorubicin	30 mg/m^2 IV on day 1
	L-asparaginase	6000 U/m^2 IM on days 1, 3, 5 and 7
	6-mercaptopurine	75 mg/m^2 orally daily for 3 of every 4 weeks for a total of 12 weeks; begin on day 15
	Methotrexate	15 mg/m^2 orally once a week for 3 of every 4 weeks for a total of 12 weeks; begin on day 15

*Administered with 5–10 ml normal saline, at a dose of 8 mg at 1–2 yr, 10 mg at 2–3 yr, 12 mg for >3 yr

Intensification (Consolidation) Therapy

This is a period of intensified treatment administered shortly after remission induction with administration of new chemotherapeutic agents to tackle the problem of drug resistance. There is clear evidence that intensification has improved the longterm survival in patients with ALL, especially those with high-risk disease. Commonly used agents for intensification therapy include high dose methotrexate, L-asparaginase, epipodophyllotoxin, cyclophosphamide and cytarabine.

Maintenance (Continuation) Therapy

It has been estimated that approximately two to three logs of leukemic blasts are killed during the induction therapy, leaving a leukemic cell burden in the range of 10^9–10^{10}. Additional therapy is therefore necessary to prevent a relapse.

Once remission is achieved, maintenance therapy is continued for an additional 2–2.5 yr. Without such therapy, patients of ALL relapse within the next 2–4 months. A number of drug combination and schedules are used, some based on periodic reinduction, others on continued delivery of effective drugs. The main agents used include 6-mercaptopurine daily and methotrexate once a week given orally, with or without pulses of vincristine and prednisone or other cytostatic drugs. Monthly pulses of vincristine and prednisolone appear to be beneficial. In intermediate high-risk ALL most investigators use aggressive treatment and additional drugs during maintenance therapy.

Infant ALL

Outcome of ALL remains poor in this group of patients even with very intense therapy including stem cell transplant. Only 30–40% of children with *MLL* t(4;11) gene rearrangement are cured. Role of transplantation remains controversial. Therapy usually includes high dose cytarabine and methotrexate in addition to standard ALL therapy.

Philadelphia chromosome positive ALL

The 3 yr survival for Philadelphia chromosome positive ALL has improved to 80% with use of imatinib.

Other high-risk groups

Hypodiploidy (<44 chromosomes), t(17;19), remission induction failure and presence of minimal residual disease >1% at end of induction is associated with poor prognosis. Most such patients undergo stem cell transplantation.

20

Supportive Care

Because of the complications encountered with treatment and the need for aggressive supportive care like blood component therapy, detection and management of infections, nutritional and metabolic needs and psychosocial support, these children should be treated at centers with appropriate facilities. These children should be given cotrimoxazole as prophylaxis against *Pneumocystis jiroveci* pneumonia. They should be vaccinated against hepatitis B infection and screened for HIV infection. Oral hygiene should be taken care of. Facilities for blood component therapy should be available.

Prognosis

Hypodiploidy, Philadelphia chromosome positivity, T cell ALL, *MLL* rearrangement, *IKZF1* gene deletion, age <1 yr and >10 yr, leukocyte count >50,000/cu mm and presence of CNS disease are poor prognostic features.

Assessment of minimal residual disease (MRD) by PCR assay using immunoglobulin/T cell receptor gene rearrangements or by flow cytometry has been shown to be an important determinant of outcome. These methods can detect one leukemic cell in 10,000 to 100,000 normal cells. Patients with MRD <0.01% on day 29 of induction are at low-risk of relapse.

More that 80% of children with ALL are longterm survivors in the developed countries. However, survival remains poor in the developing nations, chiefly due to infection related mortality.

Approximately 15–20% of patients develop bone marrow relapse with current therapy. Bone marrow relapse occurring within 18 months of diagnosis has worst prognosis. Patients with early bone marrow relapse have very poor survival even with stem cell transplantation. Late isolated CNS relapse (>18 months) can be effectively cured in most cases with cranial radiation and systemic chemotherapy. While children with average risk leukemia may not have many longterm complications, children with high risk disease receive intensive therapy and are at risk for longterm complications. Significant complications include neurocognitive deficits, obesity, cardiomyopathy, avascular necrosis, secondary leukemia and osteoporosis. Children who receive cranial radiation are at risk for neurocognitive deficits, growth hormone deficiency and brain tumors.

Treatment after Relapse

Despite success of modern treatment, 20–30% of children with ALL relapse. The main cause of treatment failure in leukemia is relapse of the disease. Common sites of relapse are the bone marrow (20%), central nervous system (5%) and testis (3%). The prognosis for children with ALL who relapse depends on the site and time of relapse. Early bone marrow relapse before completing maintenance therapy has the worst prognosis and long time survival of only 10–20% while late relapses occurring after cessation of maintenance therapy have a better prognosis (30–40% survival). Relapse in extramedullary sites, particularly testes, is more favorable in terms of survival. The treatment of relapse must be more aggressive than the first line therapy with use of new drugs to overcome the problem of drug resistance.

Allogenic bone marrow transplantation offers a better chance of cure than conventional chemotherapy for children with ALL who enter a second remission after hematologic relapse.

Late Effects of Treatment

Continued followup of these patients for prolonged periods is necessary. Patients who have received cranial irradiation at a younger age are at risk for cognitive and intellectual impairment and development of CNS neoplasms. There is a risk of development of secondary AML after the intensive use of epipodophyllotoxins (etoposide or teniposide) therapy. Endocrine dysfunction leading to short stature, obesity, precocious puberty, osteoporosis, thyroid dysfunction and growth retardation are reported. Patients having received treatment with an anthracycline are at risk of cardiac toxicity.

Down Syndrome and Acute Leukemia

Children with trisomy 21 have a 15–20 fold higher risk of acute leukemia as compared to general population with a cumulative risk of developing leukemia of approximately 2.1%. The ratio of ALL to AML in Down syndrome is as for childhood acute leukemia. Approximately one half–two-thirds of cases of acute leukemia in children with Down syndrome are ALL. The exception is during the first 3 yr of life when AML predominates and exhibits a distinctive biology. In addition, approximately 10% of children with Down syndrome develop a preleukemic clone, transient myeloproliferative disorder, with somatic mutations in hematopoeitic transcription factor *GATA1*. These children have a high leukocyte count, circulating blasts in peripheral blood, hepatosplenomegaly, effusions, anemia and thrombocytopenia in the neonatal period, which resolves by 3 months. About 20% of children with transient myeloproliferative disorder develop AML. Of the patients with Down syndrome and AML, two-thirds have megakaryocytic leukemia (FAB M7). Children with Down syndrome and AML have a superior outcome than those not having Down syndrome. The outcome of children with Down syndrome and ALL is inferior to those with ALL not associated with Down syndrome.

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) also termed as acute non-lymphoblastic leukemia, accounts for 15–20% of leukemia in children. AML is a more complex and resistant disease than ALL and results from clonal proliferation of hematopoeitic precursors of myeloid, erythroid and megakaryocytic lineage.

Epidemiology

AML can occur at any age but the incidence is more during adolescence; males are affected as frequently as females. Congenital leukemia (occurring during first 4 weeks of life) is mostly AML. While the etiology of AML is not known, there is an association following exposure to ionizing radiation. Down syndrome is the most common genetic predisposing factor associated with risk of developing AML during the first three years of life. Other predisposing factors are Fanconi anemia, Blooms syndrome, Kostmann syndrome and Diamond Blackfan anemia. Medications associated with risk of AML include alkylating agents and epipodophyllotoxins.

Pathogenesis

Genetic aberrations in AML suggest alterations that regulate self renewal and differentiation cooperate in the pathogenesis of AML. Several genetic mutations have been identified in AML (Table 20.8). These include mutations in *FLT3*, *PTPN11*, oncogenic *Ras*, *BCR/ABL* and *TEL/PDGFβR*. Mutations and translocation fusion products that impair differentiation and apoptosis (class II mutations) include *PML/RARα* fusion from t(15;17), *AML-1/ETO* fusion from t(8;21), *CEBPα* mutations and

Table 20.8: Genetic abnormalities in AML

Genetic abnormality	*Frequency (%)*	*Clinical features*	*Overall survival (%)*
Gene rearrangement			
t(8;21)(q22;q22) (*ETO-AML1*)	12	Chloromas common	75–85
inv(16)(p13;q22) (*MYH 11-CBFβ*)	8	Eosinophilia	75–85
t(15;17)(q22;q12) (*PML-RARα*)	12	FAB M3; Auer rods present; sensitive retinoic acid to	90
Mutations (karyotype normal)			
NPM (nucleophosmin)	8–10		75–85
CEBPα	4–6	FAB M1 or M2 type	80
FLT3-ITD	10–15		<35
WT1	8–10		35–55
Del 5q	1		<35
Monosomy 7	2		<35

MLL rearrangements. Presence of both types of genetic changes in the hematopoeitic precursor cells leads to AML. Mutations in *GATA1*, a gene regulating hematopoietic differentiation of erythroid and megakaryocytic lineage, are primarily found in acute megakaryocytic leukemia in children with Down syndrome.

Classification

AML is divided into several subgroups according to the FAB classification: M0 undifferentiated, M1 acute myeloblastic leukemia with minimal maturation, M2 acute myeloblastic leukemia with maturation, M3 acute promyelocytic leukemia, M4 acute myelomonocytic leukemia, M5 acute monoblastic leukemia, M6 erythroblastic leukemia, M7 acute megakaryoblastic leukemia. About 30–40% patients with AML are M1 and M2 and about same percentage is M4 and M5. M3 type of AML constitutes about 50–10% and M7 is strongly associated with Down syndrome. Specific chromosomal abnormalities are found in the various subgroups. Translocation between chromosome 8 and 21 t(8;21) translocation is found almost exclusively in M1 and M2. Almost all patients with M3 carry the translocation t(15;17) and M5 is associated with t(9;11). Abnormalities of chromosome 16 are seen in mainly M4 subtype. FAB classification along with the most commonly employed histochemical stains is usually sufficient to distinguish the various subtypes of AML and differentiate it from ALL. Staining for myeloperoxidase activity and positive stain with Sudan black B is observed in AML. Auer rods, needle shaped accumulation of primary granules, are commonly found in M2, M3 and M5 subtypes of AML.

Clinical Features

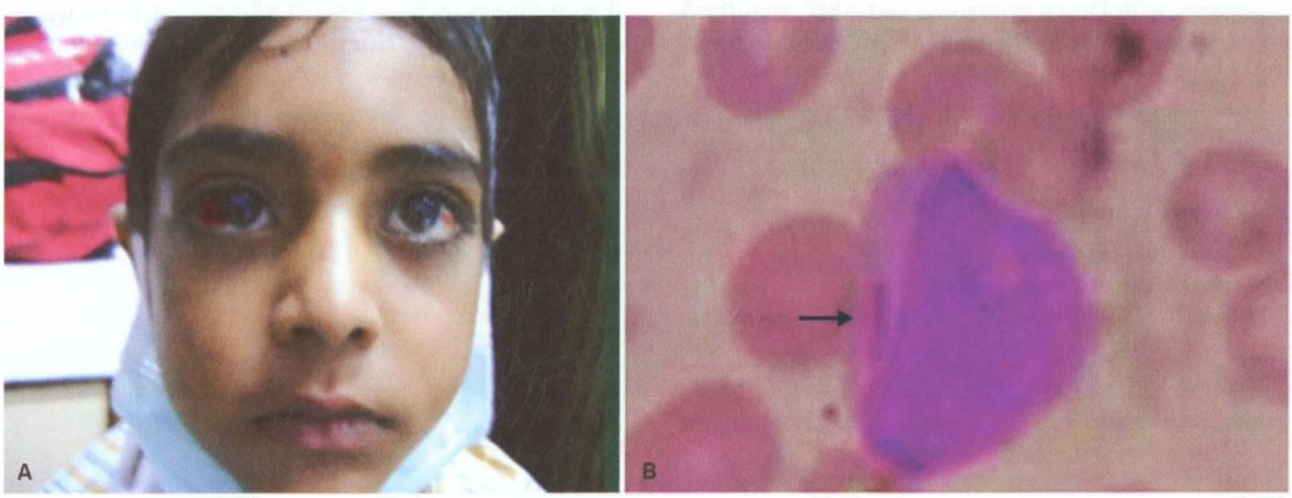
Clinical presentation is similar to ALL but more likely to have higher white cell count at presentation and have higher incidence of infections at time of presentation. Most patients with AML present with pallor, fatigue, bleeding or fever as manifestations of underlying anemia, thrombocytopenia and neutropenia (Fig. 20.2A). Unlike ALL, lymphadenopathy and massive hepatosplenomegaly is not common. However, infants and toddlers with AML have more organomegaly, high leukocyte counts and CNS disease at diagnosis. They are mostly M4 and M5 subtypes. Disseminated intravascular coagulation may occur with any subgroup, but is common in acute promyelocytic leukemia (M3). Chloromas are localized collections of leukemic cells seen exclusively in patients with AML. They may occur at any site including CNS, neck, bones (typically orbit) and skin. Gingival hypertrophy may be present. Patients with high WBC count may present with signs of leukostasis such as pulmonary infiltrates causing respiratory distress or stroke. Central nervous system involvement may occur in up to 15% patients.

Diagnosis is ascertained as in ALL by a peripheral smear and bone marrow examination; the morphologic, cytochemical, immunophenotypic and genetic characteristics of blast cells should be determined (Fig. 20.2B).

Sometimes the diagnosis of AML is preceded by a prolonged preleukemic phase lasting several weeks or months. This is characterized by a lack of one of the normal blood cell lineages, resulting in refractory anemia, a moderate neutropenia or thrombocytopenia. The condition is referred to as a myelodysplastic syndrome. Some patients may show hypoplastic bone marrow that may develop later into an acute leukemia.

Treatment

The longterm survival for children with AML has increased from less than 10% to almost 50% during the past two decades. This is due to intensification of therapy along with



Figs 20.2A and B: A 5-yr-old boy presented with fever, epistaxis and petechiae; (A) Note bilateral subconjunctival bleeding; (B) peripheral smear showed myeloblasts. The arrow points to an Auer rod within a myeloblast, representing pink colored aggregated lysosomes. A diagnosis of acute myeloid leukemia of M2 type was made

improved supportive care. However, compared to ALL, the cure rate is hampered by low remission rate, an increased relapse rate due to the development of resistance to multiple chemotherapeutic drugs and a greater risk of death in remission due to infections and hemorrhage. The main drugs used for induction therapy are combination of cytosine arabinoside and an anthracycline (daunorubicin). The induction regimen most commonly used is cytosine arabinoside (100 mg/m^2/day given as continuous infusion for 7 days) plus daunorubicin (45 mg/m^2/day for 3 days) with or without additional drugs (etoposide, thioguanine). With the current regimen, remission is induced in about 70–80% patients. Consolidation therapy includes high dose chemotherapy including cytosine arabinoside and etoposide. Risk based approach is also used for treatment of AML. Various prognostic factors in childhood AML have been identified: older age, obesity, M0 and M7 subtype of AML FAB classification, presence of CNS disease at diagnosis, absence of minimal residual disease and cytogenetics characteristics like Inv16, t(8;21) and t(15;17) are associated with a favorable outcome. M3 subtype and AML with Down syndrome are associated with a favorable outcome. Patients with favorable genetic features or with normal cytogenetics are treated with chemotherapy alone. Patients with unfavorable genetic alterations undergo stem cell transplantation in first remission.

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (M3), accounting for about 10–15% of patients of AML, is treated differently with all *trans* retinoic acid or arsenic and systemic chemotherapy (anthracyclines and high dose cytarabine).

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CHRONIC MYELOID LEUKEMIA

Chronic myeloid or myelogenous leukemia (CML) is a myeloproliferative disorder. CML is primarily a disease of middle age; the peak incidence is in the fourth and fifth decade. However, it may occur at any age including infants and young children. Two main types of well differentiated myelogenous leukemia have been recognized. One is clinically and hematologically comparable with the adult form of CML and occurs in children above the age of 4 yr. The other presents earlier in infancy and early childhood usually below the age of 4 yr, called juvenile CML.

Adult Variety of CML

Though the adult variety of CML is one of the commonest leukemias in adults, it is rare in children accounting for 3–5% cases. The natural history is divided into chronic, accelerated and blast phases. In the chronic phase, patient has nonspecific symptoms such as fever, malaise and weight loss. Occasionally, patients present with acute symptoms such as bone or joint pain or priapism. Splenomegaly is the most common physical finding and is usually massive (Fig. 20.3). Mild hepatomegaly and lymphadenopathy may be present. Symptoms of leukostasis such as headache, dizziness and visual disturbances may occur rarely. Leukocytosis is present in all cases and 80% patients have leukocyte counts above 1,00,000/mm^3. The differential count shows all forms of myeloid cells from promyelocytes to polymorphonuclear leukocytes; basophilia is common. Mild anemia and thrombocytosis are common, but thrombocytopenia is rare. Bone marrow examination shows extreme hypercellularity. Myeloid blasts and promyelocytes constitute <20% of cells in the bone marrow in chronic phase. Chronic phase typically progresses to blast crisis which shows sudden rise in leukocytes and blast count and is indistinguishable from acute leukemia. Leukocyte alkaline phosphatase activity is low. Philadelphia chromosome, which involves a reciprocal translocation between long arms of chromosomes 22 and 9; t(9;22) is present in 90% cases. This may be detected by cytogenetics, FISH or RT-PCR.

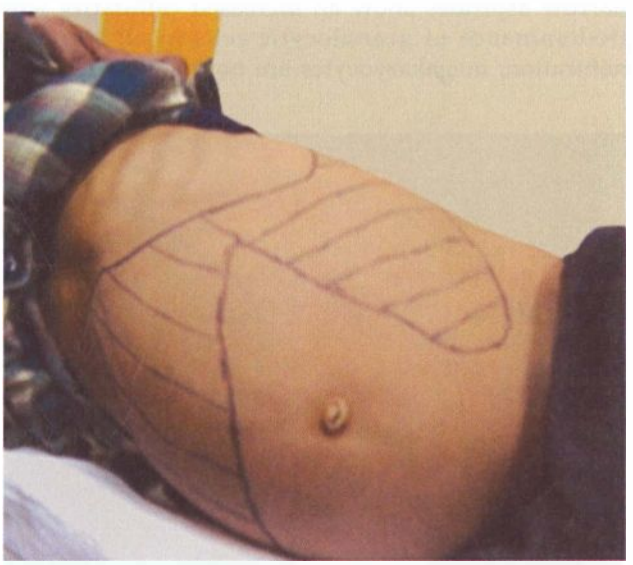

Fig. 20.3: A 6-yr-old boy presented with fever, pallor and progressive abdominal distension for 6 months. Significant splenomegaly and hepatomegaly was noted. A diagnosis of chronic myeloid leukemia was made

The aim of treatment during chronic phase is to control the increasing white cell counts. This can usually be achieved by single agent chemotherapy with either busulfan or hydroxyurea. However, these agents are being replaced with β-interferon and tyrosine kinase inhibitor, imatinib mesylate. Majority of patients achieve complete hematologic and cytogenetic response with this therapy and the rate of progression to accelerated or blast crisis is decreased. The blood counts return to normal or near normal in almost all patients within 6–8 weeks. Spleen size also decreases. With conventional treatment, the average survival is 3–4 yr. Survival after development of accelerated phase is usually less than a year and after blast transformation only a few months. Allogeneic stem cell transplantation is now used for patients who do not respond to tyrosine kinase inhibitors.

Juvenile Chronic Myeloid Leukemia

JCML, also termed as juvenile myelomonocytic leukemia, is an uncommon malignancy accounting for less than 2% leukemias in children. Patients with neurofibromatosis are at high risk for this condition. JCML is a disease of infancy and early childhood below the age of 5 yr, has a more acute and severe course with frequent lymphadenopathy, anemia, hepatosplenomegaly, skin involvement (eczema, xanthoma and café au lait spots), infection and thrombocytopenia (Fig. 20.4).

Peripheral smear shows leukocytosis (usually less than 1,00,0000/mm^3) with the full spectrum of granulocytic precursors and increased normoblasts; monocytosis is often striking. Thrombocytopenia and anemia are common. Leukocyte alkaline phosphatase score is normal or low and fetal hemoglobin levels are elevated. Bone marrow aspirates show an increased cellularity with predominance of granulocytic cells in all stages of maturation; megakaryocytes are normal or decreased.

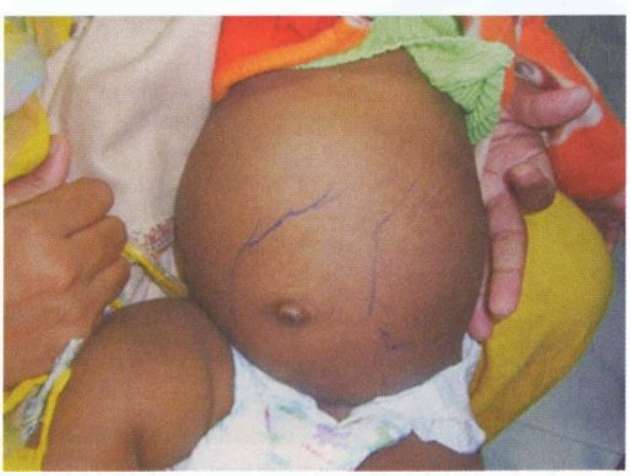

Fig. 20.4: A 1-yr-old boy presented with fever, rashes, anemia and massive splenomegaly and hepatomegaly. He was diagnosed with juvenile myelomonocytic leukemia

Most patients have normal karyotypes or nonspecific chromosomal abnormalities. Philadelphia chromosome is negative; monosomy 7 is found in 30% patients.

JCML has a fulminant and rapidly fatal course. Management involves supportive care including packed red cell and platelet transfusions, treatment of infections and allogeneic stem cell transplant if a matched sibling donor is present. Even with transplant, there is 30–50% event-free survival rate at 3 yr. *Cis*-retinoic acid has been tried with some benefit.

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LYMPHOMA

Lymphomas are the third most common malignancy in children and adolescents, after leukemia and brain tumors. About 60% are non-Hodgkin lymphoma and 40% are Hodgkin lymphoma. Lymphomas are uncommon below the age of 5 yr and the incidence increases with age.

Hodgkin Lymphoma

Hodgkin lymphoma, a lymphoreticular neoplasm primarily of B cell lineage involving lymph nodes and the lymphatic system has unique molecular, histologic, immune phenotypic and clinical features. Hodgkin lymphoma occurs in 5–7/1,00,000 population. Hodgkin lymphoma is uncommon below the age of 5 yr and exhibits three distinct forms in developing countries: The childhood form (younger than 14 yr), a young adult form (15–44 yr) and an older adult form (55–74 yr). There is a significant male preponderance (10:1) in children affected below 7 yr of age with an almost equal sex distribution (1:1) beyond 12 yr of age.

The majority of patients achieve disease remission with multiagent chemotherapy with or without radiotherapy. Therapy is based on risk stratified approach based on disease stage and the presence of adverse prognostic factors.

Epidemiology

The etiology of Hodgkin lymphoma is believed to be multifactorial. Siblings have a seven fold increase in the risk and multiple studies have confirmed a gender concordance of sibling pairs. A strong evidence for genetic susceptibility comes from a 100-fold increased risk in monozygotic twins compared with dizygotic twins. Epidemiologic studies suggest link between Hodgkin lymphoma and viral illnesses like Epstein-Barr virus (EBV). EBV viral DNA can be found in Reed-Sternberg cells suggesting that monoclonal proliferation of the neoplastic clone takes place after EBV infection. EBV-

positive classic Hodgkin lymphoma tumors differ geographically and are more common in developing countries. EBV infection is commonly seen in young children with mixed-cellularity Hodgkin lymphoma. Immune deficiency and autoimmune conditions (rheumatoid arthritis, SLE, sarcoidosis) are known to be associated with increased risk of Hodgkin lymphoma.

Pathology

Lymph nodes are the most common tissue on which the diagnosis of Hodgkin lymphoma is made. However, liver, spleen, bone marrow or lung may provide material for histological examination. It is necessary to obtain the entire node by excision biopsy for proper histologic examination. Fine needle aspiration biopsy and frozen section material are not optimal. The WHO classification of Hodgkin lymphoma recognizes two major subtypes: (i) *nodular lymphocytic–predominant Hodgkin lymphoma (NLPHL),* (ii) *classical Hodgkin lymphoma.*

The NLPHL subtype of Hodgkin lymphoma is characterized by large cells with multilobed nuclei referred as popcorn cells. These patients are generally asymptomatic and present with localized nonbulky disease. The hallmark of classic Hodgkin lymphoma is the Reed-Sternberg cell. This is a binucleated or multinucleated giant cell that is often characterized by a bilobed nucleus with two large nucleoli, giving an owl eye appearance to the cells. There are four varieties of this subgroup each characterized by the number of Reed-Sternberg cells, characteristics of inflammatory milieu and the presence or absence of fibrosis (nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted). Nodular sclerosis is the most common type in developed countries, whereas in developing countries including India, the mixed cellularity type is common, accounting for 60% cases (Table 20.9).

On immunophenotyping, classic Hodgkin lymphoma are positive for CD15 and CD30 and may be positive for CD20, whereas NLPHL is negative for CD15 and CD30 but positive for CD20 and CD45.

Clinical Features

Children with Hodgkin lymphoma present with painless cervical or supraclavicular lymphadenopathy; the nodes are firm and rubbery in consistency (Fig. 20.5). Cervical lymph nodes are the most frequent (80%) site of primary involvement; 50% patients may also have mediastinal adenopathy and superior mediastinal syndrome. Less commonly, axillary or inguinal lymphadenopathy is the presenting feature. About 20–30% of children present with systemic 'B' symptoms, as defined by the Ann Arbor staging criteria, with fever over 38°C, night sweats and unexplained weight loss of >10% body weight at presentation. The frequency of these symptoms increases with advanced disease and indicate an unfavorable prognosis. The presence of unexplained pruritus should prompt complete physical examination and chest radiography.

Table 20.9: Histological subtypes of Hodgkin lymphoma

Histology	*Frequency*	*Prognosis*
Nodular lymphocyte predominance	10%	Excellent
Classical Hodgkin lymphoma		
Nodular sclerosis	20–50%	Very good
Mixed cellularity	20–40%	Good
Lymphocyte rich	<10%	Excellent
Lymphocyte depletion	5–15%	Poor

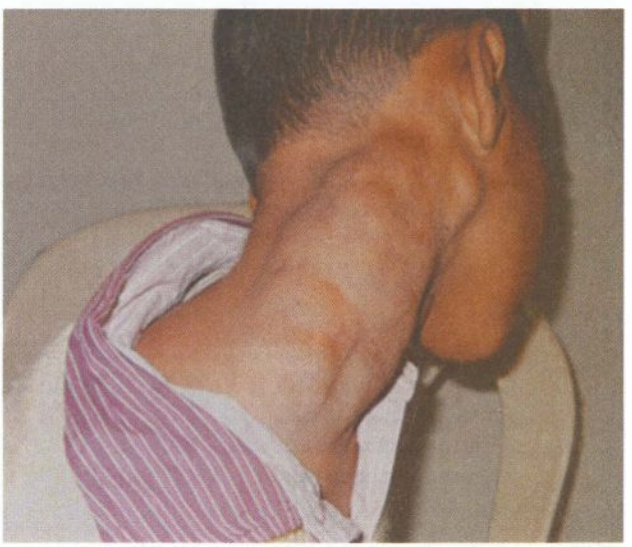

Fig. 20.5: A 12-yr-old boy presented with intermittent fever and significant bilateral cervical lymphadenopathy. Lymph node biopsy showed features of Hodgkin lymphoma

Besides presence of 'B' symptoms, other prognostic factors include stage of disease, histopathological subtype (risk increases from lymphocyte predominant to nodular sclerosis to mixed cellularity to lymphocyte depletion), bulky mediastinal disease, extensive splenic involvement and more than 5 nodal sites in stage III. Bone marrow involvement rarely results in cytopenias and has been associated with a variety of paraneoplastic syndromes that may be the presenting feature of the disease. Other uncommon sites of involvement include the gastrointestinal tract and skin. Splenic involvement occurs in 30–40% cases.

Diagnostic Workup and Staging

Evaluation of a patient includes careful physical examination with assessment of all lymph node bearing areas. Chest radiograph provides information about enlargement of the mediastinum. CT scan of the chest provides information about pulmonary parenchyma, chest wall, pleura and pericardium that may not be apparent on chest X-ray. CT scan of the abdomen and pelvis is done to

examine for involvement of the viscera and lymph nodes. Although lymphangiography is a reliable method for retroperitoneal lymph nodes, it is rarely performed in children. Bone marrow biopsy should be performed in all children with systemic symptoms and in advanced stage (III and IV) disease. A staging laparotomy is not performed because of concerns related to operative morbidity and splenectomy. Diagnostic staging and workup are outlined in Tables 20.10 and 20.11.

Table 20.10: Modified Ann Arbor staging for Hodgkin lymphoma

Stage	*Involvement*
I	Single lymph node region (I) or one extralymphatic site (I_E)*
II	Two or more lymph node regions on same side of diaphragm (II) or one or more lymph node regions on same side of diaphragm plus local extralymphatic extension (II_E)*
III	Lymph node regions on both sides of the diaphragm (III) which may be accompanied by local extralymphatic extension (III_E)*
IV	Diffuse involvement of one or more extralymphatic* organ or sites
A	No B symptoms
B	Presence of at least one of the following B symptoms: Unexplained weight loss >10% baseline during 6 months before staging Recurrent unexplained fever >38°C Recurrent night sweats
X	Bulky tumor**

*E lesion: Localized extranodal extension of Hodgkin lymphoma from a contiguous or nearby nodal site is noted with the designation E

**Defined as either a single mass of tumor tissue exceeding 10 cm in largest diameter or a mediastinal mass extending one-third of the maximum transverse intrathoracic diameter

Table 20.11: Diagnostic evaluation in Hodgkin lymphoma

Physical examination with measurement of lymph nodes
Complete hemogram with ESR, C reactive protein
Liver and renal functions tests, alkaline phosphatase
Lactate dehydrogenase
Chest X-ray, mediastinal mass to thoracic cavity ratio
CT scan of neck, chest and abdomen
Bone marrow biopsy (all children except stages IA/IIA)
Biopsy from lymph node or involved extranodal site
Bone scan (if bone pain or raised serum alkaline phosphatase)
CT scan brain (if indicated)
Cerebrospinal fluid examination (if indicated)
PET-CT scan (higher sensitivity for stage and residual mass than conventional imaging)
Surgical staging with lymph node sampling and lymphangiography (selected cases)

CT computed tomography; ESR erythrocyte sedimentation rate; PET positron emission tomography

Management

Treatment modalities have varied from total nodal radiation therapy to chemotherapy to combination of chemotherapy and radiotherapy with significant improvement in survival rate throughout the last three decades. All children generally receive combination chemotherapy as initial treatment.

With the emerging concept of risk directed therapy most children are treated with combination chemotherapy alone or in combination with radiotherapy. Superior treatment results and absence of leukemogenesis and permanent gonadal toxicity have made ABVD the preferred front line regimen for Hodgkin lymphoma; however the concerns of this protocol include cardiomyopathy and pulmonary fibrosis. The dose of radiation therapy used ranges between 15 and 25 Gy. Several studies have demonstrated that chemotherapy alone is effective therapy for pediatric Hodgkin lymphoma. The advantage of this approach is elimination of radiation associated adverse effects like myocardial dysfunction, musculoskeletal growth deficits and second malignancy.

With favorable clinical presentation (localized nodal involvement [stage I, II, IIIA], absence of B symptoms and no evidence of bulky disease treatment) consists of 2–4 cycles of chemotherapy (ABVD/others) and low dose involved field radiation. Several studies have reduced the dose of radiation in patients achieving a favorable response to chemotherapy. Unfavorable clinical presentation is defined as presence of B symptoms, bulky mediastinal/peripheral lymphadenopathy, extranodal extension of disease and advanced disease [stage IIIB–IV]. Localized disease (stage I, II, IIIA) with unfavorable features may be treated similarly to advanced stage disease in some protocols or given a therapy of intermediate intensity. Unfavorable disease or localized disease with B symptoms are treated with 4–6 cycles of ABVD with/without radiotherapy (Table 20.12). Other combinations include COPP/ABVD, MOPP/ABVD, OPPA, Stanford V regimen and BEACOPP regimes.

The role of additional radiotherapy in stage III and IV disease remains controversial. Adjuvant radiotherapy presents no survival advantage though better local tumor control is obtained. The use of hemopoietic stem cell transplantation (HSCT) as initial therapy remains controversial because of the overall excellent prognosis of children with advanced and unfavorable Hodgkin lymphoma to chemotherapy alone or in combination with radiotherapy. At present HSCT should be reserved for patients after relapse or for those who are refractory to conventional therapy.

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Table 20.12: Commonly used drug combinations for Hodgkin lymphoma

ABVD	Inj Doxorubicin or Adriamycin	25 mg/m^2	IV day 1 and 15
	Inj. Bleomycin	10 mg/m^2	IV day 1 and 15
	Inj. Vinblastine	6 mg/m^2	IV day 1 and 15
	Inj. Dacarbazine	375 mg/m^2	IV day 1 and 15
	Inj. Dexamethasone	0.15 mg/kg	IV day 1 and 15
Keep off therapy from day 16–28. Repeat on day 28			
COPP	Inj. Cyclophosphamide	600 mg/m^2	IV day 1 and 8
	Inj. Oncovin (Vincristine)	1.5 mg/m^2 (max 2 mg)	IV day 1 and 8
	Tab Prednisolone	40 mg/m^2 (max 60 mg)	PO day 1 to 14
	Cap Procarbazine	100 mg/m^2	PO day 1 to 14
Keep off therapy from day 16–28. Repeat on day 28			

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of lymphoid neoplasms derived from cells of the immune system. NHL most commonly occurs during the second decade of life and occurs less frequently in children less than three years of age. Together with Hodgkin lymphoma they comprise the third most common childhood malignancy. Low grade lymphomas, which are common in adults are rare in children. Pediatric NHL are high grade, diffuse and aggressive with propensity for dissemination. With current treatment regimes about 80% of children and adolescents with NHL will survive for at least 5 yr.

Epidemiology

There is male preponderance, with male to female ratio of 3:1. Lymphomas are uncommon before 3 yr of age. Also age specific trend of incidence of NHL have been observed that correlate with histologic subtype. Burkitt and Burkitt like lymphoma characteristically occurs in children between 5 and 15 yr whereas the incidence of lymphoblastic lymphoma is reasonably constant across all age groups. Diffuse large B cell lymphoma is a disease of older adolescents. In equatorial Africa, 50% of all cancers are lymphomas (Burkitt lymphoma being predominant). In United States and Europe, one-third of childhood NHL are lymphoblastic, one-half small, noncleaved cell lymphomas (Burkitt and non-Burkitt or Burkitt like) and the rest are large cell lymphomas. In India, lymphoblastic lymphoma is more common. NHL is also characterized on basis of their T or B cell nature. NHL may follow previous chemotherapy for Hodgkin disease, or be associated with immunodeficiency and DNA repair deficiency syndromes (Wiskott-Aldrich syndrome, X-linked lymphoproliferative disorders, ataxia-telangiectasia), acquired immunodeficiency syndrome and organ transplantation (post-transplant lymphoproliferative disease). Infection with malaria and EB virus are considered risk factors for Burkitt lymphoma.

Pathology

There are 4 major pathological subtypes of NHL in children. These include Burkitt or Burkitt like lymphoma, lymphoblastic lymphoma, diffuse large B cell lymphoma. and anaplastic large cell lymphoma. All pediatric NHL are high grade and aggressive while NHL in adults is often indolent.

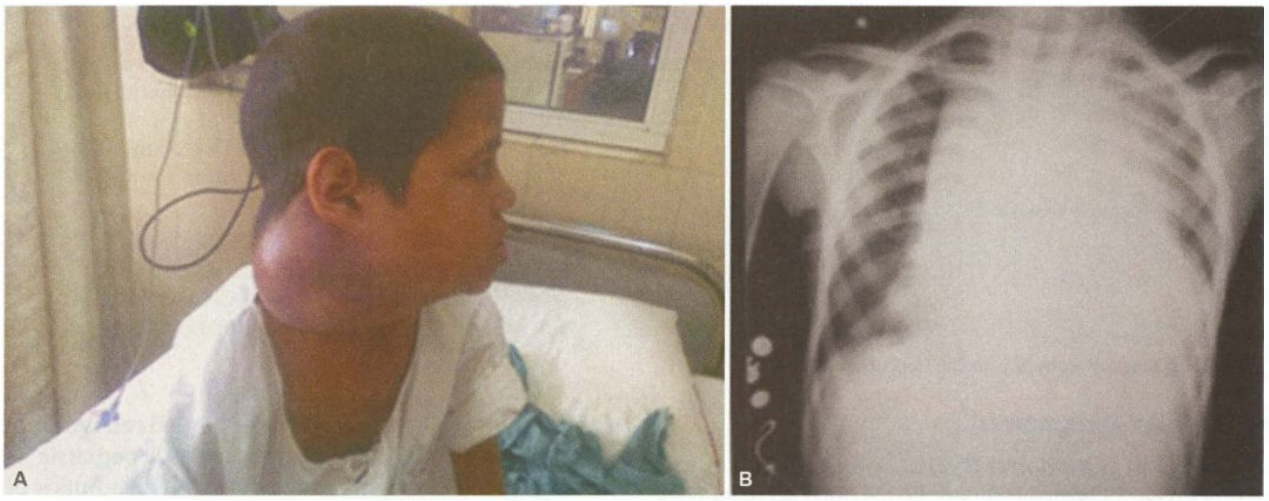
Clinical Presentation

NHL in children has distinct clinical and behavior properties when compared to adults. Lymphomas in adults are commonly low or intermediate grade and are dominantly nodal, have variable growth fraction with poor longterm outcome. NHL in children is high grade, extranodal with high growth fraction and good outcome.

Children with NHL typically present with extranodal disease involving the mediastinum, abdomen, or head and neck region (Figs 20.6A and B). Intrathoracic NHL most often T cell lymphoma may present with features of superior mediastinal or superior vena caval syndrome. There may be associated pleural and/or pericardial effusion. Cervical adenopathy, abdominal pain, ascites, palpable abdominal mass, intestinal obstruction or intussusception (typically B cell disease), cranial nerve palsy, bone involvement, jaw swelling and cytopenias due to bone marrow involvement are other features.

Diagnosis

NHL are rapidly growing tumors; prompt diagnosis is therefore essential. Almost two-thirds of patients have widespread disease at the time of diagnosis, involving bone marrow, central nervous system or both. Selection of the appropriate lymph node or mass for histological diagnosis is necessary. Histology is the primary means for diagnosis and is supplemented, if possible, with immunophenotypic and cytogenetic studies. If the clinical condition is not suitable for biopsy, due to a large mediastinal mass causing superior vena cava syndrome, the diagnosis may be made with less invasive procedures, e.g. percutaneous needle aspiration of accessible lymph node, examination of body fluids (e.g. pleural fluid) or bone marrow. Table 20.13 shows the St Jude staging system, which is applicable to all types of childhood NHL. In newly diagnosed patients, a detailed workup and relevant investigations should be done (Table 20.11).



Figs 20.6A and B: (A) A 10-yr-old child with fever was diagnosed as Burkitt lymphoma. Note significant right cervical lymphadenopathy; (B) chest X-ray of a 7-yr-old boy with continuous fever. Note the mediastinal mass with shift of mediastinum to the right and left-sided pleural effusion. The diagnosis of non-Hodgkin T-lymphoblastic lymphoma was confirmed on lymph node biopsy

Table 20.13: St Jude staging system for childhood non-Hodgkin lymphoma

Stage	*Definition*
Low-risk (localized)	
I	Single tumor (extranodal); single anatomic area (nodal) excluding mediastinum and abdomen
II	Single tumor (extranodal) with regional node involvement; primary gastrointestinal tumor (completely resected, with or without involvement of mesenteric node); two or more tumors or nodal areas on one side of diaphragm
High-risk (advanced)	
III	Primary intrathoracic (mediastinal, pleural and thymic) tumor; extensive primary intra-abdominal disease; paraspinal or epidural tumors regardless of other tumor sites; two or more nodal or extranodal areas on both sides of diaphragm
IV	Any of the above with central nervous system and/or bone marrow involvement

Management

The dramatic improvement in the survival of patients with NHL is because of development of highly effective chemotherapy and supportive care. Surgery has limited role in treatment other than for diagnostic purposes. Radiotherapy is also restricted to emergency situations, e.g. superior vena cava syndrome or spinal cord compression due to paraspinal disease. Different chemotherapeutic regimens are used for treatment of B and T cell lymphomas. The regimens for lymphoblastic lymphoma are usually based on protocols for ALL. These are intensive protocols that use combinations of 8 to 10 drugs. Cranial irradiation or prophylactic intrathecal chemotherapy is given in stage III and IV disease. Chemotherapy is give for a period of 1 to 2 yr depending on the stage and extent of the disease. The longterm survival in patients with lymphoblastic lymphoma with limited disease is 80–90% and for advanced disease 70–80%.

The chemotherapeutic regimens for B cell lymphoma (Burkitt and non-Burkitt) is different. Most protocols consist of short duration (6 months), intensive alkylating high dose methotrexate, vincristine, anthracyclines, etoposide and cytarabine; CNS prophylaxis is provided with intrathecal chemotherapy. Longterm survival is highly satisfactory with survival in more than 90% patients with limited disease and 75-85% in patients with extensive disease. Survival rates in patients with bone marrow disease have also improved dramatically. The use of anti-CD20 monoclonal antibodies (e.g. rituximab) directed against B cell antigens has been safely combined with standard chemotherapy to improve survival.

Suggested Reading

Gross TG, Perkins SL. Malignant non-Hodgkin lymphomas in children. In: Principles and Practice of Pediatric Oncology. Eds. Pizzo PA, Poplack DG, Lippincott Williams and Wilkins, Philadelphia 2011;663–82

Srinivas V, Soman CS, Naresh KN. Study of the distribution of 289 non-Hodgkin lymphomas using WHO classification among children and adolescents in India. Med Pediatr Oncol 2002;39:40–3

BRAIN TUMORS

Tumors of the central nervous system (Table 20.14) are the second most common neoplasms in children in the developed countries. They account for 25% of all childhood cancers. Medulloblastomas are the most common malignant brain tumors in children.

Epidemiology

Exposure of CNS to significant doses of radiation and presence of certain genetic syndromes increases the risk

Table 20.14: Common pediatric brain tumors

Glial tumors
Astrocytoma
Low grade
High grade
Ependymoma
Embryonal tumors
Medulloblastoma
Primitive neuroectodermal tumor
Atypical teratoid rhabdoid tumor
Germ cell tumors
Germinoma
Non-germinomatous germ cell tumors
Choroid plexus tumors
Papilloma
Carcinoma
Craniopharyngioma

of developing brain tumors. Meningiomas and malignant gliomas arise within the radiation field several years or decades after radiation therapy. Children who have received cranial or craniospinal radiation for treatment of ALL are at risk for developing these tumors.

Several genetic syndromes predispose to developing CNS tumors (Table 20.15). Of these NF1 is the most common disorder. Approximately 15% of patients with NF1 develop optic gliomas during their lifetime. Optic gliomas in patients with NF1 have a more benign course and may even regress spontaneously. However, the majority of pediatric CNS tumors are sporadic and have no known cause.

Clinical Presentation

Clinical presentation of brain tumors depends on location of the tumor and the rate of growth. Symptoms arise because of raised intracranial pressure or from direct infiltration or compression of parts of the CNS.

Symptoms from Raised Intracranial Pressure

Infratentorial tumors are more common than supratentorial tumors in children and hence more likely to develop acute or chronic hydrocephalus (Fig. 20.7). Recurrent headaches that are worse at night or early morning and worsen with lying down, early morning vomiting, vision loss, features of VI nerve palsy or sunset sign are indicative of raised intracranial pressure. Acute increase in intracranial pressure may present with Cushing triad of hypertension, bradycardia and altered respiration.

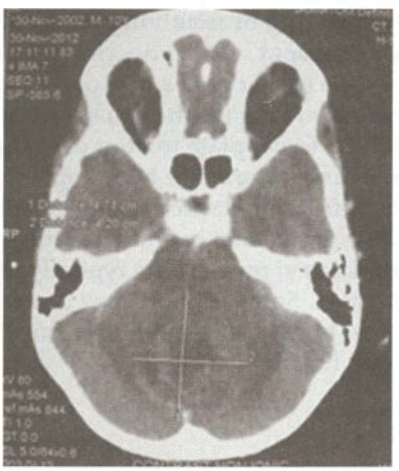


Fig. 20.7: A 6-yr-old boy presented with headaches, vomiting and seizures for 6 months. Computed tomography of the brain showed glioma of cerebellum with obstructive hydrocephalus

Symptoms from Compression or Infiltration

Headaches can occur from direct compression of skull and meninges. Vomiting may be due to raised intracranial pressure but can also occur because of direct infiltration of one of the vomiting centers in the *area postrema* at the base of the fourth ventricle. Head tilt may develop in a child as a correction for diplopia arising from a cranial nerve palsy.

Table 20.15: Genetic disorders associated with brain tumors

Genetic disorder	*Gene; chromosome*	*Brain tumor*	*Other features*
Neurofibromatosis type 1	*Neurofibromin*; chromosome 17	Optic glioma	Autosomal dominant
Neurofibromatosis type 2	*Merlin*; chromosome 22	Acoustic neuromas; schwannoma	Peripheral nerve sheath tumors; cardiac sarcoma
Li-Fraumeni syndrome	*P53*; chromosome 17	Choroid plexus carcinoma	Sarcoma; adrenocortical cancer; breast cancer
Bilateral retinoblastoma	*Rb1*; chromosome 13	Pineal tumor	Sarcoma
Tuberous sclerosis	*TSC1*; chromosome 9; *TSC2*; chromosome 13	Subependymal cell astrocytoma, malignant glioma	Autosomal dominant
von Hipplel-Lindau	*VHL*; chromosome 3	Hemangioblastoma tumors	Renal, adrenal and pancreatic tumors
Gorlin syndrome	*PATCH1*; chromosome 9	Medulloblastoma	Sensitive to radiation; basal cell carcinoma
Turcot syndrome	*APC*; chromosome 5	Medulloblastoma; malignant glioma	Adenomatous polyps in colon

Diencephalic syndrome (emaciation, euphoria and emesis) is associated with tumors in the diencephalon. *Parinaud's syndrome* of supranuclear upgaze palsy with pupils reactive to accommodation but not to direct light is associated with tumors of pineal region or upper brainstem. Seizures are very rarely associated with tumors. Low grade tumors of cerebral cortex may present with seizures as the main manifestation.

Frontal lobe tumors present with personality changes, seizures and headaches. Tumors in the temporal lobe cause seizures and speech changes. Suprasellar tumors are associated with endocrinopathies and visual changes. Tumors compressing or involving the hypothalamic-pituitary axis present with endocrinopathies. Tumor should always be ruled out in a new onset diabetes insipidus. Tumors involving the thalamus lead to motor and sensory deficits. Tectal plate (on top of brainstem) and pineal tumors cause obstructive hydrocephalus. Multiple cranial nerve deficits are classic presentation of brainstem gliomas. Nystagmus, ataxia and vomiting because of increased intracranial pressure are typically present with cerebellar tumors. Spinal tumors may cause back pain, scoliosis, numbness, weakness and impairment of bladder/bowel function.

Diagnosis

Imaging

MRI, with and without contrast, is the imaging study of choice. CT scan is necessary in the setting of acute presentation suggestive of raised intracranial pressure.

Histology

While the distinction between benign and malignant tumors is critical, location of the tumor in the CNS is often as important a determinant of prognosis as the histology itself. A benign tumor in an unresectable location in the brain has as poor a prognosis as a malignant tumor in a surgically accessible area of the brain. Also, the age of the child determines the type of treatment to be used and hence impacts the prognosis. The grade of the tumor refers to microscopic appearance, 1 being the lowest and 4 being the highest grade. However, the grade does not always reflect the prognosis. Histological diagnosis of brain tumors is challenging. Special stains, immunohistochemistry and molecular testing is required to make the diagnosis.

Treatment

Treatment of pediatric brain tumors requires a multidisciplinary approach. Surgery, chemotherapy and radiation therapy are important for therapy. Complete surgical resection without damaging the critical structures of the brain is usually the desired goal. However, this may be difficult to achieve depending on the location of the tumor. Some patients may need urgent surgical intervention to relieve raised intracranial pressure. Radiation therapy utilizing photons is most commonly used for treating brain tumors. Chemotherapy may also be used concurrently with radiation therapy as a radiation sensitizer for some tumors. Newer agents such as antiangiogenic drugs and inhibitors of tyrosine kinases, histone deacetylases and the sonic hedgehog pathway are under investigation for brain tumors.

Suggested Reading

Fleming AJ, Chi SN. Brain tumors in children. Curr Probl Pediatr Adolesc Health Care 2012;42:80–103

Ulrich LJ, Pomory SL. Pediatric brain tumors. Neurol Clin 2003; 21:897–13

RETINOBLASTOMA

Retinoblastoma is the most common primary ocular tumor of childhood, a tumor of the embryonic neural retina. It has an incidence of 11 new cases per million population (age less than 5 yr). About 90% cases are diagnosed by age 3–4 yr and 98% by 5 yr. Bilateral disease is diagnosed earlier then unilateral disease. There is increased frequency of retinoblastoma in some developing countries especially Latin America, Africa and Asia including India. Also there is marked disparity in the mortality associated with retinoblastoma between developed and developing countries. 40–70% of children with retinoblastoma in the developing countries die as opposed to only 3–5% in the developed counties, predominantly due to delayed diagnosis and extraocular disease.

Genetics and Inheritance

The retinoblastoma (*RB1*) gene, encoded on chromosome 13q14, was the first described tumor suppressor gene. Constitutional loss of one *RB1* allele causes cancer predisposition and loss of the second allele in developing retinal cells leads to retinoblastoma.

Retinoblastoma can be sporadic or inherited. Sporadic tumors are unilateral, unifocal and occur at an older age while inherited tumors occur at an earlier age and are often bilateral and multifocal. One-third of all cases have bilateral tumors. All cases with bilateral disease have germline mutaions of *RB1* and are heritable. Only a small proportion of unilateral tumors are heritable.

Most cases of hereditary retinoblastoma have spontaneous new germline mutation while their parents have both wild type *RB1* alleles. The risk of an offspring inheriting an *RB1* mutation from a parent with germline mutation of *RB1* is 50% and 97% of these offsprings with the inherited mutation will go onto develop retinoblastoma. A constitutional (germline) mutation of *RB1* also causes an increased risk of a second cancer of lung, soft tissue, bladder, skin, bone and brain lifelong and this risk is even higher when these patients are treated with radiation therapy for their retinoblastoma. A small proportion (5–10%) of unilateral tumors are hereditary.

Clinical Presentation

Leukocoria (white pupillary reflex) is the most common presentation (Fig. 20.8). It may be first noticed on flash photography. Strabismus, poor visual tracking and glaucoma are other presenting features. Orbital inflammation, hyphema and irregular pupil, fungating ocular mass are signs of advanced disease. Pain may be present secondary to glaucoma. In developing countries, retinoblastoma presents very late in its extraocular stage, either with an orbital mass (proptosis) or with distant metastasis in the bone, bone marrow, lymph nodes and central nervous system. Coat's disease, cataract, toxocariasis and retinopathy of prematurity are other conditions causing leukocoria.

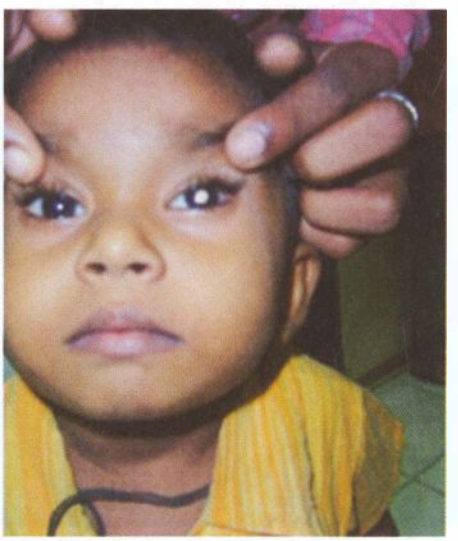


Fig. 20.8: Leukocoria and squint in a 3-yr-old boy with retinoblastoma

Diagnosis

Diagnosis is established by characteristic ophthalmologic findings often requiring examination under anesthesia. Imaging studies such as ultrasound, CT/ MRI (preferred) scans are used for assessment of orbital, optic nerve and intracranial extension (Fig. 20.9).

Rarely children with hereditary retinoblastoma have pineal tumor (trilateral retinoblastoma) that may be found on imaging. CSF and bone marrow evaluation should only be done if indicated clinically or by other imaging studies (i.e. in advanced disease).

Where possible, both eyes should be examined under general anesthesia. Proper staging requires ultrasonography and imaging of the orbit and brain, for assessment of orbital and intracranial extension.

Second neoplasms are a major concern in retinoblastoma survival. Approximately 30% of individuals cured of hereditary retinoblastoma will have a second malignancy within 30 yr. Osteosarcoma is the commonest second malignancy; other second neoplasms include rhabdomyosarcoma and melanoma.

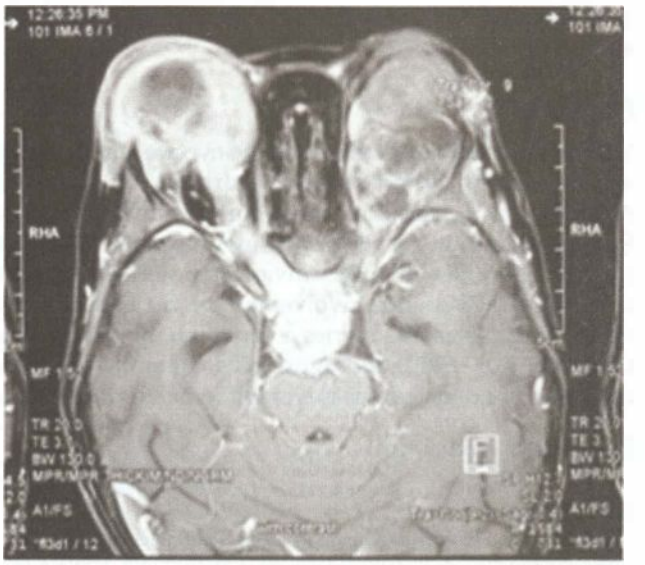


Fig. 20.9: Bilateral extraocular retinoblastoma with optic nerve involvement and intracranial spread

Treatment

The aims of treatment is survival with maintenance of vision. Treatment depends on size and location of the tumor and whether it is hereditary or sporadic. Retinoblastoma is curable when the disease is intraocular. Therapeutic plans usually require a multidisciplinary approach. Treatment should be highly individualized. The major concern is to avoid enucleation and or external beam radiation and trends are towards focal conservative treatment.

In cases of unilateral disease with large tumors where no useful vision can be preserved, enucleation must be performed early. Delay in this can lead to extraocular disease and ultimately loss of life. Survival from metastatic disease is extremely poor. In children with bilateral disease systemic chemotherapy is used to shrink the tumors followed by local treatment with laser photocoagulation or cryotherapy in order to preserve vision. The eye with no useful vision should be enucleated in cases with bilateral disease. Systemic chemotherapy includes vincristine, carboplatin and etoposide. External beam radiation therapy should only be considered in cases where chemotherapy and focal therapy fail. Radiation therapy leads to orbital deformity and increased risk of second malignancy in patients with hereditary form of the disease. Several reports document longterm survival of patients with metastatic disease treated with high dose chemotherapy with autologous bone marrow transplantation.

Routine eye examination should be done in these children till they are over 7 yr of age. All first degree relatives of children with known or suspected hereditary retinoblastoma should have eyes examined for retinomas or retinal scars. Patients with hereditary form of the disease are at a high-risk of other cancers particularly

osteosarcoma, soft tissue sarcomas, malignant melanoma and carcinomas.

Prognosis

Most tumors that are confined to the eye are cured. Cures are infrequent when extensive orbital/optic nerve extension has occurred or patient has distant metastasis. Reported mortality is 29% with involvement of lamina cribrosa, 20–30% with tumor invasion posterior to lamina cribrosa and 78% with involvement of cut end of optic nerve. CNS metastasis carries a very high mortality.With the advent of HSCT and aggressive chemotherapy the outcomes of extensive diseases are showing improvement.

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Dimaras H, Kimani K, Dimba EAO, et al. Retinoblastoma. Lancet 2012;379:1436–46

Hurwitz RL, Shields CL,Shields JA, et al. Retinoblastoma. In: Principles and Practices of Pediatric Oncology. Eds. Pizzo PA, Poplack DG. Lippincott Williams & Wilkins, Philadelphia, 2011;809–37

NEUROBLASTOMA

Neuroblastoma is the most common intra-abdominal and extracranial solid tumor in children, accounting for 7–8% of all cancers. It is a malignant tumor of the autonomic nervous system derived from the neural crest. Neuroblastoma is a disease of early childhood with approximately 90% of patients presenting before 5 yr of age and almost 50% within the first 2 yr of life. The etiology is not known but familial cases occur and there is an association with neurofibromatosis, Hirschsprung disease, heterochromia, fetal hydantoin and fetal alcohol syndromes, and Friedreich ataxia. Rearrangement or deletion of the short arm of chromosome 1 has been found in 80% cases. Neuroblastoma is one of the very few childhood cancers that can undergo spontaneous regression.

Genetics

MYC-N oncogene is used as a biomarker for risk stratification in neuroblastoma. *MYC-N* amplification is defined as greater than or equal to 10 copies of *MYC-N* per nucleus and is associated with more aggressive disease, and poor outcome. Hyperdiploidy in the tumor tissue is associated with a favorable prognosis in children <2 yr of age at diagnosis. Loss of heterozygosity of 1p, 11q, 14q and gain of 17q are common in neuroblastoma and associated with worse prognosis.

Clinical Features

The clinical features are related to the localization of the sympathetic nervous system and site of metastasis. The most common sites of primary tumors are the adrenal gland (30%), paravertebral retroperitoneum (28%), posterior mediastinum (15%), pelvis (5%) and cervical area. Cervical neuroblastoma can present with Horner syndrome. The patient may be asymptomatic with a paraspinal, localized intrathoracic or retroperitoneal mass found incidentally. This presentation has an excellent prognosis. At the other extreme is an anxious, febrile patient with periorbital ecchymoses known as raccoon eyes (Fig. 20.10), scalp nodules, bone pain, limping and anemia from widespread metastasis. Neuroblastoma staging is discussed in Table 20.16.

Five percent of patients have stage IVS (S = special) disease. This is characterized by a small primary tumor in an infant with metastatic disease involving the liver, skin and bone marrow and regresses spontaneously. Infants younger than 2 months may show a rapid progression of intrahepatic disease causing respiratory distress (metastasis in liver). Another unusual presentation (5–15%) is the occurrence of spinal cord signs secondary

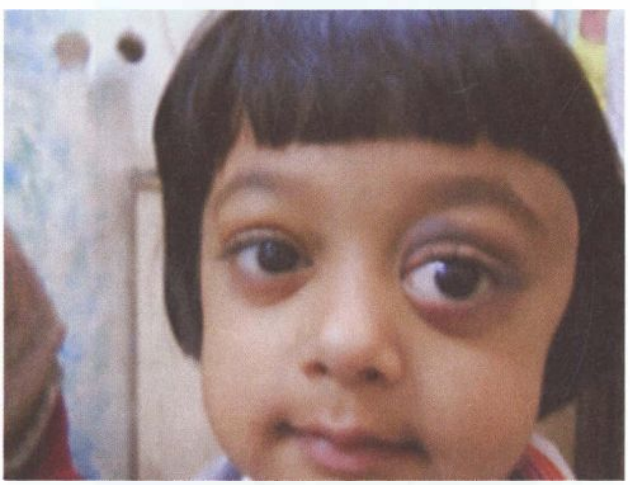

Fig. 20.10: Left eyelid appears like a 'raccoon's eye' in a child diagnosed with metastatic neuroblastoma

Table 20.16: International neuroblastoma staging system

Stage I: Localized tumor confined to the area of origin; complete excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage II: Localized tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage IIB: Localized tumor with complete or incomplete gross excision with positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically
Stage III: Tumor infiltrating across the midline with or without regional lymph node involvement; or unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral regional lymph node involvement
Stage IV: Tumor disseminated to distant lymph nodes, bone, bone marrow, liver or other organs (except stage IVS).
Stage IVS: Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin and/or bone marrow (only in infants)

to 'dumb-bell' tumor growth. The primary paraspinal tumor grows through the intervertebral foramen and forms an intraspinal mass with neurologic signs. Metastasis present in 60–70% children, are usually to the skeleton (facial bones, skull), bone marrow and lymph nodes. Two paraneoplastic syndromes attributed to metabolic and immunologic disturbances are associated with localized disease opsoclonus-myoclonus and watery diarrhea associated with VIP secretion by the tumor. Opsoclonus-myoclonus syndrome is characterized by rapid eye movements, ataxia and irregular muscle movements and occurs in 2-4% of patients. Most children with opsoclonus-myoclonus have a favorable outcome with respect to their neuroblastoma but are left with longterm neurological deficits.

Diagnosis

The gold standard for the diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunohistochemistry. Other investigations include blood counts, urinary catecholamine excretion, bone marrow aspiration and biopsy, abdominal ultrasound, and X-ray and bone scan for metastasis. Nuclear scanning with ^{123}I or ^{131}I MIBG detects tumors and metastasis accurately. CT scan of chest, abdomen and pelvis is indicated to assess extent of disease (Fig. 20.11). MRI is preferred for paraspinal tumors to assess spinal cord compression. Quantitation of serum neuron-specific enolase and ferritin, amplification of the *MYC-N* oncogene, tumor, cell ploidy and age-based histologic classification of the tumor are of prognostic value. Children with neuroblastoma can be divided into two groups: those with favorable and those with unfavorable features. The favorable group has a survival expectancy of 90% or more. It is characterized by young age (<1.5 yr), favorable stage (I, II and IVS), normal levels of serum ferritin and favorable histology. Older patients with stage III or IV disease, serum ferritin levels greater than 150 ng/ml and tumors of unfavorable histology have survival rates of 20% or less.

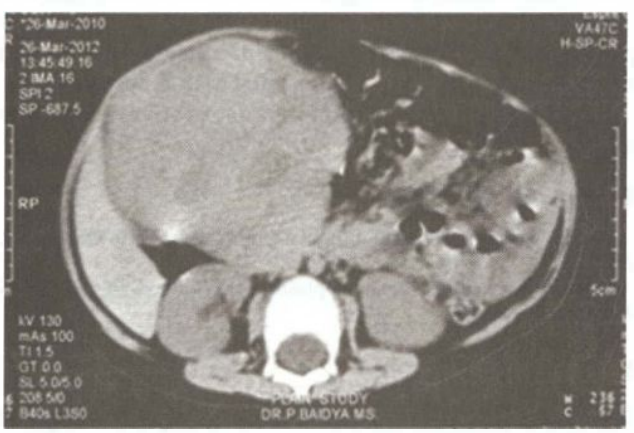

Fig. 20.11: Computed tomography of abdomen shows suprarenal mass suggestive of neuroblastoma

Treatment

Age and clinical stage are the two most important independent prognostic factors. Even with advanced disease, children less than 1-yr-old at diagnosis have a better outcome than those diagnosed later. Treatment modalities for neuroblastoma include chemotherapy, surgery and radiation therapy. Localized neuroblastoma has better prognosis; it can be treated with surgery alone and does not require chemotherapy. Observation alone is needed for stage 4S patients. Chemotherapy is the chief therapy for most patients with neuroblastoma in advanced stage. Chemotherapy includes vincristine and alkylating agents in combination with anthracycline and epipodophyllotoxins. Chemotherapy regimens widely used are OPEC (vincristine, cyclophosphamide, cisplatinum, teniposide (VM-26), CADO (vincristine, cyclophosphamide, doxorubicin) and PECADO (vincristine, cyclophosphamide, doxorubicin, cisplatinum, teniposide), etc. Other modalities include surgery, radiotherapy and autologous bone marrow transplantation.

Suggested Reading

Brodeur GM, Hogarty MD, Mosse YP, Maris JM. Neuroblastoma. In: Principles and Practice of Pediatric Oncology. Eds. Pizzo PA, Poplack DG, Lippincott Williams and Wilkins, Philadelphia 2011;886–922

WILMS TUMOR

Wilms tumor (nephroblastoma) is the most common malignant tumor of the kidney, accounting for 6–7% of all childhood malignancies. Eighty percent of patients with Wilms tumor present under 5 yr of age; the frequency is similar in boys and girls. The peak age at diagnosis is 2–3 yr; 6% patients have bilateral disease. While a vast majority of Wilms tumors are sporadic, 1–2% may be familial. Bilateral disease is more common in patients with familial Wilms tumor.

The tumor is thought to develop in the foci of embryonal kidney tissue called nephrogenic rests. Up to 1% of newborns may have nephrogenic rests. Nephrogenic rests may transform into Wilms tumors.

WT1 is the best characterized Wilms tumor gene. It is located at chromosome 11p13 and encodes for a transcription factor that is critical for normal development of kidneys and gonads. *WT2* is localized to a cluster of genes at 11p15. Children with some genetic syndromes are predisposed to developing Wilms tumor. These include WAGR Wilms tumor, aniridia, genitourinary abnormalities like horseshoe or fused kidney and mental retardation, del 11p13, Denys Drash syndrome (renal failure, renal mesangial sclerosis, male hermaphrodism, *WT1* misense mutation) and Beckwith-Wiedeman syndrome (hemihypertrophy, macroglossia, omphalocele, organomegaly, del 11p15.5-*WT2*).

Loss of heterozygosity (LOH) of 1p and/or 16q and high expression of telomerase have been associated with poorer outcome in children with Wilms tumor.

Clinical Features

Most patients present with an asymptomatic abdominal mass detected by parents or physician during routine examination. Features at diagnosis include hematuria (10–25%), hypertension (25%), abdominal pain (30%), fever (20%), anorexia and vomiting. Tumor thrombus extending into the inferior vena cava is found in 4–10% of cases. Other features include anemia, thrombocytosis, acquired deficiency of von Willebrand factor and factor VII and polycythemia. Important differential diagnosis includes neuroblastoma, hydronephrosis, multicystic kidney and rarely abdominal lymphoma and retroperitoneal rhabdomyosarcoma. Features of congenital syndromes may be present in 13–28% of patients.

Investigations

Ultrasonography is the most important investigation since it can differentiate solid from cystic renal mass. CT scan and MRI provide detailed view of the extent of the tumor (Fig. 20.12). Contralateral kidney must be carefully evaluated on imaging studies. Metastasis in the liver can be detected on ultrasonography and CT scan. CT or MRI of the brain must be done in cases of rhabdoid tumor of the kidney (Table 20.17).

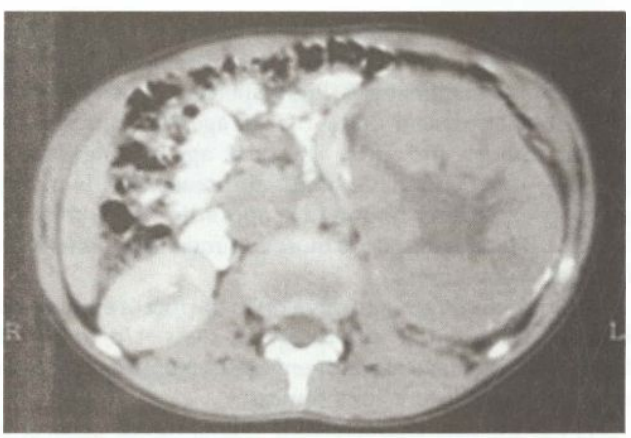

Fig. 20.12: Abdominal CT in 6-yr-old boy with hematuria and abdominal mass suggests Wilms tumor

Table 20.17: Investigations for suspected Wilms tumor

Abdominal ultrasound and Doppler	Identifies organ of origin, involvement of contralateral kidney and presence or absence of tumor thrombus in inferior vena cava
CT scan	Evaluation of tumor extension into adjoining structures such as liver, spleen and colon; visualization and function of contralateral kidney; evaluation for pulmonary metastasis
Chest X-ray	Evaluation for pulmonary metastasis
Fine needle cytology	Cytological confirmation prior to chemotherapy

Prognostic Factors

Stage I: Tumor confined to kidney and completely excised.
Stage II: Tumor extends beyond kidney but completely excised.
Stage III: Tumor infiltrates renal fat; residual tumor after surgery. Lymph node involvement of hilum, para-aortic region or beyond.
Stage IV: Metastasis in lung or liver, rarely bone and brain.
Stage V: Bilateral renal involvement at time of initial diagnosis.

Besides staging another prognostic factor is pathology. 3% tumors show *favorable pathology* (focal anaplasia) for which only surgical excision is necessary. Another 6% have unfavorable histology (diffuse anaplasia); these tumors are pleomorphic and ruptured and show early metastasis to bones. The majority of patients have standard histology, where precise treatment is determined by staging. Ploidy is another prognostic sign, diploid tumors have a better prognosis than hyperdiploid tumors.

Treatment

Therapy for Wilms tumor is based on stage of the disease and histology. The immediate treatment for unilateral disease is removal of the affected kidney. Many experts prefer preoperative chemotherapy because it diminishes the size of the tumor and allows better staging. By preoperative chemotherapy, using actinomycin D and vincristine for a period of 4 weeks, 85% of the patients may not require any local radiotherapy. Stage I and II tumors with favorable histology are usually treated postoperatively with vincristine and actinomycin D. The commonly used drugs for advanced Wilms tumor are a combination of vincristine, actinomycin D and adriamycin along with abdominal radiation. Abdominal radiation is used in stage III disease. Pulmonary radiation is used for pulmonary metastasis.

With modern therapy, 80–90% of patients with Wilms tumor are cured. Overall approximately 90% of children with Wilms tumor are longterm survivors. Young age, low stage and low tumor weight (<550 g) are favorable prognostic factors. Presence of anaplasia and loss of heterozygosity of 1p or 16q increase risk recurrence.

Survivors of Wilms tumor have relatively few late effects.

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SOFT TISSUE SARCOMA

Pediatric soft tissue sarcomas are a group of malignant tumors that originate from primitive mesenchymal tissue and account for 6–7% of all childhood tumors. Rhabdo-

myosarcomas, tumors of striated muscle (commonest childhood soft tissue sarcoma), account for more than half of all cases. The remaining nonrhabdomyosarcomatous soft tissue sarcomas (NRSTSs) account for approximately 3% of all childhood tumors; these include fibrosarcoma, leiomyosarcomas, synovial sarcomas and malignant peripheral nerve sheath tumors.

BONE TUMORS

Osteogenic sarcoma and Ewing sarcoma are the two major types of bone tumors in children and adolescents. Both tumors occur more common during the second decade of life and show male predominance.

Osteogenic Sarcoma

The peak incidence of osteogenic sarcoma is during adolescence, correlating with the rapid bone growth; it is rare below the age of 5 yr. The distal femur and proximal tibia are the most frequent sites followed by proximal humerus and middle and proximal femur. Flat bones, e.g. vertebrae, pelvic bones and mandible may rarely be involved. Radiation exposure is a causal factor for osteogenic sarcoma. Localized painful swelling in the bone is the usual presentation, which may be mistakenly attributed to traumatic or infective conditions, delaying the diagnosis by months. Metastasis occurs early to the lungs and other bones. Several germline mutations of tumor suppressor genes are associated with increased incidence of osteosarcoma. Hereditary retinoblastoma associated with the germline mutation in the *RB1* gene have a significantly increased risk of osteosarcoma. Li-Fraumeni syndrome, a familial cancer syndrome associated with germline mutation of the *p53* gene is also associated with osteosarcoma. High dose radiation therapy such as that used for Ewing sarcoma or brain tumors predisposes to development of osteosarcoma. Benign bone lesions such as Paget disease, multiple hereditary exostoses, fibrous dysplasia and enchondromatosis can undergo malignant transformation and develop osteosarcoma.

Radiographic examination shows sclerotic or lytic bone lesions and periosteal new bone formation over the metaphyseal region. The differential diagnosis includes osteomyelitis and other bone tumors. Biopsy must be done to confirm the diagnosis. This is a pleomorphic, spindle cell tumor that forms extracellular matrix or osteoid. Imaging studies include CT chest and radionuclide bone scan to rule out metastasis.

Successful treatment requires multiagent chemotherapy with complete surgical resection. Amputation is rarely needed with present day management comprising chemotherapy and surgery. Chemotherapeutic agents include doxorubicin, cisplatin, ifosfamide, cyclophosphamide and high dose methotrexate. The tumor is unresponsive to radiotherapy. With current treatments, more than two-thirds of patients presenting without metastasis have longterm survival.

Ewing Sarcoma

Ewing sarcoma is the second most common malignant bone tumor in children and adolescents. Ewing sarcoma occurs most often in the second decade, but can occur below the age of 10 yr. They most often arise from flat bones such as pelvis, chest wall and vertebrae and the diaphyseal region of long bones. Common sites of metastasis are lungs and other bones; bone marrow metastasis is not uncommon.

The typical presentation is with pain, swelling, a lump and/or a limp. Systemic symptoms such as fever and weight loss may be present. The duration of symptoms varies from few weeks to sometimes more than a year. Osteomyelitis and Langerhan cell histiocytosis particularly eosinophilic granuloma are the differential diagnosis. Other small round cell tumors, which metastasize into the bone marrow are neuroblastoma, rhabdomyosarcoma and NHL. Plain radiographs may show destructive lesions of the diaphysis of bone in the form of lytic or mixed lytic and sclerotic lesions with a classical appearance called 'onion skinning' (Fig. 20.13). Biopsy must be done to confirm the diagnosis. Chest CT bone scan and bone marrow biopsy are performed to evaluate for metastasis. Reciprocal chromosomal translocation t(11;22) (q24;q12) is pathognomonic of ES and is present in 85% of cases.

These tumors are responsive to both chemotherapy and radiotherapy. Local surgery is also an effective way to treat Ewing sarcoma, however, surgical amputation is rarely indicated. Tumor control with radiotherapy requires moderately high doses ranging from 5500 to 6000 cGy. Multiagent combination chemotherapy includes vincristine, dactinomycin, cyclophosphamide and doxorubicin.

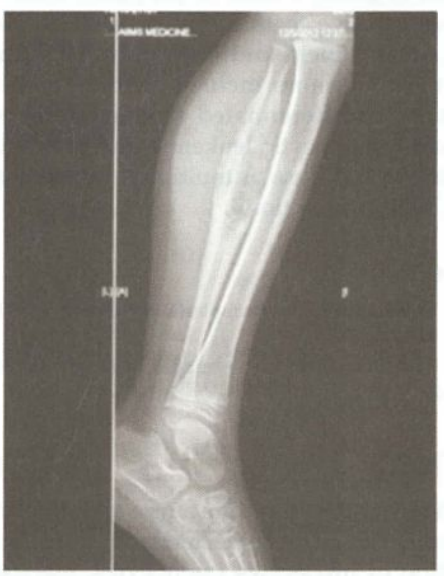

Fig. 20.13: Radiograph of leg shows permeative lytic lesion with a prominent soft tissue mass extending from the bone and periosteal reaction. The 'onion-skin' or 'sun-burst' pattern indicates an aggressive process suggesting Ewing sarcoma

MALIGNANT TUMORS OF THE LIVER

Primary tumors of the liver are rare and account for approximately 1% of all childhood malignancies. Hepatoblastoma and hepatocellular carcinoma are the two most common malignant disorders of the liver. Over 80% of malignant liver tumors in children are hepatoblastomas. Most commonly hepatoblastoma presents as an asymptomatic abdominal mass in a young child. As the disease progresses child may develop symptoms such as abdominal pain, weight loss, vomiting and anorexia. Metastatic spread occurs to regional lymph nodes and lungs; patients do not have jaundice.

Serum α-fetoprotein (AFP) is a useful diagnostic marker that can be used for disease assessment during and after completion of therapy. AFP is elevated in almost all hepatoblastomas. Tumor thrombi extending into the hepatic veins and inferior vena cava may be present at diagnosis.

Diagnostic imaging should include CT or MRI of the abdomen along with the CT of the chest for evaluation of metastatic disease. Complete resection of the tumor either by partial hepatectomy or by liver transplantation is critical for successful treatment of malignant liver tumors. Two more cycles of chemotherapy are administered after surgical resection.

Hepatocellular carcinoma is associated with chronic hepatitis B and C infections. Abdominal distention, pain, anorexia and weight loss are common presenting symptoms. Patients may present with acute abdominal pain secondary to tumor rupture and hemoperitoneum. Serum AFP is elevated in about 60% of cases. Liver enzymes may be elevated. Complete resection can only be achieved in about a third of the cases. Chemotherapeutic agents active in this disease include cisplatin, etoposide, doxorubicin and 5 flourouracil. Other rare malignant liver tumors include rhabdomyosarcoma, embryonal or undifferentiated sarcoma and angiosarcoma. Acute lymphocytic leukemia and neuroblastoma may present with diffuse or multifocal infiltration of the liver with liver dysfunction.

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20

HISTIOCYTOSES

The childhood histiocytoses are a rare and diverse group of proliferative disorders characterized by infiltration and accumulation of histiocytes (monocytes, macrophages, dendritic cells, Langerhans cells) within various tissues. The International Histiocyte Society has proposed a classification for histiocyte disorders (Table 20.18).

Table 20.18: Classification of histiocytic disorders

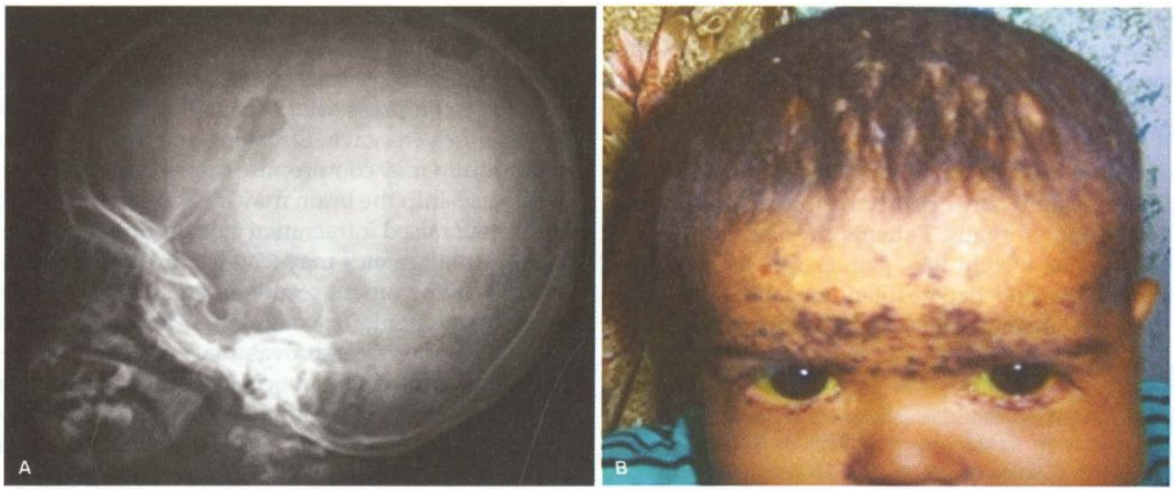
Dendritic cell disorders
Langerhans cell histiocytosis (LCH)
Secondary dendritic cell processes
Juvenile xanthogranuloma
Solitary histiocytoma with dendritic phenotype
Macrophage related disorders
Hemophagocytosis syndromes (primary and secondary)
Rosai-Dorfman disease
Solitary histiocytoma with macrophage phenotype
Malignant histiocyte disorders
Monocyte related leukemias
Extramedullary monocytic tumors
Dendritic cell or macrophage related histiocytic sarcoma

Langerhans Cell Histiocytosis (LCH)

LCH is a rare nonmalignant disease characterized by a clonal proliferation of pathologic cells with the characteristics of Langerhans cells in single/multiple sites and an unpredictable course. This is usually a sporadic and nonhereditary condition. The clinical presentation is heterogeneous ranging from single-system involvement to a multisystem life-threatening disease. The hallmark of LCH is the presence of Birbeck granules on electron microscopy and positivity for S-100 protein and CD1a. The number of cells with Birbeck granules can vary in different lesions with limited numbers seen in tissues taken from liver, spleen, gastrointestinal tract or CNS. As a result other pathognomonic surface markers are being sought. Langerin (CD207), a novel monoclonal antibody directed against a type II transmembrane protein associated with Birbeck granules, is considered sensitive and specific for Langerhans cells. This may be a key component of an immunocytochemical panel to diagnose LCH.

The spectrum of LCH (eosinophilic granuloma, Hand-Schuller-Christian disease, Letterer-Siwe disease) reflects varying extents of the disease. The course of disease is unpredictable, varying from rapid progression and death, to repeated recurrence and recrudescence with chronic sequelae, to spontaneous regression and resolution. Patients with disease that is localized (skin or bone) have a good prognosis and are felt to need minimum or even no treatment. In contrast, multiple organ involvement, particularly in children under 2-yr-old, carries relatively poor prognosis.

The most common involvement is of the skeleton (80%). Bone lesions can be single or multiple affecting skull bones, long bones, vertebrae, mastoid and mandible (Fig. 20.14A) The lesions may be painless or present with pain and local swelling; X-rays show sharp lytic lesions. Clinical manifestation includes vertebral collapse and spinal compression, pathological fractures in long bones, chronic draining ears and early eruption of teeth. Other manifestations include seborrheic skin rash (Fig. 20.14B) on



Figs 20.14A and B: Langerhans cell histiocytosis (LCH). (A) Radiograph of skull showing lytic lesions; (B) note the seborrhea, skin lesions and jaundice

scalp and back (60%), lymphadenopathy (33%), hepatosplenomegaly (20%), tachypnea, air leaks, parenchymal lung infiltrates (15%), jaundice, abdominal distension, neurodegenerative symptoms and features of malabsorption. Bilateral infiltration of retroorbital area may cause exophthalmos. Gingival mucous membrane may be involved with lesions, which look like candidiasis. Pituitary dysfunction may result in growth retardation and/or diabetes insipidus. Severe disease is characterized by fever, weight loss, malaise, failure to thrive and liver dysfunction. Liver involvement may result in sclerosing cholangitis and cirrhosis. Bone marrow involvement may lead to anemia and thrombocytopenia. Multiorgan dysfunction is associated with poor prognosis.

Diagnostic work up should include appropriate biopsies, complete blood count, liver function tests, coagulation studies, skeletal survey, chest X-ray and urine specific gravity. In addition, evaluation of involved organ system should be under taken. These include ultrasound abdomen, CT chest and or abdomen and MRI brain. Bone marrow biopsies are required to exclude infiltration.

Treatment for localized disease or single bony lesion varies from observation, curettage, indomethacin, bisphosphonates, low dose radiation or systemic chemotherapy Multisystem disease is treated with chemotherapy, combining vinblastine, prednisone and 6 mercaptopurine. If there is response based on clinical evaluation and investigations these children are treated for a total duration of 12 months.

Hemophagocytic Lymphohistiocytoses

Hemophagocytic lymphohistiocytoses (HLH) is an aggressive and potentially fatal syndrome which results from an inappropriate prolonged activation of lymphocytes and macrophages which lack Birbeck granules and CD1a positivity. Young children with HLH and known gene mutations, or a family history of HLH are described as having primary HLH. Older children with HLH or children without identifiable mutations are described to have secondary/acquired HLH. Common causes of secondary HLH are infection, systemic juvenile rheumatoid arthritis and SLE.

Clinical features include fever (91%), hepatomegaly (90%), splenomegaly (84%), neurological symptoms (47%), rash (43%) and lymphadenopathy (42%). HLH patients often develop liver failure with hyperbilirubinemia, pancytopenia, coagulopathy, renal failure, ARDS and features of encephalopathy. In the absence of a known gene mutation, a diagnosis of HLH can be made when atleast 5 of the 8 criteria are identified (Table 20.19).

Treatment comprises dexamethasone and etoposide. Cyclosporine may be added. Treatment of underlying infections should be undertaken. HLH patients require multiple transfusions of blood components and prophyl-

Table 20.19: Clinical criteria for the diagnosis of hemophagocytic lymphohistiocytoses

One of the two is required to establish the diagnosis:

1. Presence of pathogenic mutation in PERF, SAP or MUNC gene
2. Five of the following 8 criteria are fulfilled:
   - i. Fever
   - ii. Splenomegaly
   - iii. Cytopenias in at least two cell lines (hemoglobin <9 g/dl, platelets <100 × 10^9 cells/l and/or neutrophils <1 × 10^9 cells/l)
   - iv. Hypertriglyceridemia (fasting triglycerides >3 mmol/l or >265 mg/dl) and/or hypofibrinogenemia (fibrinogen <1.5 g/l)
   - v. Hemophagocytosis in bone marrow or spleen or lymph nodes
   - vi. Low or absent activity of natural killer cells
   - vii. Serum ferritin >500 µg/l
   - viii. Soluble interleukin-2 receptor (CD25) >2400 units/ml

axis against *Pneumocystis jirovecii* and fungi. Other modalities having a role for familial HLH include antithymocyte globulin and stem cell transplantation.

Malignant Histiocytosis

These conditions represent malignancies of the monocyte macrophage system with proliferation of malignant histiocytes in many organs. Patients present with fever, weakness, anemia, weight loss, skin eruptions, jaundice lymphadenopathy and hepatosplenomegaly. Treatment is with intensive chemotherapy and CNS prophylaxis.

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ONCOLOGIC EMERGENCIES

The survival of children with cancer has improved as a result of advances in diagnosis and newer therapies including hematopoietic cell transplantation and use of growth factors. Oncologic emergencies may come as initial presentation of the malignancy, during course of the disease or as a consequence of therapy. A solid tumor may invade or compress vital organs like trachea, esophagus or superior vena cava. Effusions into the pleural space or pericardium may compromise functions of heart and lung. Metastasis into the brain may lead to cerebral edema and features of raised intracranial tension. Spinal cord involvement by malignancy may lead to cord compression. Bone marrow involvement results in anemia, bleeding due to thrombocytopenia or coagulation abnormalities, leukostasis, thrombosis, cerebrovascular episodes and infections. Hormonal problems can occur because of paraneoplastic secretions. Metabolic complications may occur prior to or at onset of chemotherapy. Therapy related complications, include myocardial dysfunction (anthracyclines), extravasation of drugs (anthracyclines, vinca alkaloids), hemorrhagic cystitis (cyclophosphamide), cerebrovascular accidents (methotrexate, l-asparaginase) and pancreatitis (l-asparaginase, corticosteroids) may be encountered. Early diagnosis and urgent management of these conditions will save the life of the child and allow for treatment of the underlying malignancy. Common oncologic emergencies are discussed in Table 20.20.

Other emergencies include (i) *Cardiac tamponade:* This occurs due to massive pericardial effusion, constrictive

Table 20.20: Presentation and treatment of common oncologic emergencies

Oncologic emergency	*Manifestation*	*Underlying disease*	*Treatment*
Tumor lysis syndrome	Hyperkalemia leading to arrhythmias; hyperphosphatemia; hyperuricemia; acute kidney injury; hypocalcemia with tetany; metastatic calcifications	Acute lymphoblastic leukemia, non-Hodgkin lymphoma (most commonly Burkitt lymphoma), acute lymphoblastic leukemia	Hydration, alkalinization, allopurinol, rasburicase (if uric acid >10 mg/dl), dialysis for renal failure
Hyperleukocytosis (leukocyte count >100,000/mm^3)	Thrombosis, stroke, pulmonary infiltrates, hemorrhage and/or hypoxia	Leukemia	Hydration, hydroxyurea, leukopheresis, chemotherapy
Superior vena cava or mediastinal syndrome	Swelling of face and neck, dyspnea; orthopnea; dysphagia; hoarse voice; proptosis; Horner syndrome; chest pain; wheezing; pleural or pericardial effusion; type II respiratory failure	Superior mediastinal mass, most commonly NHL, ALL or germ cell tumor	Establish histological diagnosis by tissue sampling; administer corticosteroids. Avoid intravenous access in upper limbs; monitor for tumor lysis; chemotherapy; radiation
Spinal cord compression	Paraplegia, back pain, urinary retention, loss of deep tendon reflexes and hypotonia	Neuroblastoma; Ewing sarcoma; lymphoma involving vertebral body	Dexamethasone; definitive management; surgery if required
Increased intracranial pressure	Headache, emesis, hypertension, bradycardia, cranial nerve palsy; seizures	Medulloblastoma, astrocytoma, brainstem glioma	Dexamethasone; surgical intervention; phenytoin
Febrile neutropenia*	Sepsis, shock, pneumonia, typhlitis (inflammation of cecum), disseminated intravascular coagulation	Any child with malignancy and on chemotherapy	Broad spectrum antibiotics and antifungal agents

*Fever defined as oral or axillary temperature, lasting at least one hour, of greater than 38.3°C or 101°F once, or greater than 38.0°C or 100° F twice within a 12-hr period; neutropenia defined as an absolute neutrophil count below 500 cells/mm^3 or <1000 cells/mm^3 with an expected decline.

pericarditis from radiation, intracardiac thrombus or tumors. (ii) *Syndrome of inappropriate antidiuretic hormone secretion* may occur due to various chemotherapeutic agents (cyclophosphamide, vinca alkaloids, cisplatin) or with certain malignancies (craniopharyngioma, nasopharyngeal carcinoma). (iii) *Gastrointestinal emergencies*: These include acute abdomen, ileus, massive hepatomegaly and typhlitis. Infants with stage IV neuroblastoma may present with massive hepatomegaly sufficient to cause respiratory compromise. Typhlitis presents usually with fever, neutropenia and acute abdominal pain. It is a necrotizing colitis caused by bacterial invasion of the caecum that may progress to bowel infarction and perforation.

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CHILDHOOD CANCER SURVIVORSHIP

The overall survival of children with malignancies has increased. Over 80% children and adolescents with cancer survive 5 or more years from diagnosis in many centers and are effectively cured of the disease. This is however at the cost of increased morbidity with various long/late effects of cancer treatment. Longterm side effects are those complications of treatment that occur during therapy and persist even after the treatment is over. Late effects appear months or years after the completion of treatment. One-third to half of childhood cancer survivors will experience a late/longterm effect of cancer therapy; of which up to half may be life-threatening.

These effects are more common with more intensive treatment regimens and more frequently seen with radiation therapy in young children. Neurocognitive deficits, growth retardation, cardiomyopathy, infertility and second malignancy are some of the most serious late adverse effects of therapy. Risk of cardiomyopathy and second cancer increases with increasing time from initial diagnosis. Up to 12% patients may develop a second cancer 25 yr after diagnosis of the first cancer.

The main goals of the Cancer Survivorship Program are to improve the health and well-being of childhood cancer survivors by promoting adherence to a schedule of followup appointments and routine screening tests, educate patients, parents and health care professionals about the longterm effects of cancer treatment, integrate them appropriately into society, provide referrals to specialists as needed and offer psychological counseling and transition of patients to adult care when ready.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) refers to the administration of hematopoietic progenitor cells from bone marrow, peripheral blood or umbilical cord from the same individual (i.e. autologous) or another donor (i.e. allogeneic) to reconstitute the bone marrow (*see* Chapter 12). Autologous and allogeneic HSCT are used increasingly to treat a variety of hematologic malignancies in children.

HSCT is indicated in the following pediatric malignancies; (i) acute myeloid leukemia, following first or subsequent remission in patients with favorable cytogenetics such as translocation t(15; 17) or inversion (16); or in presence of residual disease; (ii) acute lymphoblastic leukemia, following first or subsequent remission in patients with Philadelphia chromosome positive disease, t(4:11) positivity, biphenotypic disease or >1% minimal residual disease; as salvage therapy for resistant disease; and following second or subsequent remission; (iii) chronic myeloid leukemia; (iv) certain lymphomas (e.g. peripheral T cell lymphoma, follicular lymphoma, diffuse large B cells lymphoma); and (v) some solid tumors (neuroblastoma, retinoblastoma, brain tumors, sarcomas).

The outcomes following transplantation have improved due to advances in supportive care, refinement in techniques of HLA matching and improved diagnosis and therapy for infectious morbidities. Disease stage at the time of HSCT and cytogenetic abnormalities are important determinants of disease relapse after transplantation.

21 Rheumatological Disorders

Surjit Singh

ARTHRITIS

Approach to Diagnosis

Arthritis is a common complaint in children. It is said to be present if there is swelling or effusion in a joint or if there are any two of the following 4 features: (i) limitation of range of motion, (ii) pain, (iii) tenderness and (iv) increased heat. It can be secondary to an underlying illness (infectious or noninfectious), or may be a primary disease condition in itself. Clinical assessment based on a good history and physical examination would provide more diagnostic clues than indiscriminate laboratory tests. A convenient way to classify arthritis is based on the duration of illness at the time of presentation (Table 21.1).

Table 21.1: Classification of arthritis

Acute arthritis (usually <2 weeks)
Arthritis associated with acute rheumatic fever
Transient ('toxic') synovitis
Arthritis associated with Kawasaki disease, Henoch-Schönlein purpura
Septic arthritis *(S. aureus, H. influenzae, N. meningitidis)*
Subacute arthritis (2–6 weeks)
Reactive arthritis
Arthritis associated with systemic lupus erythematosus, dermatomyositis, polyarteritis nodosa
Bone pains associated with leukemia or neuroblastoma
Arthritis associated with Lyme disease or brucellosis
Sickle cell disease
Arthritis associated with hypogammaglobulinemia
Chronic arthritis (>6 weeks)
Juvenile idiopathic arthritis
Ankylosing spondylitis
Tubercular arthritis
Legg-Calvé-Perthes disease
Psoriasis

Transient Synovitis

This is a common condition seen in young children and is characterized by sudden onset of pain in the hips, thighs or knees following an upper respiratory catarrh. It is a self limiting disorder, lasts only 2–4 days and must not be confused with a septic arthritis or acute osteomyelitis. Skin traction and judicious use of nonsteroidal anti-inflammatory drugs (NSAIDs) brings prompt relief.

Septic Arthritis

This is usually seen in neonates and infants. It presents almost always as a monoarthritis and is accompanied by fever, tenderness and limitation of joint movement. Causes include gram-negative bacilli, group B streptococci (in neonates), *Haemophilus influenzae* type B and *Streptococcus pneumoniae* (in infants) and *Staphylococcus aureus* (in older children). Ultrasonography, magnetic resonance imaging and radionuclide scans provide useful clues to the diagnosis. A diagnostic arthrocentesis is necessary to confirm the diagnosis (Table 21.2). Appropriate antimicrobials, aspiration and, in some cases (e.g. the hip joint), open drainage are required for treatment.

Tubercular Arthritis

This has become less common in our experience. It can result from an actual infection with *Mycobacterium tuberculosis* or from an allergic phenomenon (Poncet disease). The former type usually presents as a mono-arthritis (e.g. hip or ankle joint) while the latter type presents as a polyarthritis with a strongly positive Mantoux reaction. Arthrocentesis may be diagnostic (Table 21.2).

Reactive Arthritis

This is not as common in children as in adults. It is diagnosed on the basis of Berlin criteria: (i) peripheral arthritis: usually lower limb asymmetric oligoarthritis; (ii) evidence of preceding gastrointestinal or genitourinary

Table 21.2: Synovial fluid characteristics in childhood arthritides

Type of arthritis	*Physical characteristics*	*Cytology*	*Biochemistry*	*Comments*
Septic arthritis	Turbid; serosanguineous	Polymorphonuclear cells present; Gram stain may be positive	Glucose reduced; protein elevated	Synovial fluid culture may be positive; synovial fluid should also be inoculated in blood culture bottles to increase the yield
Tuberculous arthritis	Opaque	Lymphocytes present; stain for acid fast bacilli may be positive	Glucose may be normal; protein elevated	Polymerase chain reaction may be positive
Juvenile inflammatory arthritis	Cloudy	Polymorphs present; Gram stain negative	Glucose low; protein elevated	Fluid characteristics often mimic those of septic arthritis
Systemic lupus erythematosus	Clear	Lymphocytes present; LE cell phenomenon may be positive	Protein normal or elevated; glucose may be normal	Synovial fluid complement C3 may be low

infection (usually by *Shigella*, *Chlamydia* or *Yersinia*), in absence of clinical symptoms and (iii) exclusion of other arthritides.

A small proportion of children with acute lymphocytic leukemia show bone and joint pains. Bone pain (more marked at night), rather than joint swelling, is the predominant complaint in affected children. The hemogram shows lymphocytic predominance and thrombocytopenia, in contrast to a polymorphonuclear predominance and thrombocytosis characteristic of juvenile idiopathic arthritis. A bone marrow examination is required to confirm the diagnosis. X-linked agammaglobulinemia (Bruton disease) may sometimes present as an unusual 'aseptic' arthritis (due to *Mycoplasma* infection), but accompanying respiratory and other infections are also usually present.

Arthritis can sometimes be the presenting complaint of hemophilia.

Legg-Calvé-Perthes Disease

This is characterized by an avascular necrosis of the femoral head, occurring usually in boys 5–10 yr of age. It is now believed to be a manifestation of an underlying hypercoagulable state (hypofibrinolysis or a deficiency of protein C or protein S). Familial occurrence can occur and the condition is bilateral in 10% patients. Affected children present with a limp. Initial X-rays may be normal. Isotope bone scans and magnetic resonance imaging are required to confirm the diagnosis. Subsequent X-rays show a characteristic sequential progression: (i) widening of joint space, (ii) fragmentation of epiphysis with patchy areas of increased lucency or density, (iii) abnormalities of shape of femoral head and neck and (iv) deformed head. Treatment options include femoral varus osteotomies or containment splints.

Juvenile Idiopathic Arthritis

The term Juvenile Idiopathic Arthritis (JIA) was proposed by the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR). It refers to a group of conditions characterized by chronic inflammatory changes of the joints. It is defined as arthritis of one or more joints with onset below the age of 16 yr and persisting for at least 6 weeks. It has the following subtypes:

i. Systemic
ii. Oligoarthritis: (a) persistent (b) extended
iii. Polyarthritis: rheumatoid factor negative
iv. Polyarthritis: rheumatoid factor positive
v. Psoriatic arthritis
vi. Enthesitis related arthritis
vii. Undifferentiated arthritis: (a) fits no other category; (b) fits more than one category

JIA is not a rare disease; its estimated prevalence ranging from 0.4 to 1.3 per 1000 children below 16 yr of age. It is the commonest rheumatological disorder of childhood and one of the most common causes of disability, chronic morbidity and school absenteeism. While the Western studies suggest that JIA is more common in girls, in India the female predominance is not marked.

Etiology

The immune system is intimately involved in the evolution of the disease. There also appears to be a major histocompatibility complex (MHC) associated genetic predisposition. For instance HLA DR5 and DR8 are linked to early onset oligoarthritis (seen more in girls), B27 to late onset oligoarthritis (seen more in boys) and DR4, Dw4 and DR1 to rheumatoid factor positive polyarthritis. JIA does not appear to be a homogeneous disease entity and the different subtypes may, in fact, represent separate clinical conditions.

The etiopathogenesis of JIA remains an enigma. Several environmental triggers (e.g. infection with rubella virus, parvovirus B19, *M. tuberculosis*, *M. pneumoniae* and enteric organisms; physical trauma; psychological stress) are linked to the onset of JIA, but their exact role is not clear. Lymphocyte subset analysis shows increased numbers of

activated T cells in children with polyarthritis and oligoarthritis, while children with systemic disease have low numbers of natural killer cells. Cytokines like tumor necrosis factor-α (TNF-α), IL-6 and IL-1 have to have an important role to play in the pathogenesis of the disease. A number of autoantibodies (for instance, antinuclear antibody) may be seen in the sera of children with JIA. The classical IgM rheumatoid factor is almost never detectable in preschool children with JIA. Older girls with polyarticular small joint disease of the hands (especially involving the metacarpophalangeal and proximal interphalangeal joints) may, however, be RF positive.

Clinical Subtypes

Three major types of onset are described according to the presentation during the first 6 months of disease, viz. systemic (with fever and rash), oligoarthritis (4 or fewer joints involved) and polyarthritis (more than 4 joints involved).

Systemic onset JIA About 5–15% of patients with JIA may have acute onset disease with prominent systemic features. These systemic features can sometimes precede joint manifestations by weeks or months. This condition should, therefore, be considered in the differential diagnosis of any child with prolonged fever. The illness can occur at any age and is more common in boys.

The illness usually begins as an intermittent fever with a characteristic twice daily peak (quotidian fever). Fever is prominent in the evening hours. It is accompanied by a characteristic evanescent maculopapular rash (with central clearing), which is prominent on the trunk. This rash may be difficult to recognize in individuals with dark skins. Affected children show marked irritability, which decreases with subsidence of fever. Serosal involvement (in the form of pericarditis or pleuritis) may be prominent. Hepatosplenomegaly and lymphadenopathy are common at presentation and can lead to diagnostic confusion. There is a moderate neutrophilic leukocytosis and an elevated erythrocyte sedimentation rate along with thrombocytosis. The rheumatoid factor is negative.

Oligoarthritis Oligoarthritis is the most frequent type of JIA accounting for approximately 60–70% of patients. Four or fewer joints (usually large) are affected during the first 6 months of the disease. The involvement is often asymmetrical. Joint swelling, rather than joint pain, is the usual complaint. Two subtypes are described: persistent (if number of affected joints continues to be 4 or less) and extended (if number of affected joints exceeds 4 during the disease course).

Oligoarthritis is more common in young girls, typically 3–5 yr of age. The knees and ankles are commonly affected. Small joints of the hands and feet are not involved. Asymptomatic and potentially blinding, iridocylitis can be seen in 25% patients.

Polyarthritis Polyarthritis occurs in 25–30% of patients and is more common in girls. Joint pain, out of proportion to the degree of joint swelling, is the usual complaint. Fever and malaise can be significant. Two subtypes are known:

Rheumatoid factor negative. This subtype may occur at any age in childhood. The knees, wrists and hips are the joints usually affected. Small joints of hands and feet are less commonly involved and rheumatoid nodules are not seen. Joint disease in this subtype of JIA is far less severe than that seen in patients who are rheumatoid factor positive.

Rheumatoid factor positive. The age at onset is late childhood or early adolescence. The arthritis is symmetrical, additive, severe and deforming and typically involves the small joints of the hand, especially the metacarpophalangeal and the proximal interphalangeal. Cervical spine and temporomandibular joints can also be affected. This subtype is the only category of JIA which is somewhat similar phenotypically to adult onset rheumatoid arthritis. Rheumatoid nodules are present in some patients and they usually manifest severe disease.

Psoriatic arthritis Psoriatic arthritis is said to be present when there is arthritis in association with psoriasis or any 2 of the following features: dactylitis, nail pitting and psoriasis in a first degree relative. Arthritis may precede, accompany or follow the occurrence of psoriasis in children. Simultaneous occurrence of small and large joint arthritis or involvement of the distal interphalangeal joint are important clinical clues to the condition.

Enthesitis-related arthritis This condition is more common in boys, typically older than 8 yr. Large joints of lower extremities are commonly affected. Many children are HLA B27 positive, and a proportion of these may go on to develop ankylosing spondylitis later as adults. However, sacroiliitis and spondylitis are usually not significant till late adolescence. Self limiting acute symptomatic iritis may occur in some patients but it does not progress onto the chronic iridocyclitis seen in the oligoarthritis of young girls. A family history of ankylosing spondylitis, psoriasis, Reiter disease and low back pain may be obtained in these children.

Laboratory Investigations

The clinician should recognize the differing patterns of joint involvement in various types of JIA. This 'pattern recognition' is often the most important diagnostic clue. Laboratory investigations may be of little or no help in arriving at a diagnosis.

Synovial fluid aspiration for microscopy and culture is indicated in children with monoarthritis because septic arthritis may need to be excluded in such cases (Table 21.2). Complete blood counts should be requested along with an erythrocyte sedimentation rate. Acute lymphocytic leukemia can sometimes have an arthritic presentation and

such children may be mistakenly diagnosed as having JIA. Bone marrow aspiration is therefore necessary if use of glucocorticoids is being contemplated for treatment of JIA.

C-reactive protein measurement is a surrogate marker of disease activity and are helpful on followup. Plain radiographs of affected joints are obtained at the time of initial diagnosis and may be repeated for assessment of erosive disease. It should be noted that screening for rheumatoid factor is not a useful test for diagnosis of arthritis in young children, but it is an important prognostic factor in situations where it is positive.

Treatment

Management of JIA is multidisciplinary. Physiotherapy and occupational therapy should be tailored to the specific needs of an individual child, in order to prevent deformities and facilitate 'mainstreaming' and rehabilitation. Physical therapy helps in relieving pain, maintenance of posture and joint mobility, improves muscle strength and prevents fixed flexion deformities. Patient should be assessed by an ophthalmologist so that uveitis can be detected early and treated appropriately. Children with oligoarthritis need regular ophthalmological followup as uveitis can develop later.

Medical therapy. NSAIDs are the mainstay of symptomatic management. The conventional NSAIDs inhibit both isoforms of the enzyme cyclo-oxygenase, i.e. COX-1 (constitutive; mediates physiologic prostaglandin production necessary for gastrointestinal mucosal integrity and adequacy of renal blood flow) and COX-2 (inducible; mediates pathologic prostaglandin production, especially at sites of inflammation). The NSAIDs commonly used in children are naproxen and ibuprofen. Indomethacin is believed to be of particular use in enthesitis related arthritis. Doses of commonly used NSAIDs are given in Table 21.3.

The development of Reye syndrome is a distinct possibility while a child is receiving NSAIDs, especially if there is an intercurrent viral illness. All children with NSAIDs must be also monitored for gastrointestinal adverse effects. The recently introduced selective COX-2 inhibitors (e.g. rofecoxib, valdecoxib) have lower gastrointestinal adverse effects, but are not recommended for use in children.

Table 21.3: Doses of commonly used NSAIDs

	Dose, mg/kg/day	*Maximum dose, mg/day*	*Frequency of administration*
Naproxen	15–20	750	Twice daily
Ibuprofen	35–45	2400	Four times daily
Indomethacin	1–2	150	Three times daily
Diclofenac	2–3	150	Four times daily
Piroxicam	0.3–0.6	20	Once daily

The analgesic dose is usually half the anti-inflammatory dose

Although the mechanism of action of all NSAIDs is the same, idiosyncratic responses are well known and a given patient may respond to one NSAID and not to the other. Response to therapy is usually slow and this fact must be explained to the parents. Treatment must continue for at least 4–6 weeks before a decision to switch over to another NSAID is made.

Disease modifying anti-rheumatic drugs (DMARDs) need to be started in almost all children with polyarthritis. Weekly methotrexate (15–25 mg/m^2/week given subcutaneously or orally) has simplified the management of severe forms of JIA. Children seem to tolerate methotrexate better than adults and have fewer adverse effects. Once the child is in stable remission (usually achieved after several months), the drug can be tapered to the minimum effective dose and then stopped. Methotrexate should always be given under close medical supervision. Periodic testing of liver functions is mandatory. Development of hepatic fibrosis, a dreaded adverse effect, is uncommon. Hydroxychloroquine is a useful adjunct and is often used along with methotrexate. Leflunomide, an inhibitor of pyrimidine synthesis, has been used in adults with rheumatoid arthritis, but experience in children is limited.

Intra-articular injections of glucocorticoids (usually triamcinolone) are the preferred therapy for children with oligoarthritis who do not respond to an initial trial of NSAIDs. In addition, local steroid instillation (along with mydiatrics) may be required for patients with iridocyclitis. Systemic glucocorticoids (usually prednisolone 1–2 mg/kg/day; occasionally methylprednisolone 10–30 mg/kg) are necessary for severe unremitting arthritis, systemic manifestations (e.g. pericarditis, myocarditis, vasculitis) and rapidly progressive disease. Prednisolone, when used in this manner, is usually given as bridge therapy for a few weeks while awaiting the clinical response of methotrexate.

Newer modalities of treatment include recently introduced biologicals. These include anakinra (IL-1 receptor antagonist); canakinumab (monoclonal antibody to IL-1); tocilizumab (monoclonal antibody to IL6 receptor); infliximab, golimumab and adalimumab (monoclonal antibodies to TNFα); etanercept (recombinant soluble TNF receptor p75 fusion protein) and abatacept (inhibitor of T cell activation). Both etanercept and infliximab are powerful biological agents against TNFα. While etanercept has been used in children with polyarticular JIA not responding to methotrexate, infliximab has been more commonly used in adults with spondyloarthropathy. Tocilizumab has found favour in children with severe forms of systemic onset disease. While these agents are effective in children with difficult forms of arthritis, longterm safety of these products in children is still unclear.

Course

Oligoarthritis usually has a good prognosis but localized deformities can develop due to asymmetric growth of limbs. Children with enthesitis related arthritis can develop

spondylitis and sacroiliitis later, especially if they are HLA B27 positive.

Children with rheumatoid factor positive polyarthritis have a disease pattern similar to adults and show erosive and deforming arthritis. Response to therapy is not predictable. The prognosis is relatively better for seronegative polyarthritis as remissions are obtained more often and residual joint lesions may be minimal.

The course of systemic onset disease can be extremely variable and the response to therapy is not always satisfactory. Approximately 50% patients undergo remission with minor residual joint involvement while others may develop progressive arthritis or have recurrent episodes of systemic disease. The presence of HLA DR4 is associated with severe, persistent arthritis.

Inappropriately treated or untreated patients with JIA may develop flexion contractures of hips, knees and elbows, resulting in permanent disability. Neck stiffness is an especially debilitating problem and can result in torticollis. Temporomandibular joint involvement results in restricted opening of the mouth and may require surgical intervention.

Complications

Anemia, due to chronic ongoing inflammation, is almost always present in children with persistent active arthritis and serial hemoglobin levels mirror disease activity rather closely. Blood loss induced by NSAIDs can also be a contributory factor for the anemia. Chronic anterior uveitis may be clinically silent and potentially blinding. Girls below 6 yr of age with oligoarthritis and who have antinuclear antibodies are at the highest risk of developing this complication.

Children with systemic onset disease are especially prone to develop macrophage activation syndrome, a potentially life-threatening complication manifesting as sudden onset icterus, bleeding tendency, leukopenia, thrombocytopenia, elevated triglycerides and raised ferritin levels. Prompt administration of intravenous methylprednisolone pulses is often curative.

Growth disturbances, limb length discrepancies and joint contractures can be seen in children with long-standing disease. Growth failure may occur secondary to severe inflammation or treatment with glucocorticoids. Treatment with recombinant human growth hormone may be an option in children with growth disturbances. Secondary amyloidosis is a rare complication, presents with asymptomatic proteinuria and hypoalbuminemia, and is often irreversible.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by inflammation of blood vessels and connective tissues resulting in multisystem involvement. The clinical manifestations are variable and the course unpredictable. Childhood SLE is usually more severe and has a poorer prognosis than adult SLE. The hallmark of SLE is the presence of antinuclear antibodies. The female predominance characteristic of adult SLE is usually not apparent in young children.

Diagnosis

The diagnosis of SLE is facilitated by the classification criteria given by American College of Rheumatology (Table 21.4). Presence of four of these criteria, either at presentation or sequentially, gives a sensitivity and specificity of 96% in adults. However, SLE is a clinical diagnosis, the criteria provide helpful guidelines for arriving at a diagnosis. In many patients, especially children, treatment is initiated even when they do not fulfil the requisite criteria.

Table 21.4: ACR 1997 criteria for classification of systemic lupus erythematosus

Malar rash
Discoid rash
Photosensitivity
Oral or nasal mucocutaneous ulcerations
Nonerosive arthritis
Nephritis (proteinuria >0.5 g/day or cellular casts)
Encephalopathy (seizures or psychosis)
Pleuritis or pericarditis
Cytopenia
Positive immunoserology (antibodies to dsDNA/Smith nuclear antigen) or positive finding of antiphospholipid antibodies (IgG/IgM anticardiolipin antibodies or lupus anticoagulant or VDRL)
Positive antinuclear antibody test

The malar rash, which is virtually pathognomonic of SLE, may not be apparent initially. It involves the cheek, bridge of nose and lower eyelids but spares the nasolabial folds (Fig. 21.1). Discoid lesions are rare in childhood onset SLE. Oral ulcerations may involve the buccal mucosa or palate and are characteristically painless. Some children may have prominent frontal alopecia (Fig. 21.2). Arthritis is usually mild and always non-erosive.

Renal involvement is a dreaded complication of SLE and one of the commonest causes of mortality in children. Lupus nephritis can be classified as follows: *Class I:* Minimal mesangial; *Class II:* Mesangial proliferative; *Class III:* Focal proliferative; *Class IV:* Diffuse proliferative; *Class V:* Membranous; *Class VI:* Advanced sclerosing. Class III and Class IV lesions require the most aggressive forms of therapy.

Neurological features may include psychosis, seizures and chorea. There may be no correlation between the severity of clinical involvement and findings on neuroimaging. Hematologic abnormalities include a Coombs' positive hemolytic anemia, leukopenia, lymphopenia and thrombocytopenia. In addition, there may be coagulation abnormalities due to secondary antiphospholipid antibody syndrome. Cardiac manifestations include pericarditis, myocarditis, or verrucous (Libman-Sacks) endocarditis.

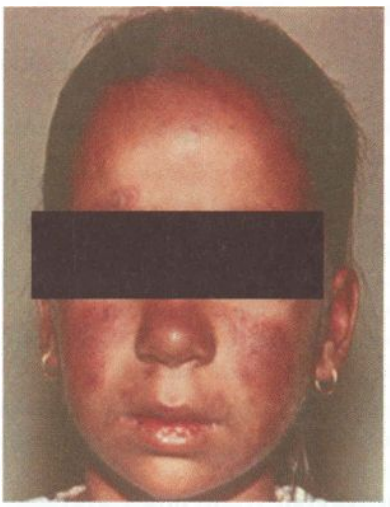

Fig. 21.1: Malar rash in SLE

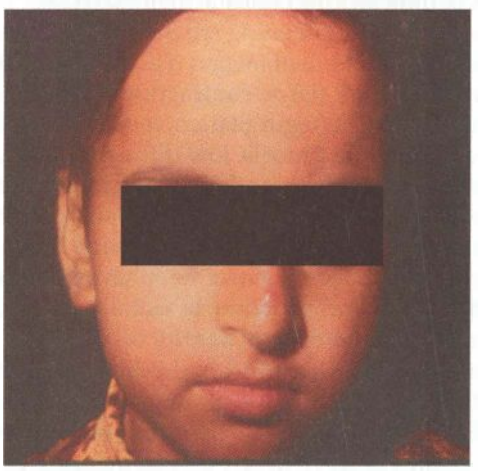

Fig. 21.2: Frontal alopecia in SLE

Serology

Almost all patients with SLE have demonstrable antinuclear antibodies. Presence of anti-double stranded DNA antibodies is highly specific of SLE. The titers of these antibodies usually correlate with disease activity. Anti-histone antibodies are characteristic of drug-induced lupus (e.g. following phenytoin, isoniazid, hydralazine) but in such cases anti-dsDNA antibodies are usually absent and serum complement (C3) level is not decreased. Anti-Ro antibodies are believed to play a role in the development of congenital heart block characteristic of neonatal lupus syndromes. These heart blocks are permanent. Anti-Sm antibodies are a marker for CNS lupus.

Treatment

Glucocorticoids and hydroxychloroquine form the main stay of therapy of lupus. Prednisolone is started in doses of 1–2 mg/kg/day and gradually tapered over several months, according to disease activity. Arthritis usually responds to NSAIDs. Sunscreen lotions (with sun protection factor of 15–20) must be prescribed for all children with lupus and applied 3–4 times/day, even on cloudy days.

Life-threatening complications (e.g. class IV lupus nephritis, mycocarditis, encephalopathy) may warrant use of intravenous pulses of methylprednisolone (30 mg/kg/day) for 3–5 days. Rituximab, a monoclonal antibody to CD20, has also been found to be effective in such situations. Use of monthly pulses of IV cyclophosphamide (500 mg/m^2) has considerably improved the longterm outcome in children with severe forms of lupus nephritis. Once remission is achieved, the patient can be treated with longterm azathioprine. Mycophenolate mofetil is being increasingly used for the therapy of severe forms of lupus nephritis in children.

Low dose prednisolone (2.5–5 mg/day) and hydroxychloroquine (5–6 mg/kg/day) may need to be continued for several years depending on the clinical response.

Infections must be treated aggressively with appropriate antimicrobials and the steroid dose hiked up during such episodes. With appropriate therapy, the longterm outlook of SLE in children is quite encouraging.

Antiphospholipid Antibody (APLA) Syndrome

The APLA syndrome is a common accompaniment of systemic lupus erythematosus but can be seen in association with other rheumatological disorders as well. The syndrome can, at times, arise *de novo* when it is known as primary APLA syndrome. It is a common cause of hypercoagulable states in children and can manifest with arterial and venous thrombosis, livedo reticularis and thrombocytopenia. The presentation can sometimes be catastrophic and may result in fatality. Laboratory diagnosis is suggested by a typical coagulation profile (normal prothrombin and prolonged partial thromboplastin times) and confirmed by the detection of anticardiolipin antibodies (IgM and IgG) and the lupus anticoagulant test. Treatment is with longterm oral anticoagulation.

JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is a multisystem disease characterized by nonsuppurative inflammation of striated muscle and skin and a systemic vasculopathy. Unlike adults, pure polymyositis (i.e. in absence of dermatological changes) is uncommon in children. The diagnosis can be made on the basis of the following criteria:

i. Characteristic heliotrope discoloration over the upper eyelids (Fig. 21.3)
ii. Symmetrical proximal muscle weakness
iii. Elevated levels of muscle enzymes (AST, ALT, CK, aldolase)
iv. Electromyographic evidence of myopathy
v. Muscle biopsy showing myonecrosis, myophagocytosis and perifascicular atrophy

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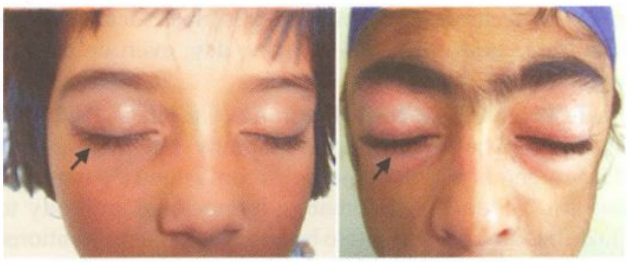

Fig. 21.3: Heliotrope rash in juvenile dermatomyositis

A *definite* diagnosis of JDM can be made if a child fulfils the first criterion along with any three of the remaining four; it is considered *probable* if two of the four criteria are met and *possible* if only one of the four criteria is met in addition to the first criterion. Other typical dermatological changes include Gottron papules (collodion patches) over the dorsal aspects of metacarpophalangeal and interphalangeal joints of fingers or toes are usually not involved (Fig. 21.4); edema over eyelids; photosensitivity; a truncal rash and calcinosis. From the clinical point of view a child with characteristic dermatological findings along with proximal muscle weakness can be confidently diagnosed as having JDM and started on treatment irrespective of the biopsy findings. Magnetic resonance imaging (MRI) shows characteristic hyperintense signals on T2 weighted images suggestive of muscle edema and inflammation while the T1 weighted images may show fibrosis, atrophy and fatty

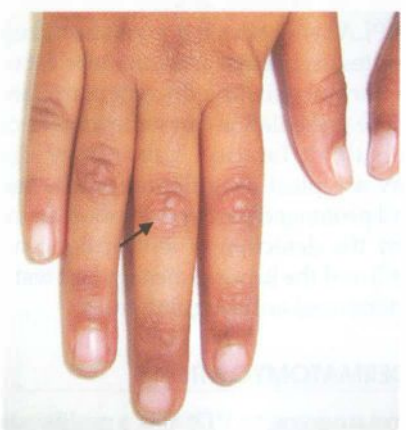

Fig. 21.4: Gottron papules in juvenile dermatomyositis

infiltration. Typical findings on MRI may preclude the need for a muscle biopsy.

Treatment is with intravenous methylprednisolone (30 mg/kg/day) for 3–5 pulses followed by oral prednisolone (1.5–2 mg/kg/day). Prednisolone is then gradually tapered depending on the clinical response. Weekly methotrexate (15–25 mg/m^2/week given subcutaneously or orally) is now increasingly being used as first-line therapy in combination with prednisolone. The usual duration of therapy is 18–24 months. Rapid tapering of steroids may result in disease relapse. The long term prognosis is excellent.

SCLERODERMA

Scleroderma refers to hardening of the skin. It can be classified as follows:

i. Systemic scleroderma (e.g. diffuse cutaneous, limited cutaneous)
ii. Overlap syndromes
iii. Localized scleroderma (e.g. morphea, linear scleroderma, eosinophilic fasciitis)
iv. Chemically induced scleroderma (e.g. with polyvinyl chloride, pentazocine, bleomycin)
v. Pseudosclerodermas (e.g. phenylketonuria, scleredema, progeria and porphyria cutanea tarda)

Diffuse cutaneous systemic scleroderma is usually associated with widespread visceral involvement including the gastrointestinal tract, heart, lungs and kidneys. It is believed that fetomaternal graft-versus-host reactions are involved in the pathogenesis of this condition. Onset of disease is insidious and may be difficult to recognize in the initial stages. The child presents with skin tightening (edema, atrophy and acrosclerosis), Raynaud phenomenon (i.e. blanching, cyanosis and erythema), soft tissue contractures, arthralgias and myalgias, dysphagia (regurgitation, reflux and aspiration), dyspnea (interstitial fibrosis, low diffusing capacity) and characteristic subcutaneous calcifications. In addition, many children have abnormalities of nailfold capillaries which can be seen as capillary dropouts and dilated loops with a magnifying glass or the +40 lens of the ophthalmoscope. Onset of hypertension and proteinuria usually indicate renal involvement and should be a cause for concern.

Systemic scleroderma is rare in children but can result in severe disability. Investigations show presence of antinuclear antibodies (with nucleolar pattern on immunofluorescence) and antibodies to Scl-70 (DNA-topoisomerase1) or centromere. No form of drug therapy has been found to be curative. Penicillamine and colchicine can produce beneficial results in some patients, especially if used early in the course of disease. Pulse dexamethasone therapy has also been shown to be effective. Monthly pulses of IV cyclophosphamide (followed by maintenance daily azathioprine or weekly methotrexate) can be life-saving in patients with interstitial lung disease. Nifedipine is useful for management of Raynaud phenomenon while enalapril can result in control of blood pressure and stablization of renal function. The latter is also the drug of choice for scleroderma renal crises. With appropriate management, 10 yr survival rates of up to 90% have been reported in children.

Scleredema is a benign, self limiting condition characterized by nonpitting indurated edema over face, neck, shoulders and chest, but always excluding the hands and feet.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

MCTD is a multisystemic overlap syndrome characterized by features of rheumatoid arthritis, systemic scleroderma, SLE and dermatomyositis occurring in conjunction with

high titers of anti-ribonucleoprotein (RNP) antibodies (specific for U1 RNP). Nephritis is usually less common and less severe than in SLE. Many children show good response to low-dose glucocorticoids and NSAIDs. Oral weekly methotrexate is also a useful therapeutic option. Treatment must be individualized and should focus on the particular disease component which is predominating in a given child.

VASCULITIDES

The vasculitides are best classified according to the size of the vessel involved:

i. Large vessel (i.e. aorta and major branches) vasculitis e.g. Takayasu arteritis, giant cell arteritis (not seen in children)
ii. Medium vessel (i.e. coronary, renal, hepatic, mesenteric) vasculitis, e.g. Kawasaki disease, polyarteritis nodosa
iii. Small vessel (i.e. arterioles, capillaries, venules) vasculitis, e.g. Henoch-Schönlein purpura, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, cutaneous leukocytoclastic angiitis.

Takayasu Arteritis

This is characterized by a segmental inflammatory panarteritis resulting in stenosis and aneurysms of aorta and its major branches causing weak arterial pulses. It is believed to be the commonest cause of renovascular hypertension in India. It is classified according to the site of involvement: *Type I*: aortic arch; *Type II*: descending aorta; *Type III*: aortic arch and descending aorta; *Type IV*: aorta and pulmonary artery. Many children with Takayasu arteritis show a strongly positive tuberculin reaction. The classification criteria for childhood Takayasu arteritis are given in Table 21.5.

Diagnosis is confirmed by angiography. Treatment involves longterm immunosuppression with prednisolone and methotrexate (used in weekly doses). Mycophenolate mofetil has also been found to be useful. Angioplasty procedures are now being increasingly performed even in small children and have shown promising results. Cyclophosphamide or azathioprine may be required in children who fail to show an adequate response to steroids. Hypertension must be managed appropriately.

Kawasaki Disease

Kawasaki disease is an acute febrile mucocutaneous lymph node syndrome mainly affecting infants and young children. More than 80% of cases are seen in children below the age of 5 yr. It is a common vasculitic disorder of childhood and has replaced acute rheumatic fever as the leading cause of acquired heart disease in children in many countries. The condition has been reported from all parts of the world. In India, this condition is now being increasingly recognized but the vast majority of patients still continue to remain undiagnosed probably because of lack of awareness amongst pediatricians.

Table 21.5: Classification criteria for childhood Takayasu arteritis

Angiographic abnormalities (conventional, CT or MRI) of the aorta or its main branches, plus at least one of the following 4 features:

i. Decreased peripheral artery pulse(s) and/or claudication of extremities
ii. Blood pressure difference >10 mm Hg
iii. Bruits over aorta and/or its major branches
iv. Hypertension (based on childhood normative data)

It is important to remember that the diagnosis of KD is based entirely on the recognition of a temporal sequence of characteristic clinical findings (Figs 21.5 to 21.8) and that there is no specific laboratory test. The diagnostic criteria for KD are as follows:

A. Fever lasting for at least 5 days

B. Presence of any 4 of the following 5 conditions:

i. *Bilateral nonpurulent conjunctival injection* (no discharge)

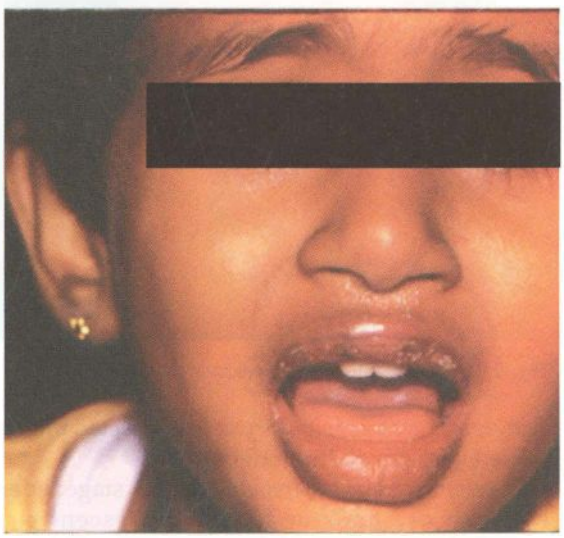

Fig. 21.5: Red cracked lips in Kawasaki disease

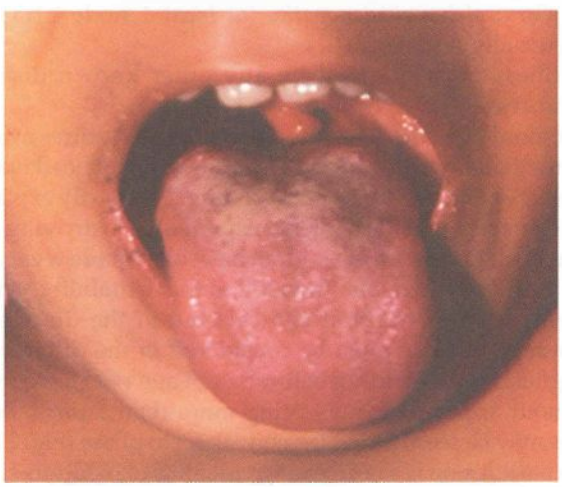

Fig. 21.6: Strawberry tongue in Kawasaki disease

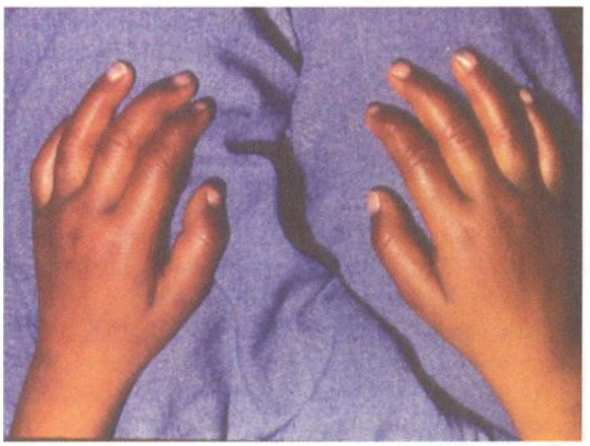

Fig. 21.7: Swelling on dorsum of hands in Kawasaki disease

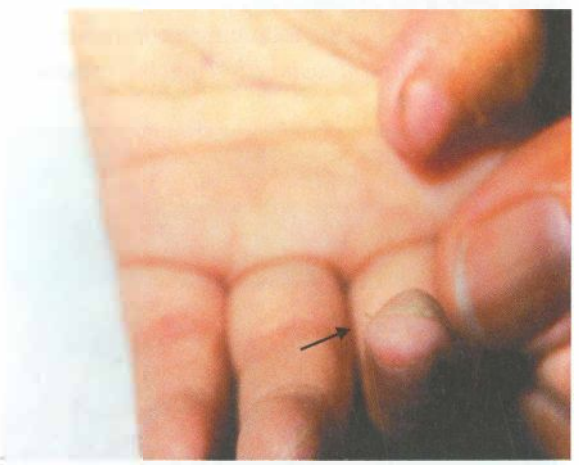

Fig. 21.8: Periungual desquamation in Kawasaki disease

ii. *Changes of mucosae of oropharynx* (e.g. injected pharynx, injected lips, strawberry tongue)
iii. *Changes of peripheral extremities* (acute stage: edema, erythema of hands or feet; convalescent stage: desquamation, which usually begins periungually)
iv. *Polymorphous rash* (never vesicular)
v. *Cervical lymphadenopathy* (at least 1 node ≥1.5 cm; usually unilateral)

C. Illness not explained by any other known disease process.

It should be noted that the above clinical features evolve sequentially over a period of few days and all need not be present at one particular point of time. This partly explains the difficulty that the clinician experiences in arriving at a correct diagnosis. Most children have high grade fever and are extremely irritable. In fact it is this irritability which often provides the first clinical clue to the diagnosis. Kawasaki disease must be considered in the differential diagnosis of all children below 5 yr of age who have fever without apparent focus lasting more than 5 days. Beau lines may be seen during the convalescent phase (Fig. 21.9). The basic lesion is a necrotizing vasculitis of medium-sized muscular arteries (especially coronaries), which may result

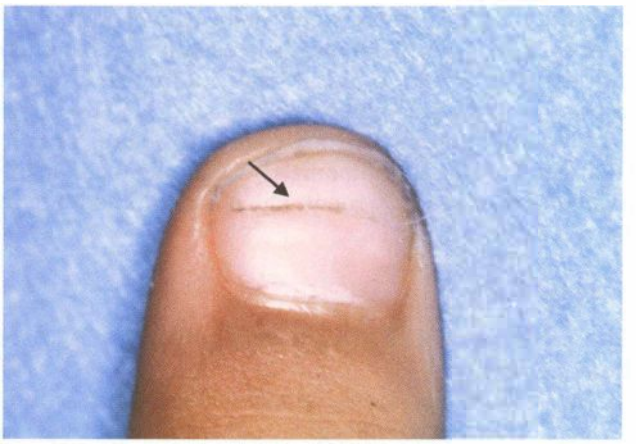

Fig. 21.9: Beau line in Kawasaki disease

in aneurysms, dilatations, and stenoses in untreated patients.

Treatment is with a single dose of intravenous immunoglobulin (2 g/kg) and aspirin in anti-inflammatory doses (75–80 mg/kg) until the child becomes afebrile. Low dose aspirin (3–5 mg/kg/day) is then continued for a few weeks for its antiplatelet activity. In appropriately treated children, the longterm prognosis is excellent with less than 3% patients developing coronary artery abnormalities as compared to 15–25% in the untreated category.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is rare in childhood. The clinical manifestations can be variable because of multisystemic involvement and include fever, hypertension (seen in 80%), abdominal pain, arthritis, myalgia, skin involvement (especially livedo reticularis, Fig. 21.10). Neurological involvement (seizures, encephalopathy) and peripheral neuropathy (mononeuritis multiplex). Pathological diagnosis consists of demonstration of fibrinoid necrosis in medium sized arteries with segmental involvement and a predilection for bifurcation of vessels. On angiography, aneurysms may be demonstrable in the renal arteries or celiac axis (Fig. 21.11). The diagnostic criteria for childhood PAN have been recently revised (Table 21.6). Treatment consists of longterm immunosuppression (initially with cyclophosphamide and prednisolone, followed by azathioprine).

Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is one of the most common vasculitic disorder of childhood and is characterized by the presence of a nonthrombocytopenic (and usually) palpable purpura, transient arthralgia (occasionally arthritis) and abdominal symptoms. The criteria for diagnosis of childhood HSP are given in Table 21.7.

The illness begins with a purpuric rash more prominent over the extensor aspects of lower extremities and buttocks. It may be macular, maculopapular or even urticarial to

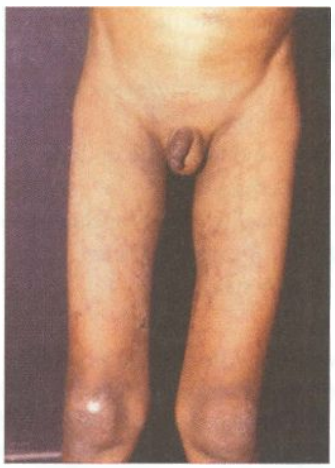

Fig. 21.10: Livedo reticularis in polyarteritis nodosa

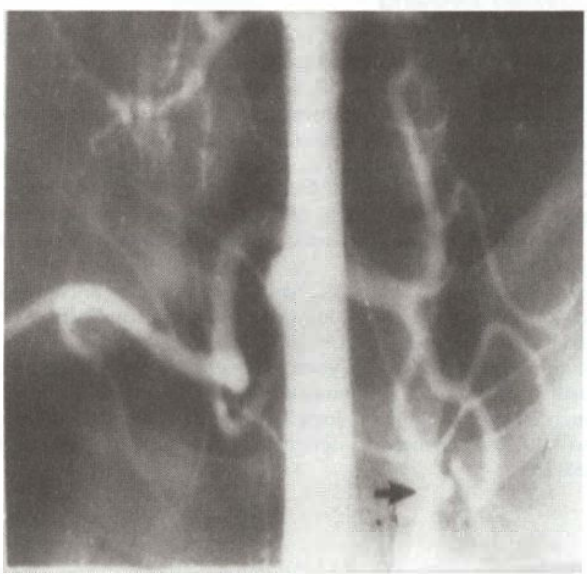

Fig. 21.11: Microaneurysms in polyarteritis nodosa

Table 21.6: Classification criteria for childhood polyarteritis nodosa

A childhood illness characterized by the presence of either a biopsy showing small and mid-size artery necrotizing vasculitis or angiographic abnormalities (aneurysms or occlusions)*, plus at least 2 of the following:

i. Skin involvement
ii. Myalgia or muscle tenderness
iii. Systemic hypertension (based on childhood normative data)
iv. Abnormal urinalysis and/or impaired renal function
v. Mononeuropathy or polyneuropathy
vi. Testicular pain or tenderness
vii. Signs or symptoms suggesting vasculitis of any other major organ systems (gastrointestinal, cardiac, pulmonary or central nervous system)

* Should include conventional angiography if magnetic resonance angiography is negative

Table 21.7: Classification criteria for childhood Henoch-Schönlein purpura

Palpable purpura in the presence of at least one of the following 4 features:

i. Diffuse abdominal pain
ii. Any biopsy showing predominant IgA deposition
iii. Arthritis or arthralgia
iv. Renal involvement (any hematuria and/or proteinuria)

begin with and can be difficult to diagnose in the first few days of the illness. Glomerulonephritis is seen in approximately one-third, but only 10% patients have azotemia or nephrotic range proteinuria. Clinically, it may manifest as isolated hematuria, hypertension or a nephritic/nephrotic syndrome. This is the only longterm complication of HSP. Significant renal involvement is uncommon in children below 6 yr of age.

Gastrointestinal manifestations usually occur in the first 7–10 days of the illness. Affected children may be erroneously diagnosed as having a 'surgical abdomen' and even subjected to unnecessary surgery. Abdominal pain is usually intermittent, colicky and periumbilical. Vomiting occurs in about 60% of patients but hematemesis and malena are relatively less common.

Most clinical features of HSP are self limiting and resolve in a few days. Rare manifestations include CNS vasculitis, coma, Guillain-Barré syndrome, pulmonary hemorrhage, carditis and orchitis.

Laboratory Investigations

HSP is a clinical diagnosis and none of the laboratory features are pathognomonic. There may be a nonspecific increase in total serum IgA levels. Many children may have microscopic hematuria and proteinuria. Skin biopsy from the involved sites may show the characteristic leukocytoclastic vasculitis. On indirect immunofluorescence there are deposits of IgA and C3 in skin as well as renal biopsies. Ultrasound examinations may need to be repeated at frequent intervals for evolving abdominal findings.

Treatment

Management is generally supportive with maintenance of hydration and pain relief. Prednisolone (1–1.5 mg/kg/day) is often given in children with gastrointestinal involvement and is usually continued for 2–3 weeks depending on the clinical response. There is, however, no clear evidence that steroids alter the natural course of the disease.

HSP nephritis is a serious complication and can result in chronic renal failure if not managed appropriately. There is evidence to suggest that longterm treatment with prednisolone and azathioprine can result in prolonged remissions.

Prognosis

The disease usually runs its entire course in 4 weeks and majority of the children have no permanent sequelae even

when the short-term morbidity is quite significant. Children older than 6 yr with significant renal involvement (especially children with rapidly progressive glomerulonephritis and fibrous crescents) need to be followed up and the longterm prognosis is guarded. Overall 1–5% of children with HSP nephritis progress to endstage renal disease.

Granulomatosis with Polyangiitis

This condition, previously called Wegener's granulomatosis and characterized by necrotizing granulomatous angiitis affecting the respiratory tract and kidneys, is rare in children. Constitutional symptoms are quite common. Presence of antineutrophil cytoplasmic antibodies (ANCAs), especially c-ANCA, are virtually pathognomonic. The diagnostic criteria for childhood granulomatosis with polyangiitis are given in Table 21.8. With steroids and cyclophosphamide and occasionally, intravenous immunoglobulin, the longterm outlook is excellent.

Behçet Disease

This is an extremely uncommon vasculitic disorder. The clinical manifestations can be quite variable. These may be classified as:

i. *Major*. Aphthous stomatitis, genital ulceration, cutaneous manifestations and ocular disease
ii. *Minor*. Gastrointestinal disease, thrombophlebitis, arthritis, family history and neurological involvement.

Behçet disease is usually characterized by multiple relapses with the ocular and neurological manifestations resulting in significant disability. Widespread thrombosis of the large vessels may be life-threatening. Many patients have the characteristic pathergy test (cutaneous pustular reaction following needle pricks) positivity. HLA-B5 and B51 haplotypes have been associated with this syndrome. Drug therapy involves use of colchicine and thalidomide. Methotrexate and chlorambucil have also been used.

Table 21.8: Classification criteria for childhood granulomatosis with polyangiitis

Three of the following six features should be present:

i. Abnormal urinalysis
ii. Granulomatous inflammation on biopsy
iii. Nasal sinus inflammation
iv. Subglottic, tracheal or endobronchial stenosis
v. Abnormal chest X-ray or CT scan
vi. Positive c-ANCA staining

Suggested Reading

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Genetic Disorders

22

Neerja Gupta, Madhulika Kabra

Physiological Considerations

The pattern of inheritance is determined by the genetic material in the nuclei of cells, which is distributed into 23 pairs of chromosomes. The two members of 22 pairs of chromosomes that are apparently alike (or homologous) are called autosomes. The 23rd pair is homologous only in females with two X chromosomes. In the male, the 23rd pair has one X chromosome and a much smaller Y chromosome. In the germ cells of both sexes, the cell division is not of the usual mitotic variety, but is a reduction division or meiosis. The cells which are obtained after meiosis have only one representative of each pair of chromosomes, so that in human beings they have only 23 chromosomes. In the course of meiosis, not only is the number of chromosomes halved, there is also some exchange of genetic material between the two members of a pair. This phenomenon is called crossover. Since the progeny inherits half their chromosomes from the father and half from the mother, they have some characteristics of both.

The portion of a chromosome which codes for a 'character' is called a gene. The position of a gene on a chromosome is called its locus. Corresponding loci on the two members of a pair carry genes for the same character. The character coded by the two chromosomes may have different forms. For instance, one of them may code for black iris and another for blue iris. Such alternative forms of a gene are known as *alleles*. If the alleles code for the same forms, these are said to be present in the homozygous state; if they code for different traits, they are in heterozygous state. If an allele clinically manifests itself even in the heterozygous state, it is called a dominant gene or character. Its alternate form or allele which does not express itself clinically when the other allele from the other parent is normal is called a recessive gene. Recessive genes will manifest features of the disease only when present on both chromosomes in the pair (homozygous state) or when the specific abnormal gene is inherited from both parents. The genetic make up of a person is called the *genotype* and the clinically manifest characters are known as the *phenotype*. Sometimes a gene may express itself in several slightly modified forms without adverse effect on the health of the individual, known as genetic *polymorphism*.

From Chromosomes to Characters

Chemically, the chromosomes are made up of deoxyribonucleic acid (DNA) and histones. Only about 3% of DNA in the human genome symbolizes genes. About 93% has apparently no clear-cut function and is often termed as junk DNA. Many copies of the latter type of DNA are scattered at random over the chromosomes intermingled with genes. These are called repetitive sequences. There are about 30,000 genes in the human genome. Roughly 20% of these are specific genes which regulate the production of structural or functional proteins. About 80% genes are housekeeping genes responsible for basic cell functioning. DNA determines the type of messenger ribonucleic acid (mRNA) that is synthesized by a cell; mRNA is responsible for the type of protein manufactured by the cell.

Molecular Genetics

It is possible to cleave DNA at specific points by restriction endonucleases derived from bacteria. DNA probes can be made to detect specific base sequences in the DNA. The most fascinating technique in molecular genetics is the ability to form large number of copies of DNA sequences in a short time. This amplification of genetic material is now possible with *polymerase chain reaction (PCR)*. In high throughput microarray techniques, thousands of samples can be analyzed in a very short time. A *microarray* is a collection of microscopic DNA spots attached to a solid surface. DNA microarrays can be used to measure the expression of a large numbers of gene simultaneously or to genotype multiple regions of a genome. Since an array may contain thousands of probes, a microarray experiment

can perform multiple genetic tests in parallel. Microarrays are now being routinely used as rapid diagnostics and in research activities. *DNA sequencing* includes classical time tested Sanger sequencing method and many new high throughput technologies that are used for determining the order of the nucleotide bases in the DNA sequence of interest. *High-throughput sequencing* or *next generation sequencing* technologies are now available and can run parallel sequencing experiments, producing thousands or millions of sequences at one go. These techniques are more sensitive and lower the cost of DNA sequencing.

Genetics and Disease

Most diseases have probable genetic and environmental basis. The genetic component may be the major or the only factor leading to the manifestation(s) of the disease, or it may merely predispose the individual to get a disease in response to environmental stresses. Different diseases can be considered to be at different regions of the spectrum between the genetic and environmental reasons in causation of the disease. Thus, based on genetic mechanism, the disease may be one of five types: (i) chromosomal disorders, (ii) single gene disorders, (iii) polygenic disorders, (iv) mitochondrial disorders and (v) somatic cell (genetic) disorders.

CHROMOSOMAL DISORDERS

Mechanisms of Chromosomal Anomalies

Chromosomes contain a large number of genes. Loss or gain of a whole chromosome due to abnormalities in cell division may cause profound disturbances in the genetic constitution of the fetus and affect its survival. If the fetus is born alive it may die soon after birth. Even if the disturbances are not lethal, the fetus may be malformed or have intellectual disability later in life. At times, only a part of the chromosome may be deleted or lost, causing less severe genetic disturbances. Generally, loss of a whole chromosome except one X chromosome (as in Turner syndrome) is lethal. Surveys in still-born or abortuses (aborted fetuses) have shown large proportion of chromosomal anomalies. Of all live newborns, 0.5% may have a chromosomal anomaly.

Each chromosome has a short arm (p) and a long arm (q) joined by a centromere. Chromosomes are numbered based on their size and position of the centromere (Fig. 22.1). Chromosomal abnormalities are generally sporadic and therefore, the risk of their recurrence in the offsprings is low (except in situations when either parent is a balanced translocation carrier). There are two types

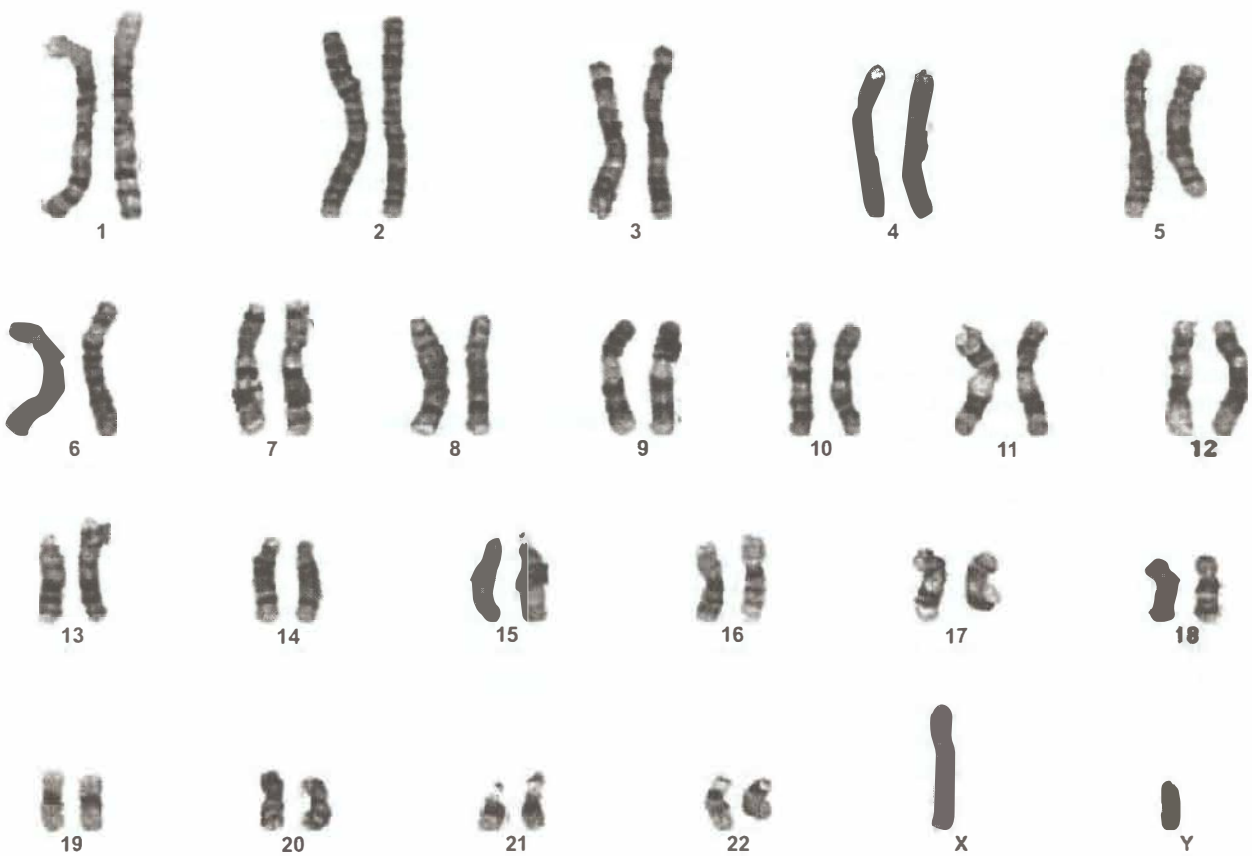

Fig. 22.1: Conventional G band karyotype

of chromosomal abnormalities—numerical (aneuploidies) and structural. There are several mechanisms which lead to chromosomal abnormalities.

Inversion. One or two breaks may occur along the length of the chromosome arm. The broken pieces may rearrange themselves in a new way. If there is no loss or gain of genetic material, there may be no significant clinical manifestations. Break point is important if it disrupts a vital gene.

Isochromosome. During mitotic cell division, the chromosome divides longitudinally. Rarely it may divide transversely across the centromere. Half of the chromosome replicates to form its complement. Thus instead of normal chromosomes, two new types of chromosomes are formed—one having both the long arms and the other with both the short arms. These are known as isochromosomes. Each isochromosome thus has excess of some genetic material and deficiency of some other genetic material, e.g. in some cases of Turner syndrome.

Anaphase lag. In the first meiotic division, the chromosomes are arranged in pairs in the equatorial plane during the metaphase. During anaphase if one of the chromosomes is slow in its migration, it might be excluded and thus be lost.

Nondisjunction. During the first meiotic division, both members of a pair of chromosomes may move jointly during anaphase to either of the daughter cells. Thus, whereas one daughter cell may have both members of a pair of chromosomes, i.e. 22 + 2 or 24 chromosomes, the other cell may have only 22 chromosomes without any representation of the erring pair. When such gametes mate with other gametes with normal chromosomal complement, the zygote will either have 47 or 45 chromosomes. Nondisjunction leads to aneuploidies. Common aneuploidies seen in live born babies include Down syndrome (trisomy 21), Edward syndrome (trisomy 18), Patau syndrome (trisomy 13) and Turner syndrome (monosomy X).

Mosaicism. If the nondisjunction occurs in the first mitotic division instead of meiosis, of the two new cells which are formed, one has 47 chromosomes and the other cell has 45 chromosomes. The error is perpetuated by repeated mitotic divisions. Thus, two cell lines with 47 and 45 chromosomes are observed in the same individual. If the nondisjunction occurs after a few mitotic divisions have already occurred, more than two cell lines may be observed, some with normal and the others with abnormal complement of chromosomes.

Translocation. A chromosome or a segment of a chromosome may break off from the parent chromosome and be joined to another chromosome. This phenomenon is called translocation. Thus one chromosome may appear shortened in this process, no loss or gain of the genetic material occurs, the translocation is balanced and the person is phenotypically normal. Translocated chromosome may be transmitted to either gamete during meiosis and when it mates with normal gamete, the resulting zygote may either have excess or deficiency of the genetic material. Such an offspring is abnormal. Viability of such zygotes would depend on the essentiality of the genes carried on translocated portion of the chromosome.

Deletion. A segment of chromosome may break off and be lost. Loss of a portion of chromosomal material large enough to be seen by light microscope is often lethal or poorly tolerated. Submicroscopic deletions are detected on special chromosomal staining or fluorescent *in situ* hybridization (FISH) (Fig. 22.2). DNA probes have been developed that make it possible for FISH to be used for diagnosis for aneuploidies and microdeletion syndromes. Gene deletion syndromes are characterized by loss of a cluster of genes, giving rise to a consistent pattern of congenital anomalies and developmental problems. Examples of these are William syndrome (7q11.23); retinoblastoma with mental retardation and dysmorphic facies (13q14.1); Prader-Willi syndrome (hypotonia, mental retardation and obesity, 15q11); Rubinstein Taybi syndrome (microcephaly, broad thumbs and big toes, dysmorphism and mental retardation; 16q13); and DiGeorge syndrome (congenital heart defect, hypoplasia of parathyroid and thymus, facial and palate anomalies; 22q11).

Genomic imprinting. Maternal and paternal sets of genes are not always functionally equal. Some genes are preferentially expressed from maternal or paternal side. Examples include Prader-Willi syndrome (microdeletion on paternal side or inheritance of both copies from maternal side) and Angelman syndrome (microdeletion on maternal side or inheritance of both copies from paternal side).

Down Syndrome

Down syndrome is the most common chromosomal disorder, occurring with a frequency of 1:800 to 1:1000 newborns. Chromosome number 21 is present in triplicate, the origin of the extrachromosome 21 being either maternal or paternal. In most cases the extrachromosome is from the mother. Down syndrome occurs more often in offspring of

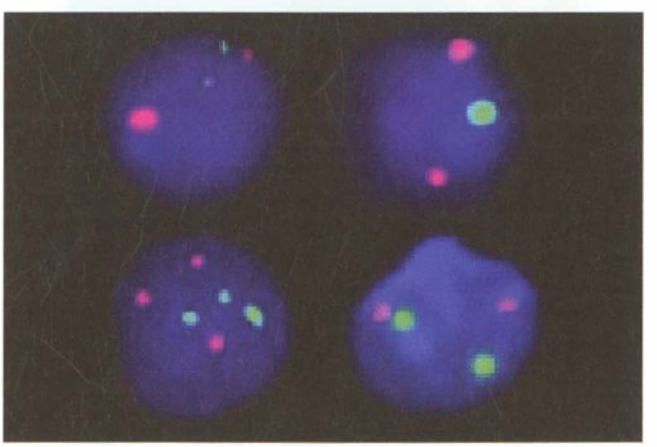

Fig. 22.2: Signals on fluorescent *in situ* hybridization (FISH) testing. Reduction or increased number of signals indicates aneuploidy

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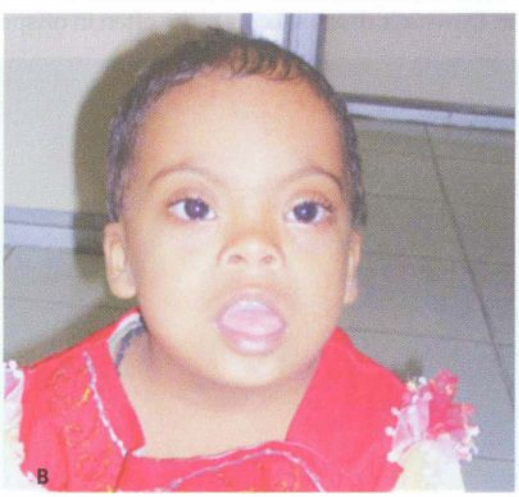
mothers conceiving at older age; the risk in the newborn is 1:1550 if maternal age is between 15 and 29 yr, 1:800 at 30–34 yr, 1:270 at 35 to 39 yr, 1:100 at 40 to 44 yr and 1:50 after 45 yr. This is attributed to the exposure of the maternal oocyte to harmful environmental influences for a longer period since Graafian follicles are present in the fetal life and exist through female reproductive life. The sperm has a short lifespan and therefore has less chances of injurious exposure.

Cytogenetics

Trisomy 21 is found in 94% cases. Approximately 1% of cases are mosaic and the rest (5%) are due to translocations, most commonly involving chromosomes 21 and 14. Karyotype of the parents is only required if the affected child has translocation underlying Down syndrome.

Clinical Features and Diagnosis

Patients with Down syndrome have mental and physical retardation, flat facial profile, an upward slant of eyes and epicanthic folds (Figs 22.3A and B). Oblique palpebral fissure is obvious only when the eyes are open. The nose is small with flat nasal bridge. Mouth shows a narrow short palate with small teeth and furrowed protruding tongue. There is significant hypotonia. The skull appears small and brachycephalic with flat occiput. Ears are small and dysplastic. There is a characteristic facial grimace on crying. Hands are short and broad. Clinodactyly (hypoplasia of middle phalanx of fifth finger) and simian crease are usual. There is a wide gap between the first and the second toe (sandle gap).



Figs 22.3A and B: Two young children with Down syndrome. Note the flat facies, upward eye slant and open mouth appearance

Associated Abnormalities

Congenital heart disease. Approximately 40% children have congenital heart disease. Endocardial cushion defects account for about 40–60% cases. Presence of heart disease is the most significant factor in determining survival. All children should have a cardiac evaluation before 9 months of age, including echocardiography.

Gastrointestinal malformations. Atresias are present in 12% of cases, especially duodenal atresia. There is an increased risk of annular pancreas and Hirschsprung disease.

Ophthalmic problems. There is an increased risk of cataract, nystagmus, squint and abnormalities of visual acuity. Routine evaluation is performed in infancy and then yearly.

Hearing defects. 40–60% patients have conductive hearing loss and are prone to serous otitis media (most commonly during the first year). Routine evaluation before 6 months of age and then every year is advisable.

Thyroid dysfunction. About 13–54% patients with Down syndrome have hypothyroidism. Thyroid function tests (T3, T4 and TSH) are recommended once in the neonatal period or at first contact, and then every year. This should ideally include antithyroid antibodies specially in older children as etiology is more likely to be autoimmune.

Atlanto-occipital subluxation. The incidence is variable, reported in 10–30% of cases. Lateral neck radiograph is recommended once between 3 and 5 yr, before surgery, for participation in special games, or earlier, if signs and symptoms suggest cord compression.

Physical growth. Regular followup for height and weight is necessary. Linear growth is retarded as compared to normal, children tend to become obese with age. Muscle tone tends to improve with age, whereas the rate of developmental progress slows with age.

Malignancies. Patients with Down syndrome are at increased risk of development of lymphoproliferative disorders, including acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplasia and transient lymphoproliferative syndrome.

Management and Prognosis

The principles of management are early stimulation, physiotherapy and speech therapy. Associated problems

need to be treated as required. Social performance is usually achieved beyond that expected for mental age. Generally, they behave as happy children, like mimicry, are friendly, have good sense of rhythm and enjoy music.

The major cause for early mortality is congenital heart disease, and almost 50% of those with cardiac anomalies die in infancy. Chronic rhinitis, conjunctivitis and periodontal disease are common. Lower respiratory tract infections pose a threat to life. Hematological malignancies are another cause of increased mortality.

Counseling

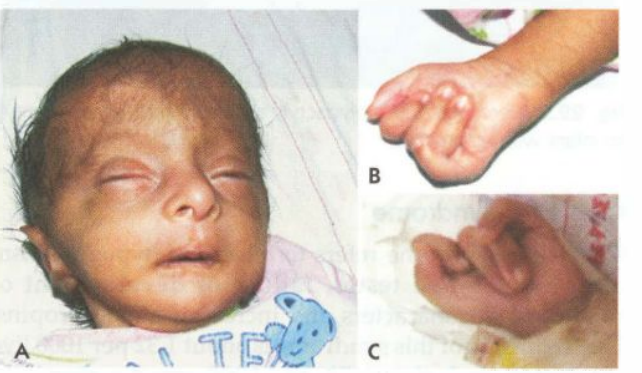
The parents of a child with Down syndrome should be counseled with tact, compassion and truthfulness. Briefly one should: (i) inform about the disorder as early as possible after diagnosis is confirmed; (ii) counsel in presence of both the parents in privacy; (iii) talk in simple and positive language giving hope and allow sufficient time to the parents to ask questions; (iv) discuss known problems and associated disorders; (v) highlight the importance of early stimulation; (vi) not discuss institutionalization and adoption, unless asked, and discourage both the options; (vii) ask the parents to contact the local Down syndrome association, if one exists; (viii) talk about genetics only after chromosomal analysis; (ix) inform about recurrence risks and possibilities of prenatal diagnosis; and (x) schedule future appointments.

Risk of recurrence. Women 35 yr of age or less who have a child with trisomy 21 have a 1% risk of having another, which is significantly greater than the general population. The risk is little increased, if any, over the usual maternal age dependent frequency if the mother at risk is 35 yr or older. For translocations inherited from the mother, the risk is about 10%, whereas it is about 4–5% when father is the carrier. Balanced translocation 21; 21 is the only situation where all viable fetuses will have Down syndrome.

Prenatal diagnosis. Parents who wish to get a prenatal diagnosis have a number of options. They can directly get a fetal karyotype by chorionic villus sampling or amniocentesis. Alternatively (if the parents do not want invasive testing) an initial screening may be performed with maternal serum markers and ultrasonography (as discussed later). Prenatal karyotyping can be done by chorionic villus sampling (CVS) between 10 and 12 weeks of pregnancy (by transcervical or transabdominal route) and allows diagnosis in the first trimester. Options for couples who come late or opt for initial screening with serum markers and ultrasonography are karyotyping by amniocentesis at 16–18 weeks, transabdominal chorionic villus sampling and cordocentesis after 18 weeks. Karyotype results are available within a week with cord blood samples and direct chorionic biopsy preparations. The results of amniotic fluid cultures take about 10–14 days.

Trisomy 18 (Edward Syndrome)

This is the second most common autosomal trisomy among live births after Down syndrome, with a frequency of 1:3000 births. This disorder is characterized by failure to thrive, developmental retardation, hypertonia, elongated skull, low set and malformed ears, micrognathia, shield-shaped chest, short sternum, joint abnormalities including flexion deformity of fingers, limited hip abduction and short dorsiflexed hallux. Congenital heart disease is common, occurring mostly as ventricular septal defect or patent ductus arteriosus. Most subjects have simple dermal arches on nearly all of the digits. They often have short fourth digits with only a single crease (Figs 22.4A to C).



Figs 22.4A to C: Note the (A) facial dysmorphism and (B and C) overlapping of fingers in an infant with trisomy 18

Majority of patients are postmature with a low birth weight. Resuscitation is often required at birth and apneic episodes are common in the neonatal period. Poor sucking capability may necessitate nasogastric feeding, but most infants fail to thrive despite optimal management. The median survival is about 3 months.

Trisomy 13 (Patau Syndrome)

The incidence of this syndrome is about one per 5000 births. It is characterized by severe developmental and physical retardation, microcephaly and sloping forehead. Holoprosencephaly with varying degrees of incomplete development of forebrain and olfactory and optic nerves, is common. Eye anomalies include microphthalmia, coloboma of iris, retinal dysplasia and cataract. Malformations of ears and cleft lip with or without cleft palate are common; many babies are deaf. Capillary hemangiomata are characteristic (Fig. 22.5). Fingers and toes are frequently abnormal, with polydactyly, flexion deformities and long and hyperconvex nails. Congenital heart disease is present in almost 80% of patients. Common defects are ventricular septal defect, patent ductus arteriosus and atrial septal defect. Majority of cases die in the first six months of life. Survivors have severe mental defects and seizures and they fail to thrive.

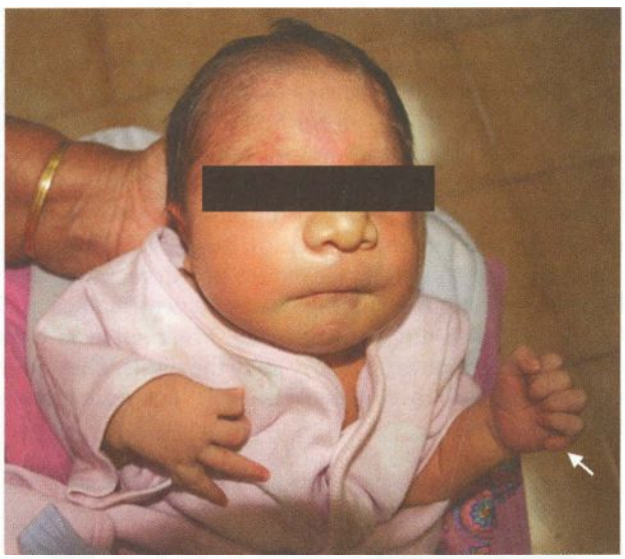


Fig. 22.5: Note postaxial polydactyly and forehead hemangioma in an infant with trisomy 13

Klinefelter Syndrome

Klinefelter syndrome refers to a form of hypogonadism comprising small testes, failure of development of secondary sex characters and increased gonadotropins. The frequency of this syndrome is about 1.32 per 1000 live newborns and about 79 per 1000 among mentally subnormal population; almost 10–20% of males attending infertility clinics have this syndrome. Cases of Klinefelter syndrome usually seek medical consultation near puberty due to the failure of appearance of secondary sexual characters. The diagnosis should also be considered in all boys with mental retardation, as well as in children with psychosocial, learning disability or school adjustment problems.

Even in the prepubertal age, the testes and penis are smaller in size for age. These patients tend to be tall and underweight, have relatively elongated legs and more eunuchoid proportions. Occasionally, hypospadias or cryptorchidism is present. Pubertal development is delayed. The growth of pubic and facial hair is often late; and the pubic hair is generally feminine in distribution. About 40% adults have gynecomastia, appearing usually soon after puberty between the ages of 14 and 16 yr. Characteristically, the testes are small and show small, shrunken and hyalinized seminiferous tubules, while some are lined exclusively by Sertoli cells. Leydig cells show hypertrophy and clumping.

Chromosomal analysis reveals 47 XXY karyotype. Individuals with XXY/XY mosaicism have better prognosis. As the number of X chromosomes increases beyond two, the clinical manifestations increase correspondingly. Management includes behavioral and psychosocial rehabilitation. Testosterone therapy should be started in middle to late adolescence with monitoring of levels.

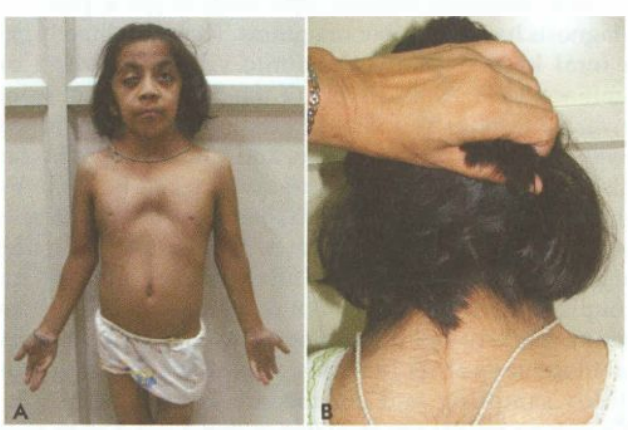
Turner Syndrome

Turner syndrome having 45 X chromosomal constitution, has an incidence of about 1:3000 newborns. However, chromosomal studies of spontaneous abortions have clearly shown that majority of 45 X fetuses are likely to be aborted; the precise reason for this is not known. Many patients with Turner syndrome shows a considerable degree of chromosomal mosaicism, i.e. 45 X/46 XX. Formation of isochromosome of long arms of X chromosome may lead to Turner phenotype with 46 chromosomes because of absence of short arms. Since there is no apparent relationship to advanced maternal age, it is likely, that this syndrome does not arise from gametic nondisjunction.

Clinical Features

Turner syndrome may be recognizable at birth. lymphedema of the dorsum of hands and feet and loose skin folds at the nape of neck. Other manifestations include short stature, short neck with webbing and low posterior hairline. Anomalous ears, prominent narrow and high arched palate, small mandible and epicanthal folds may be noted. Chest is broad shield-like with widely spaced hypoplastic nipples (Figs 22.6A and B). There is increased carrying angle at elbow. Bony anomalies include medial tibial exostosis, and short fourth metacarpals and metatarsals. Pigmented nevi may appear when older. At puberty, sexual maturation fails to occur. The phenotype is highly variable. It has been recommended that the diagnosis of Turner syndrome should be considered in all girls with short stature.

Ultrasound may show streak ovaries and hypoplastic uterus. Levels of FSH and LH are increased (hypergonadotropic hypogonadism). Adult stature is less than 145 cm. Associated congenital defects are common in the kidney (horseshoe kidney, double or cleft renal pelvis), heart (coarctation of aorta) and ears (perceptive hearing defect). Congenital lymphedema usually recedes in early infancy, leaving only puffiness over the dorsum of fingers and toes.



Figs 22.6A and B: Turner syndrome. Note (A) ptosis in right eye, shield chest, increased carrying angle, webbed neck and short neck with (B) low posterior hair line

Linear growth proceeds at about half to three-fourths the usual rate.

Hypothyroidism occurs in about 15–30% of adults with Turner syndrome. The clinical manifestations are milder in Turner syndrome with mosaicism. These patients may have normal stature and present with secondary amenorrhea.

Management

Height monitoring should be done using growth charts for Turner syndrome. Cardiac evaluation is recommended at baseline and every year. Regular measurement of blood pressure at baseline and every year is advisable.

Growth hormone therapy is useful and is approved. Therapy may increase the final height by 8–10 cm, but decision to treat should be left to the parents as the cost of treatment is prohibitive. Thyroid testing should be done in infancy or early childhood if the child is lagging in growth as per growth charts for Turner syndrome. Routine evaluation every other year should be done after 10 yr of age. Counseling regarding behavioral problems due to short stature, amenorrhea and sterility is an integral part of management. Ovarian hormone replacement should be started around 14 yr. To start with, conjugated estrogen at 0.3 mg/day or ethinyl estradiol 5–10 mg/day is given for 3–6 months, then increased to 0.625–1.25 mg of (conjugated estrogen) or 20–50 µg/day of ethinyl estradiol. After 6–12 months cyclical therapy with estrogen and progesterone is started.

Regular audiometry should done in adulthood or earlier if indicated. Evaluation for renal malformation by ultrasonography should be done at first contact. Prophylactic gonadectomy is advised for patients with Y chromosome due to the risk of developing gonadoblastoma.

SINGLE GENE DISORDERS

Drawing and interpreting a pedigree is an integral part of genetic diagnosis. Table 22.1 gives symbols used for pedigree drawing.

Autosomal Dominant Conditions

Generally, autosomal dominant mutations impair the synthesis of structural or nonenzyme proteins, e.g. Huntington chorea and connective tissue disorders. These disorders manifest even if only one of the alleles of the abnormal gene is affected. The autosomal dominant disorders are generally milder than autosomal recessive disorders. Physical examination of other siblings and parents should be done to uncover milder forms of the disorder. Homozygotes for the dominant mutant genes usually die prenatally, as in the case of the gene for achondroplasia. If the child is the only affected member, it is very likely that the observed mutation has occurred *de novo* and is not inherited. In such cases other siblings are not likely to be affected. However, one-half of the offspring of the affected individual are likely to inherit the disorder. New dominant gene mutations are more likely to occur if the paternal age is high. Examples include neurofibromatosis, achondroplasia, Marfan syndrome and Crouzon disease. A typical pedigree is shown in Fig. 22.7.

Autosomal Recessive Disorders

Autosomal recessive disorders manifest only in homozygous state, i.e. both the alleles are mutant genes. Generally, autosomal recessive mutations affect synthesis of enzyme, leading to inborn errors of metabolism. The parents of the affected individuals are apparently normal but carry the mutant genes. As they are heterozygous, the mutant recessive gene does not express itself in the phenotype. In such matings, one-fourth of the offspring are affected (homozygous for the mutant genes), one-fourth are normal (both normal alleles) and half are carriers (heterozygote with one mutant allele and one normal allele). A classical pedigree is shown in Fig. 22.8. For obvious reasons, recessive disorders are more common in consanguineous marriage or in closed communities. It is now possible to detect carrier status by biochemical and molecular techniques in a number of autosomal recessive disorders. Common examples of autosomal recessive disorders are beta-thalassemia, sickle cell disease, spinal muscular atrophy, phenylketonuria and galactosemia.

X-Linked Recessive Disorders

Since in males, there is no corresponding locus for a mutant allele of the X chromosome on the shorter Y chromosome,

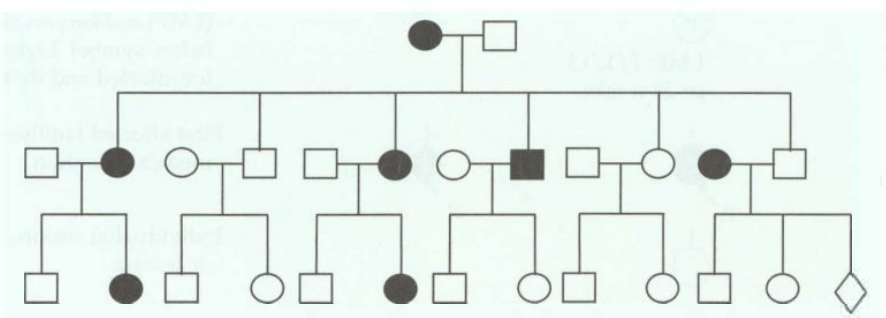
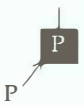


Fig. 22.7: Autosomal dominant inheritance

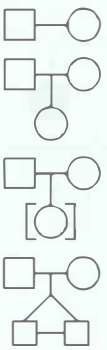
Table 22.1: Common pedigree symbols, definitions and abbreviations

Key should contain all information relevant to interpretation of pedigree (e.g. define shading)
For clinical (nonpublished) pedigrees, include:
a. Family names/initials, when appropriate
b. Name and title of person recording pedigree
c. Historian (person relaying family history information)
d. Date of intake/update
Recommended order of information placed below symbol (below to lower right, if necessary):
a. Age/Date of birth or age at death
b. Evaluation
c. Pedigree number (e.g. I-1, I-2, I-3)

	Male	*Female*	*Sex unknown*	*Comments*
Unaffected individual	 b. 1925	 30 yr	 4 mo	Assign gender by phenotype. Square represents male; circle represents a female; a diamond represents one whose sex is not known. Age/date of birth can be given at the bottom or right hand corner
Affected individual				Fillings can be shading, hatches, dots or lines
				For ≥2 conditions the symbols are partitioned correspondingly, each quadrant with different fillings/patterns representing different features
Multiple individuals; number known	 6	 6	 6	Number of the siblings is written inside the symbols; affected individuals should not be grouped
Multiple individuals; number unknown	 ?	 ?	 ?	'?' is used in the place of 'n'
Deceased individual	 d. 35 yr	 d. 4 mo		If known, write 'd' with age at death below symbol
Stillbirth (SB)	 SB 28 weeks	 SB 30 weeks	 SB 34 weeks	Birth of a dead child with gestational age noted
Pregnancy (P)	 P	 P LMP: 7/1/13 or 20 weeks	 P	Gestational age or last menstrual period (LMP) and karyotype (if known) are noted below symbol. Light shading can be used for affected and defined in key/legend
Proband	 P P	 P P	 P P	First affected family member coming to medical attention
Consultand				Individual(s) seeking genetic counseling or testing

Contd.

Table 22.1: Common pedigree symbols, definitions and abbreviations *(Contd.)*

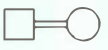


Parents

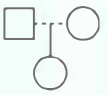
Biological parents

Adopted out of family

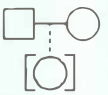
Identical twins



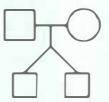
Consanguineous marriage



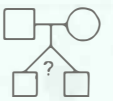
Illegitimate child



Adopted into family



Nonidentical twins



Twins with unknown zygosity

Pedigree symbols and abbreviations for pregnancies not carried to term

Symbols are smaller than standard ones and individual's line is shorter. (Even if sex is known, triangles are preferred to a small square/circle; symbol may be mistaken for symbols given in the previous table, especially in hand-drawn pedigrees.) If gender and gestational age are known, write below symbol in that order

	Male	*Female*	*Sex unknown*	*Comments*
Spontaneous abortion	 Male	 Female	 ECT	If ectopic pregnancy, write ECT below symbol
Affected spontaneous abortion	 Male	 Female	 16 weeks	If gestational age known, write below symbol. Key or legend used to define shading
Termination of pregnancy	 Male	 Female		
Affected termination of pregnancy	 Male	 Female		Key or legend used to define shading

Parents who are unaffected and unrelated may be omitted from the pedigree
To save space, huge pedigrees are sometimes drawn in circular or spiral form rather than in a rectangular form

the mutant X-linked recessive gene expresses as a clinical disorder in the male child because it is not being suppressed by a normal allele. In the female, the disorder does not manifest clinically since the mutant gene is compensated for by the normal allele in the other X chromosome. Females thus act as carriers of the mutant allele. Half of their male children inherit the mutant allele and are affected. Figure 22.9 shows a family with X-linked recessive inheritance. It is now possible to detect carrier state in the female child in case of some disorders, e.g. hemophilia, Duchenne muscular dystrophy and mucopolysaccharidosis type II (Hunter syndrome). Color blindness also has an X-linked recessive inheritance.

Diseases with X-Linked Dominant Inheritance

Dominant X-linked conditions are rare. Both the heterozygous female and hemizygous males are affected. All the sons of the affected males are normal and all the daughters are affected. The affected females transmit the disease to half of the sons and half of the daughters. *Examples:* Hypophosphatemic type of vitamin D resistant rickets, orofaciodigital syndrome and incontinentia pigmenti. In some cases, the effect of the mutant gene on development is severe, and affected males are seldom born alive. Majority of patients are heterozygous females (Fig. 22.10).

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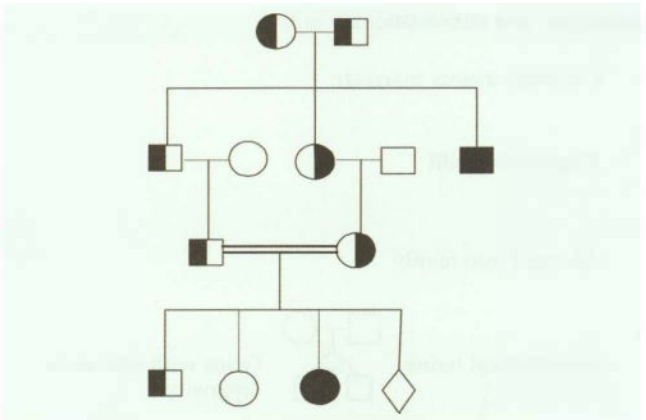

Fig. 22.8: Autosomal recessive inheritance. Carriers are indicated by partly shaded symbols

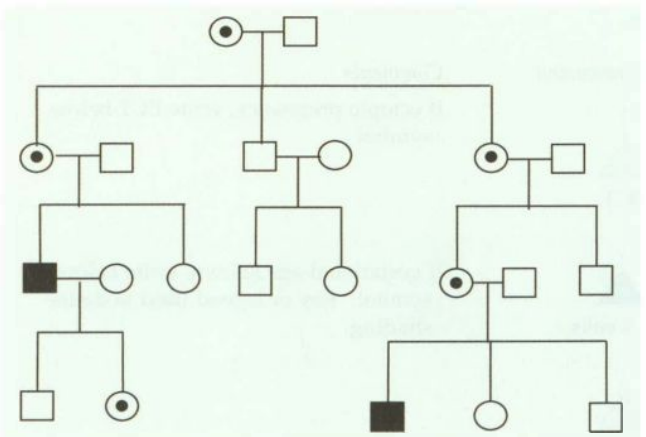

Fig. 22.9: X-linked recessive inheritance. Carriers are indicated by symbols with bold dot in the center

Mitochondrial Inheritance

Mutations within a mitochondrial gene can lead to phenotypic defects and show a pattern of maternal genetic transmission. Since mitochondria are only present in ovum and not sperms, the inheritance is maternal. All offspring of an affected female will be affected. All affected daughters will transmit the disease. Sons will be affected but will not transmit the disease (Fig. 22.11). Examples include Leigh disease and mitochondrial encephalopathy, lactic acidosis and stroke (MELAS) like syndrome.

Somatic Cell Genetic Disorders

These include cancers which can arise due to genetic changes in somatic cells.

POLYGENIC INHERITANCE

In a number of conditions, the affected individuals do not have a sharp division between the normal and the

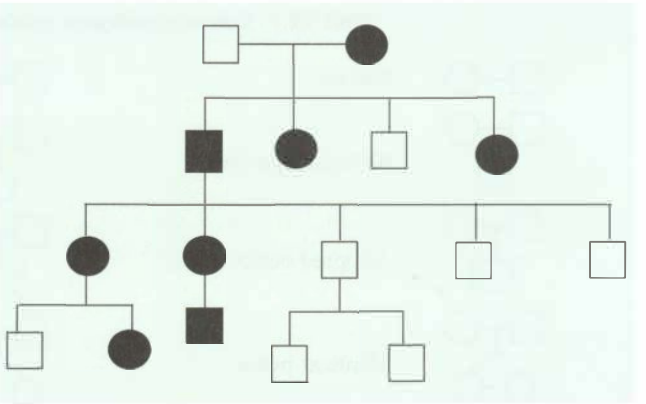

Fig. 22.10: X-linked dominant inheritance

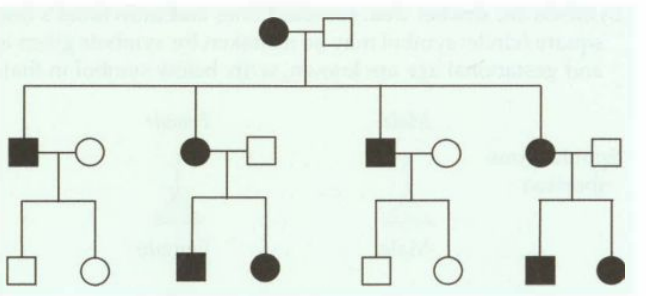

Fig. 22.11: Mitochondrial inheritance

abnormal, but merely represent a spectrum of a continuously varying attribute. Such conditions are likely to be inherited by alterations in many gene loci, each of them individually having only a small effect. Many of these conditions are also affected by numerous environmental factors, individually of small effect. Examples of polygenic disorders are: neural tube defect, cleft lip, cleft palate, Hirschsprung disease, congenital hypertrophic pyloric stenosis, diabetes mellitus, ischemic heart disease, hypertension and schizophrenia.

In diseases with multifactorial etiology, the risk to progeny and siblings is higher if the malformation is more severe, because a more severe malformation is a bigger deviation from the normal threshold, e.g. the risk of recurrence of Hirschsprung disease in a family is higher if the aganglionic segment of the colon is longer. When these diseases have a marked sex predilection, the risk of recurrence in the family is higher if the index patient belongs to the less often affected sex. This is so, because the mutant genes are likely to be more severe so as to produce the disease in the sex with an inherent resistance to the disease. The usual risk of recurrence for malformations caused by a polygenic or multifactorial cause is 2–5%.

THERAPY FOR GENETIC DISORDERS

Genetic disorders cannot generally be cured completely. However, symptoms of many disorders can be ameliorated

and the irreversible damage or handicap can be prevented or reduced through several therapeutic approaches:

i. The deficiency of the metabolic endproduct may be made up by replacement or administration of the product. Thus, thyroxine restores the thyroid function in familial goiterogenous cretinism; cortisone suppresses excess ACTH production and androgen synthesis in adrenogenital syndrome and administration of Factor VIII/IX prevents bleeding in cases of hemophilia.

ii. The intake of substances which cannot be metabolized by the body should be reduced, especially if their accumulation is potentially toxic, e.g. in galactosemia, galactose cannot be metabolized adequately. As lactose in the milk is hydrolyzed in the body to glucose and galactose, milk in the diet of the affected infant is substituted by lactose free dietary formulae to obviate damage due to excess of galactose in tissues. The phenylketonuric infants placed on restricted phenylalanine in the diet may escape irreversible neurological damage.

iii. Certain drugs, which precipitate adverse symptoms in metabolic disorders, such as barbiturates in porphyria and oxidating agents in glucose-6-phosphate dehydrogenase deficiency, should never be administered to affected patients.

iv. Patients with hemophilia and osteogenesis imperfecta should be protected from trauma and other environmental hazards to prevent excessive bleeding and fractures, respectively.

v. Surgery helps to reduce the functional or cosmetic disability in many structural defects.

vi. The excretion of certain metabolites can be promoted by chelating agents, e.g. penicillamine promotes excretion of copper in patients with Wilson disease and desferrioxamine can be used to chelate iron in patients with thalassemia and hemochromatosis.

vii. Certain enzyme systems which may be immature or reduced at certain phases of life may be induced or stabilized by the use of chemical agents. For example, phenobarbitone is used to induce hepatic microsomal enzymes like glucuronyl transferase in cases of neonatal hyperbilirubinemia or Crigler-Najjar syndrome.

viii. In some metabolic disorders, enzymatic block can be bypassed by administration of large quantities of the coenzyme, e.g. pyridoxine in homocystinuria.

ix. Enzyme replacement therapy has become feasible with the availability of deficient enzymes for Gaucher disease, Hurler syndrome, Hunter syndrome, mucopolysaccharidosis type VI, Fabry disease and Pompe disease. The cost of the treatment is prohibitive.

x. Bisphosphonates, both intravenous and oral, have been useful in cases of osteogenesis imperfecta.

xi. Stem cell transplantation is recommended for many genetic disorders like thalassemia major, severe form of Hurler syndrome and some primary immunodeficiencies. The benefit is maximized if the transplantation is done early in the course of disease.

xii. Gene therapy is possible in patients with adenosine deaminase deficiency, familial hypercholesterolemia and some cancers. The normal gene is introduced in affected individuals using viral or nonviral vectors. As the exact regulation of gene function of single gene disorders is very complex, the implementation of gene therapy is complicated.

PREVENTION OF GENETIC DISORDERS

Carrier Screening

It is now possible to detect the carrier state in a large number of autosomal recessive or X-linked recessive disorders. Female carriers of Duchenne muscular dystrophy may show high serum levels of the enzyme creatinine phosphokinase, but can be tested more precisely using molecular techniques. Female carriers of glucose-6-phosphate dehydrogenase deficiency are detected by demonstrating relatively low level of enzymes in their erythrocytes. HbA2 levels are useful in identifying carriers of β thalassemia trait in high-risk communities. Molecular techniques are increasingly used for detection of individuals who are m ore likely to give birth to offspring with hereditary disorders.

Newborn Screening

This is an example of secondary prevention by early diagnosis and treatment. Newborn infants are screened routinely for some endocrine disorders and inborn errors of metabolism in developed countries. This is of special value for detecting the affected cases during the newborn period, so that the handicap can be prevented or minimized by early treatment, e.g. in cases of congenital hypothyroidism, congenital adrenal hyperplasia, phenylketonuria, galactosemia and tyrosinemia.

Prevention of Neural Tube Defects (NTD)

Folic acid supplementation is recommended at a dose of 0.4 mg daily from one month before to three months after conception to prevent NTD. Expectant mothers at high-risk of NTD (e.g. previous fetus with NTD) should consume 4 mg of folic acid daily to prevent recurrence of neural tube defects.

Prenatal Diagnosis and Selective Termination of Affected Fetuses

This is a successfully used modality for preventing birth of affected babies and reducing the load of lethal, chronically disabling, untreatable or difficult-to-treat genetic disorders in the community. The prenatal screening or diagnostic modalities can be noninvasive or invasive. Noninvasive techniques include fetal ultrasonography and maternal serum screening.

Maternal Serum Screening

Estimation of pregnancy associated plasma protein A (PAPP-A) and free β-human chorionic gonadotropin (hCG) in the first trimester and serum alpha-fetoprotein, hCG, unconjugated estriol and inhibin A in second trimester are useful biochemical markers to detect aneuploidies. If the risk of bearing a child with Down syndrome is more than 1:250, prenatal fetal karyotyping can be offered. Fetal ultrasonography helps to detect fetuses who are at high-risk for chromosomal abnormalities. Important findings in the second trimester which are markers of Down syndrome include increased nuchal fold thickness (measured over the occiput and not the spine), short femur and humerus length and duodenal atresia. In the first trimester, nuchal translucency and nasal bone are robust markers. Ultrasound findings help in counseling, particularly if the parents have opted for initial screening with maternal serum markers. Both maternal serum screening and fetal ultrasound are screening techniques and cannot rule out Down syndrome. The detection rate of triple test in the second trimester is about 65% with a false positive rate of 5%. First trimester screening using dual markers have high detection rates, which improves further if ultrasound markers are combined. Alpha-fetoprotein and estriol are low, whereas hCG is high, in pregnancies with Down syndrome fetuses. All three markers are reduced in fetuses with trisomy 18. Elevated alpha-fetoprotein level in maternal blood is also a very sensitive marker for fetuses affected with open neural tube defects.

Invasive Prenatal Testing

This includes chorionic villus biopsy (done at 10–12 weeks of gestation or later), amniocentesis (16–20 weeks) and cord blood sampling (after 18 weeks). Procedure related risk is lowest with amniocentesis (~ 0.5%), while chorionic villus biopsy carries a risk of fetal loss in about 2%. These samples can be used for chromosomal studies, DNA based tests or enzyme assays. Amniotic fluid is the preferred sample for chromosomal studies and chorionic villus tissue for DNA based tests. Single gene disorders with a known gene can be diagnosed prenatally. Some common examples are thalassemia, sickle cell anemia, hemophilia, Duchenne muscular dystrophy and cystic fibrosis.

Genetic Counseling

Genetic counseling is a communication process, which deals with problems associated with the occurrence and recurrence of a genetic disorder in a family. Counseling should be undertaken by a physician with proper understanding of the genetic mechanisms. Some important indications for genetic counseling are as follows: (i) known or suspected hereditary disease in a patient or family; (ii) birth defects in previous children; (iii) unexplained mental retardation, dysmorphism, multiple malformations in a child; (iv) consanguinity; (v) exposure to a teratogen during pregnancy; and (vi) identification of malformation(s) by ultrasonography during pregnancy.

Suggested Reading

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Inborn Errors of Metabolism

23

Neerja Gupta, Madhulika Kabra

Inborn errors of metabolism (IEM) are conditions caused by genetic defects related to synthesis, metabolism, transport or storage of biochemical compounds. The metabolic error usually results in the deficiency of one or more enzymes required for the formation or transport of proteins. The worldwide incidence of IEMs is 3–4/1000 live births; most are inherited in an autosomal recessive manner.

SUSPECTING AN INBORN ERROR OF METABOLISM

IEMs may present in the newborn period, in early or late childhood, or in adults. The diagnosis is often delayed, and requires a high index of suspicion, since symptoms are nonspecific, leading to evaluation for other pediatric illnesses like sepsis and hypoxic ischemic encephalopathy.

Features of Metabolic Disorders

- Sudden and rapid illness in a previously normal baby precipitated by fever, vomiting or fasting
- Nonspecific, unexplained features such as poor feeding, lethargy, vomiting, hypotonia, failure to thrive, respiratory abnormalities, hiccups, apnea, bradycardia and hypothermia, with normal sepsis screen
- Rapidly progressive encephalopathy of unknown etiology
- Persistent or recurrent hypoglycemia, intractable metabolic acidosis, unexplained leukopenia or thrombocytopenia
- Hyperammonemia
- *E. coli* sepsis
- Organomegaly
- Peculiar odor (musty in phenylketonuria; cabbage like in tyrosinemia; maple syrup like in maple syrup urine disease; like sweaty feet in isovaleric acidemia, or glutaric acidemia type II; like cat urine: in 3-methylcrotonyl CoA carboxylase or multiple carboxylase deficiency)
- Family history of unexplained neonatal deaths or progressive neurological disease, HELLP (*h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelet counts) syndrome in mother
- Parental consanguinity

Classification

Based on the pathophysiology, IEMs can be classified as follows:

Intoxication group includes disorders of intermediary metabolism, with accumulation of toxic compounds resulting in acute or progressive symptoms. Amino-acidopathies (e.g. phenylketonuria and maple syrup urine disease), organic aciduria, urea cycle defects, disorders of carbohydrate and copper metabolism and porphyrias belong to this category. Symptoms are often precipitated by catabolic state (fever, infections, immunization, dehydration or fasting).

Defects in energy metabolism include conditions associated with deficient energy production or utilization within liver, muscle, heart and brain, e.g. mitochondrial disorders, disorders of glycolysis, glycogen metabolism and gluconeogenesis and hyperinsulinism. Failure to thrive, hypoglycemia, hepatomegaly, hypotonia, cardiomyopathy, myopathy, high lactate, neurological symptoms, circulatory collapse or sudden death may be seen.

Disorders of complex molecules include lysosomal storage diseases, peroxisomal disorders, α_1-antitrypsin deficiency and congenital disorders of glycosylation. Symptoms are usually progressive and permanent and do not have precipitating factors.

Metabolic disorders can have either acute or chronic presentation (Table 23.1).

Acute Presentation

Neonates with metabolic disorders appear normal at birth since the small intermediary metabolites are eliminated by the placenta during fetal life. Disorders of glucose, protein and fat breakdown usually present early, although

Table 23.1: Classification of inborn errors of metabolism

	Acute encephalopathy	*Chronic encephalopathy*
Age at presentation	Neonatal or early infancy	Late infancy, childhood, adolescence
Metabolite and type of defect	Small molecule; intoxication or energy metabolism defects	Large or complex molecule(s)
Presentation	Seizures, respiratory abnormalities, vomiting, lethargy, unexplained coma	Spasticity, hyperreflexia, ataxia; dementia, vision and hearing, impairment, liver dysfunction, cardiomyopathy

premature neonates with transient hyperammonemia of newborn (THAN) and term babies with glutaric acidemia type II or pyruvate carboxylase deficiency may present on the first day of life. In general, an early onset of clinical symptoms is associated with severe disease. The onset of illness is delayed in the intermittent or milder forms.

An important clue to diagnosis is unexpected deterioration after normal initial period in a full term baby. Neonates with organic acidurias, urea cycle disorders and some aminoacidurias may present with lethargy, poor feeding, persistent vomiting, seizures, tachypnea, floppiness and body or urine odor. Common conditions such as sepsis, hypoxic ischemic encephalopathy and hypoglycemia should be excluded.

Older children show acute unexplained, recurrent episodes of altered sensorium, vomiting, lethargy progressing to coma, stroke or stroke like episodes, ataxia, psychiatric features, exercise intolerance, abdominal pain, quadriparesis or arrhythmias. The symptom free period may be prolonged, often longer than a 1 yr and patients are normal in between the episodes. Intercurrent illnesses, high protein intake, exercise, fasting and drug intake (enzyme inducers) may precipitate symptoms. Encephalopathy occurs with little warning in previously healthy individuals; progresses rapidly, may be recurrent and show fluctuating consciousness and is not associated with focal neurological deficits.

Physical examination may show altered sensorium, apnea or hyperpnea and hypotonia. Facial dysmorphism, structural anomalies of brain, cataract, retinopathy, deafness, hypertrophic or dilated cardiomyopathy, hepatomegaly, multicystic dysplastic kidneys, myopathy and peculiar urine odor suggest specific diagnoses.

Laboratory Investigations

Biochemical tests may be normal when the child is asymptomatic. The initial screening investigations include total and differential counts and blood levels of sugar, electrolytes, bicarbonate, calcium, transaminases, ammonia, lactate and pyruvate. During neonatal period, ammonia levels are <200 µg/dl; beyond neonatal age, levels <80 µg/dl are considered normal. In urea cycle disorders, blood ammonia levels exceed 1000 µg/dl and cause respiratory alkalosis with compensatory metabolic acidosis. In organic acidurias, ammonia levels are <500 µg/dl and in fatty acid oxidation defects <250 µg/dl. Urine metabolic screen includes pH, ketones, reducing substances and ferric chloride, dinitrophenylhydrazine (DNPH) and nitroprusside tests.

Specialized tests such as quantitative urinary and plasma amino acids analysis by high performance liquid chromatography (HPLC), plasma carnitine and acylcarnitine by tandem mass spectrometry (TMS) and urinary organic acids by gas chromatography and mass spectrometry (GCMS) are helpful in reaching a conclusive diagnosis. Cerebrospinal fluid, chest X-ray, echocardiography, ultrasound abdomen, computed tomography (CT) head, magnetic resonance imaging of brain and electroencephalogram (EEG) are useful in specific cases.

Acutely presenting IEMs are classified into five major categories (Table 23.2). Figure 23.1 describes the initial approach in such patients.

Biochemical Autopsy

In a severely ill or dying child, where an IEM is suspected, parents should be advised about the need for a biochemical autopsy for confirmation of diagnosis. Following informed written consent, the following samples should be obtained postmortem to facilitate diagnosis.

Blood: 5–10 ml each in heparin (for plasma) and EDTA (leukocytes); store at –20°C

Urine: Store at –20°C

Cerebrospinal fluid: Store at –20°C

Skin biopsy (including dermis: Store at 37°C in culture medium or saline with glucose).

Liver, muscle, kidney, heart biopsy: Tissue frozen

Clinical photograph and infantogram

Management

Treatment is often instituted empirically; prompt management may be lifesaving. Dietary or parenteral intake of potentially toxic compounds (such as protein, fat, galactose, fructose) is eliminated; adequate calories are provided using 0.2% saline in 10% dextrose intravenously. Intralipids (2–3 g/kg/day) may be infused if fatty acid oxidation defect is not suspected. Metabolic acidosis (pH <7.30, bicarbonate <15 mEq/l, anion gap >16 mEq/l) should be corrected. Blood levels of sugar, pH and electrolytes should be monitored.

The excretion of toxic metabolites is enhanced by hemodialysis or using alternative pathways for nitrogen excretion. Immediate measures to decrease plasma levels of ammonia are necessary as the risk for irreversible cerebral damage is related to its concentration. IV phenylacetate and sodium benzoate with L-arginine (Table 23.3) are used as detoxifying agents. Dialysis is initiated if plasma ammonia levels exceed 500–600 µg/dl, or if levels do not

Table 23.2: Differential diagnosis of metabolic disorders with acute presentation

Group	*Acidosis*	*Ketosis*	*Plasma lactate*	*Plasma NH_3*	*Plasma glucose*	*Diagnosis*	*Special test*
I	±	+	N	N	N/↓	Aminoacidopathies	Plasma or urine amino acid and blood spot for TMS
II	+++	+	↑	↑↑	↓↓	Organic acidurias	Urine GCMS and blood spot for TMS
III	++	±	↑ ↑ ↑	N	N	Mitochondrial disorders	Lactate: pyruvate ratio, blood spot for TMS, urine GCMS; testing for mitochondrial mutations; muscle biopsy
IV	N	N	N	↑ ↑ ↑	N	Urea cycle disorder	Plasma amino acid, urine GCMS; urinary orotic acid excretion
V	±	N	±	↑	↓↓↓	Fatty acid oxidation defects, glycogen storage disorders	Blood spot for TMS for acylcarnitines and urine organic acids

GCMS Gas chromatography and mass spectrometry; TMS Tandem mass spectrometry; + present; N normal; ↑ increased

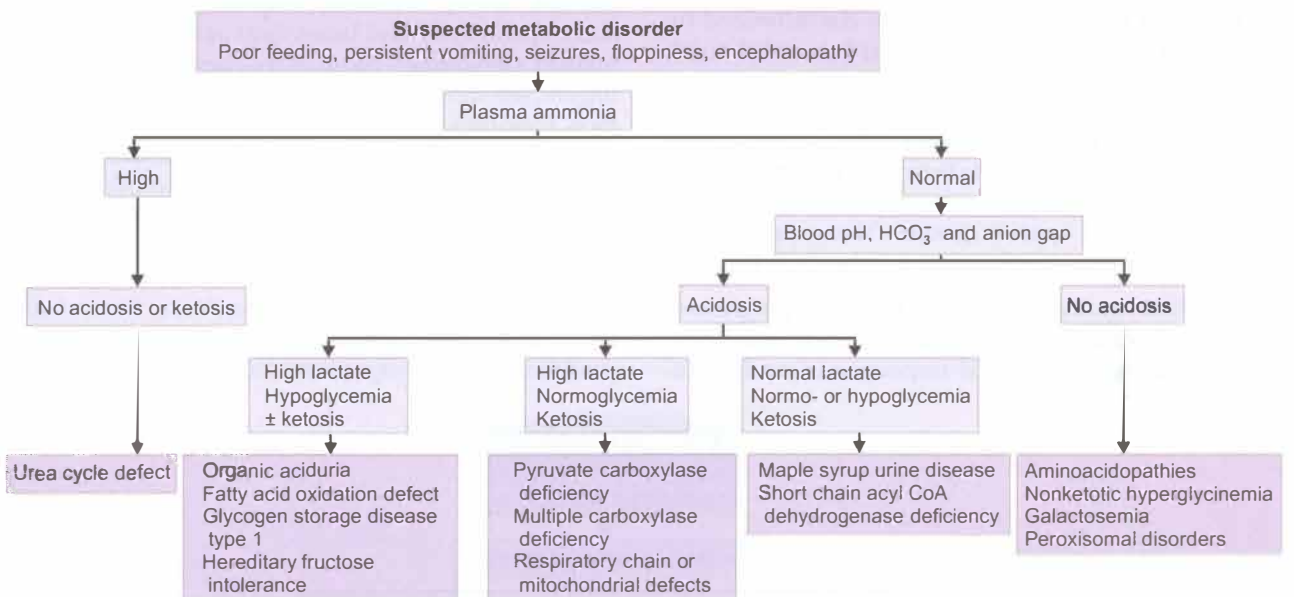


Fig. 23.1: Approach to a case with a suspected metabolic disorder

fall within 2 hr after initiation of IV treatment. Hemodialysis is preferred to peritoneal dialysis and exchange transfusion.

Carnitine eliminates organic acids as carnitine esters. Carnitine may be used in life-threatening situations associated with its deficiency, at a dose of 25–50 mg/kg IV given over 2–3 minutes, followed by 25–100 mg/kg/day orally. L-carnitine should not be administered with sodium benzoate. Intractable seizures without metabolic acidosis or hyperammonemia are treated with pyridoxine 100–200 mg IV.

If clinical improvement is observed and a final diagnosis is not established, some amino acid intake should be provided after 2–3 days of complete protein restriction. Essential amino acids or total protein is provided orally or IV at an initial dose of 0.5 g/kg/day and gradually increased to 1.0–1.5 g/kg/day, until diagnostic evaluation is complete and plans are made for longterm therapy. Appropriate amino acid formula (free of precursor amino acids) or protein free infant formula with breast milk is gradually introduced with careful clinical and laboratory monitoring. Expressed human milk is preferred as it can be measured and total protein intake quantified.

Empiric cofactor or coenzyme therapy may be administered (Table 23.4) to maximize residual enzyme activity awaiting final diagnosis. Longterm strict adherence to

Table 23.3: Management of hyperammonemia

Drug	*Loading dose*	*Maintenance dose*
Sodium benzoate and/or sodium phenylacetate	250 mg/kg (2.5 ml/kg) IV in 10% glucose over 2 hr	250–500 mg/kg in 24 hr (2.5 ml/kg/24 hr) IV as continuous infusion
L-Arginine*	600 mg/kg (6 ml/kg) IV in 10% glucose over 2 hr	600 mg/kg/day IV as continuous infusion

* The dose of arginine hydrochloride can be decreased to 200 mg/kg for carbamoyl phosphate synthetase or ornithine transcarbamylase deficiency; IV intravenous

Table 23.4: Cofactor and adjunctive therapy

Disorder	*Therapy*	*Oral dose, mg/kg/day*
Maple syrup urine disease	Thiamine	5
Methylmalonic aciduria	Vitamine B12 L-carnitine Metronidazole	1–2 mg/day 50–100 10–20
Propionic acidemia	L-carnitine Metronidazole	50–100 10–20
Isovaleric acidemia	L-carnitine L-glycine	50–100 150–300
Multiple carboxylase or biotinidase deficiency	Biotin	10–40 mg/day

dietary and pharmacologic regimen is recommended. Prompt recognition and avoidance of physiologic stresses (fever, infection, trauma, surgery, fasting) and changes in diet that may precipitate symptoms is important in preventing metabolic decompensation.

Chronic and Progressive Presentation

This group of metabolic disorders is characterized by variable but insidious onset from birth to adulthood. Unexplained developmental delay with or without seizures, organomegaly, coarse facies, cataract, dislocated lens, chronic skin lesions, abnormal hair, abnormal urine color on standing and failure to thrive are important clues. These forms are divided into subgroups depending upon the involvement of specific system. The approach to a patient with chronic encephalopathy is shown in Fig. 23.2.

Neurologic findings are developmental delay or progressive psychomotor retardation, seizures, ataxia, spasticity, variable hearing and visual impairment, and extrapyramidal symptoms. Psychomotor or developmental delay is the chief manifestation and tends to be global and progressive. History of regression of milestones may be present. Severe irritability, impulsivity, aggressiveness and hyperactivity and behavioral patterns such as automatism, stereotypes, compulsive chewing of thumbs and fingers, self-mutilation and nocturnal restlessness are common. Complex partial or myoclonic seizures occur early in course of the disease and are often resistant to therapy. Signs include change in tone and pyramidal or extrapyramidal deficit. Differentiating between involvement of either gray matter or white matter is helpful in narrowing the differential diagnosis (Table. 23.5). Movement disorders are intermittent or progressive, in form of ataxia, dystonia, choreoathetosis and Parkinsonism. Underlying conditions include organic acidurias, late-onset neuronal

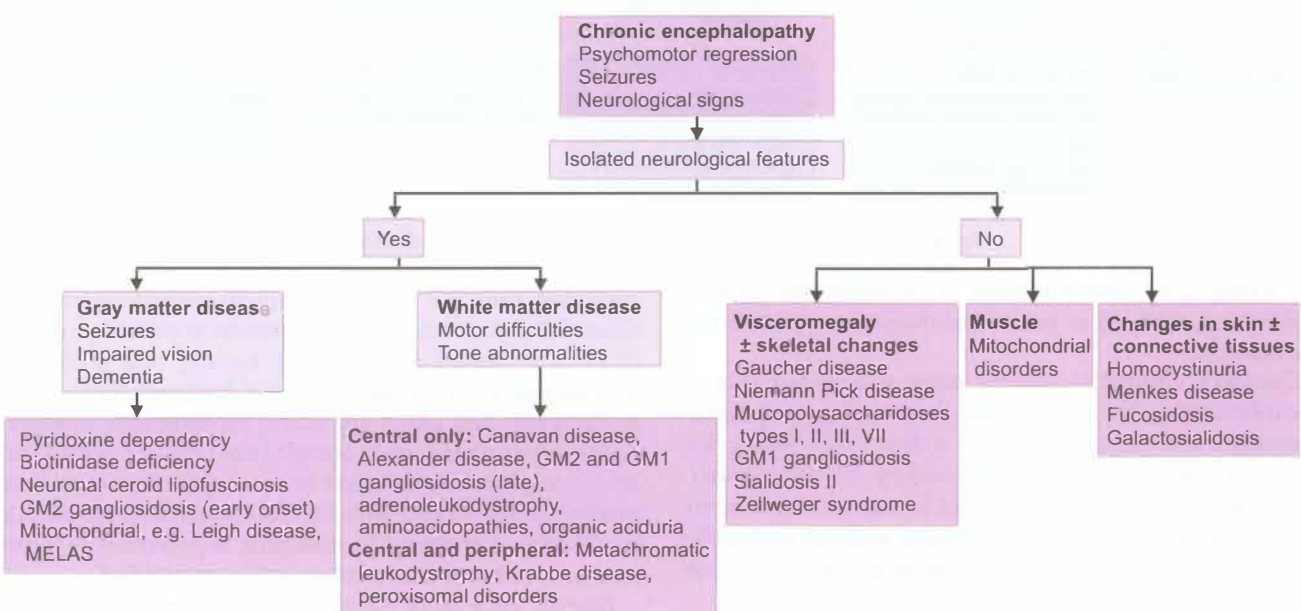


Fig. 23.2: Initial approach to a chronic encephalopathy. MELAS myopathy, encephalopathy, lactic acidosis and stroke like episodes; MLD metachromatic leukodystrophy

Table 23.5: Differentiating features of gray matter and white matter disorders

Clinical features	*Gray matter disease (poliodystrophy)*	*White matter disease (leukodystrophy)*
Age of onset	Early	Usually late childhood
Head size	Microcephaly is common	May have macrocephaly
Seizures	Early, severe	Late, uncommon
Cognitive functions	Progressive decline	Initially normal
Spasticity	At a later stage	Early, severe
Reflexes	Normal or brisk	Absent (neuropathy) or brisk (long tract involvement)
Eye	Retinal degeneration or cherry-red spot	Optic atrophy, cataract or cherry-red spot
Peripheral neuropathy	Late	Early demyelination
Electromyography	Usually normal	Slowed nerve conduction velocity
Visual evoked potentials	Usually normal	Prolonged or absent
Electroretinography	Abnormal	Normal
MRI brain	Cerebral or cerebellar atrophy	White matter involvement (demyelination or dysmyelination)

ceroid lipofuscinosis, lysosomal storage disorders and urea cycle disorders.

Muscular disorders presenting with myopathy are usually due to defects in energy metabolism. Myopathy can be progressive (glycogen storage disease, GSD types II and III), exercise intolerance with cramps and myoglobinuria (GSD V, VI), or as part of multisystem disease (mitochondrial myopathies).

Hepatic presentations include the presence of unconjugated or conjugated jaundice, hypoglycemia and hepatomegaly with or without hepatocellular dysfunction. Coexisting deranged lipid profile is seen in GSD type I and hepatosplenomegaly a feature of GSD III and lysosomal storage disorders. Hepatocellular dysfunction is seen in galactosemia, GSD IV and III, Niemann-Pick type B, α_1-antitrypsin deficiency. Disorders leading to cirrhosis include tyrosinemia, galactosemia, hereditary fructose intolerance and Wilson disease.

Cardiac manifestations may occur in fatty acid oxidation defects, mitochondrial disorders, GSD type II, methylmalonic acidemia, Fabry disease, Kearns-Sayre syndrome, familial hypercholesterolemia, mucopolysaccharidoses and GM1 gangliosidosis.

Dysmorphic features are present in patients with Zellweger syndrome, glutaric aciduria type 2 and storage syndromes.

Renal manifestations are seen in patients with cystinosis, galactosemia, hereditary fructose intolerance and tyrosinemia (renal tubular acidosis); progressive renal failure is common in patients with cystinosis. Enlarged kidneys are seen in patients with GSD type I.

Ocular findings often provide a clue to the underlying IEM. The presence of cataract(s) suggests galactosemia, peroxisomal disorders, Lowe syndrome and Wilson disease. Corneal abnormalities are seen in mucopolysaccharidoses, Wilson disease and Fabry disease. Patients with homocystinuria show lens dislocation. Cherry-red spots are found in various lysosomal storage diseases, such as Tay-Sachs disease, GM1 gangliosidosis and Niemann-Pick disease.

Skin may show an eczematous rash associated with alopecia in biotinidase deficiency. Angiokeratoma are characteristic of Fabry disease, but can be seen in fucosidosis and β-mannosidosis.

Evaluation

Investigations should include complete hemogram, liver and renal function tests and serum electrolytes. Pancytopenia may be seen in patients with methylmalonic acidemia and propionic acidemia. The peripheral smear may show vacuolated lymphocytes in neuronal ceroid lipofuscinosis, fucosidosis and sialidosis; acanthocytosis in abetalipoproteinemia and Hallervorden-Spatz disease (pantothenate kinase associated neurodegeneration). Adrenal insufficiency is frequent in patients with adrenoleukodystrophy. Metabolic acidosis and evidence of proximal renal tubular dysfunction is present in patients with Lowe syndrome, cystinosis, Wilson disease and galactosemia. Investigations that enable specific diagnosis include neurological imaging and electrophysiological studies and skeletal survey. Specific enzyme assays and estimation of plasma levels of lactate, ammonia, very long chain fatty acids and amino acids are useful in certain cases.

Management

A multidisciplinary team of metabolic specialists, pediatric neurologists, clinical geneticist, cardiologist, orthopedic surgeon and physiotherapist is required to maximize the supportive care in these patients. Other treatment options include cofactor and megavitamin therapy, special diets, enzyme replacement therapy and organ transplantation. Most IEMs are inherited in autosomal recessive manner and risk of recurrence in subsequent pregnancy is 25%. Few disorders are X-linked, autosomal dominant and mitochondrial in inheritance. Prenatal diagnosis is possible by enzyme assays or mutation testing in fetal DNA in chorionic villus biopsy metabolites in amniotic fluid and using fetal DNA (Chapter 22).

SPECIFIC DISORDERS

Aminoacidopathies

These disorders do not have a common phenotype but have unique features depending upon the site of defect.

Phenylketonuria

Phenylketonuria (PKU) is a disorder of phenylalanine metabolism and occurs due to deficiency of phenylalanine hydroxylase (PAH).

Clinical features. Affected individuals have profound and irreversible intellectual disability, microcephaly, epilepsy and behavioral problems. These patients often have a musty body odor and skin conditions such as eczema caused by excretion of excessive phenylalanine and its metabolites. Decreased skin, hair and eye pigmentation may also be present due to associated inhibition of tyrosinase and reduced melanin synthesis (Fig. 23.3).

Diagnosis. Modalities include (i) *newborn screening:* PKU can be detected in virtually 100% of cases by various methods of newborn screening such as Guthrie card bacterial inhibition assay (BIA), fluorometric analysis and tandem mass spectrometry. In classic PKU, plasma phenylalanine level is >1000 µmol/l with <1% residual PAH activity, (ii) molecular genetic testing of the *PAH* gene.

Treatment. A low-protein diet and use of phenylalanine-free medical formula as soon as possible afterbirth to achieve plasma concentrations 120–360 µmol/l (2–6 mg/dl) is recommended. A significant proportion of patients with PKU may benefit from adjuvant therapy with single daily dose of 5–10 mg/kg tetrahydrobiopterin.

Maple Syrup Urine Disease (MSUD)

MSUD is due to decreased activity of **b**ranched **c**hain alpha keto**a**cid **d**ehydrogenase (BCKAD) complex, a mitochondrial enzyme involved in degradation of branched chain amino acids (leucine, isoleucine and valine). There are five different phenotypes based on clinical findings and response to thiamine. This enzyme has four subunits: $E1_{\alpha}$, $E_{1\beta}$, E_2 and E_3.

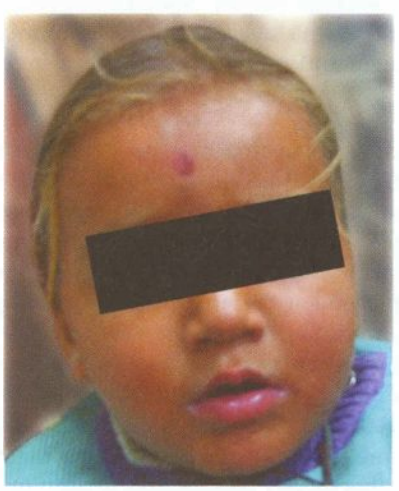


Fig. 23.3: Blond hair in a child with phenylketonuria

Clinical features. The first sign of classic MSUD in untreated neonates is maple syrup odor in cerumen at 12–24 hr afterbirth. By 48–72 hr, poor feeding, ketonuria, irritability and drowsiness develops followed by unexplained progressive coma. The characteristic urine smell develops on day 5–7 of life. In advanced stage, intermittent apnea, bradycardia, hypothermia, generalized hypertonia, opisthotonus and involuntary movements such as *fencing* and *bicycling* may appear. Individuals with acute intermittent late onset forms of MSUD can have recurrent episodes of severe metabolic decompensation and encephalopathy during any catabolic stress. Chronic progressive forms can present with variable manifestations such as developmental delay or progressive psychomotor retardation, seizures, failure to thrive, sleep disturbances, hyperactivity, mood swings and movement disorders.

Diagnosis. (i) Urine 2,4-dinitrophenylhydrazine (DNPH) test to detect ketonuria by adding DNPH to urine which produces a yellow-white precipitate due to presence of branched chain ketoacids, (ii) elevated plasma levels of leucine, isoleucine, valine (5 to 10-fold greater than normal) and alloisoleucine, (iii) enzymatic and/or genetic testing are useful for confirming the diagnosis.

Treatment. Treatment during acute stage should follow the abovementioned principles along with rapid removal of branched chain amino acids from body tissues and fluids using either peritoneal or hemodialysis. Cerebral edema is a common complication should be treated promptly in an intensive care setting with mannitol, hypertonic saline and diuretics. During recovery high calorie, branched chain amino acid free formula is initiated early with regular plasma amino acid monitoring. Some patients with milder forms may respond to thiamine. Orthotopic liver transplantation is effective therapy for classic MSUD.

Hepatorenal Tyrosinemia Type 1

The condition is caused by deficiency of enzyme fumarylacetoacetate hydrolase (FAH), encoded by *FAH* gene. Enzyme is mainly expressed in liver and kidney.

Clinical features. It is a disorder of tyrosine metabolism, classically presents as severe liver disease in young infants. Severe forms present during infancy with vomiting, diarrhea, bleeding diathesis, hepatomegaly, jaundice, hypoglycemia, ascites and coagulopathy. Children older than six months of age may come to medical attention with variable degree of renal dysfunction, hypophosphatemic rickets and aminoaciduria. Untreated children may have repeated, often unrecognized, neurologic crises lasting 1–7 days that can include change in mental status, abdominal

pain, peripheral neuropathy, autonomic dysfunction and/or respiratory failure requiring mechanical ventilation. Death in the untreated child usually occurs before age ten years, typically from liver failure, neurologic crisis or hepatocellular carcinoma.

Diagnosis The following tests are useful: (i) Deranged liver function tests; prolonged prothrombin and partial thromboplastin times, (ii) generalized aminoaciduria; radiological evidence of rickets, (iii) markedly elevated serum concentration of alpha-fetoprotein (average 160,000 ng/ml) (normal: <1000 ng/ml for infants 1–3 months; <12 ng/ml for age 3 months to 18 yr), (iv) increased succinylacetone concentration in the blood and excretion in the urine. Elevated plasma concentration of tyrosine, methionine and phenylalanine, (v) enzyme assay, and (vi) molecular genetic studies for FAH gene.

Treatment Nitisinone or 2-(2-nitro-4-fluoromethyl-benzoyl)- 1,3-cyclohexanedione (NTBC) treatment should begin as soon as the diagnosis of tyrosinemia type I is confirmed. It blocks tyrosine degradation at an early step to prevent the production of downstream metabolites such as fumarylacetoacetate and succinylacetone. It is given at doses of 1 mg/kg/day. Dietary restriction of phenylalanine and tyrosine is required to prevent tyrosine crystals from forming in the cornea. In Western countries, prior to the availability of nitisinone, the only definitive therapy for tyrosinemia type I was liver transplantation, which now is reserved for those children who have severe liver failure at presentation and fail to respond to nitisinone therapy or have documented evidence of malignant changes in hepatic tissue. Nitsinone is not readily available in India and is expensive.

Classic Homocystinuria

This occurs due to cystathionine β-synthase deficiency leading to accumulation of homocysteine, which has deleterious effects on the central nervous system, vessels, skin, joints and skeleton. Two clinical variants exist: B6 (pyridoxine)-responsive homocystinuria and B6-non-responsive homocystinuria. B6-responsive homocystinuria is typically, but not always, milder than the nonresponsive variant and has a better outcome than the nonresponsive ones.

Clinical features. Patients typically present with ocular, skeletal, CNS and vascular manifestations usually after 3-4 yr of age. Developmental delay, seizures, psychiatric problems and extrapyramidal signs such as dystonia, downward lens dislocation and/or severe myopia, marfanoid habitus, osteoporosis with or without thromboembolic complications are the usual presenting features. They can also have hypopigmentation and pancreatitis. Ectopia lentis occurs by age eight years. Thromboembolism is a major cause of early death and morbidity.

Diagnosis. Quantitative plasma amino acid analysis showing increased levels of methionine, homocysteine with no cystathionine confirms the diagnosis. Plasma total homocysteine levels are important for monitoring the treatment (normal levels <15 µmol/l; homocystinuria >200 µmol/l). Confirmation can be done by *CBS* enzyme activity or molecular testing for *CBS* gene. Urine nitroprusside test is a good screening test.

Treatment. Treatment is directed towards lowering the plasma homocysteine levels as close to normal as possible. About half of all patients respond to vitamin B6 therapy (200–1000 mg/day). In patients with folate and vitamin B12 deficiency, folic acid (5 mg/day) and hydroxycobalamin (1 mg intramuscularly per month) is also given. Patients nonresponsive to pyridoxine require lifelong methionine restricted diet with frequent biochemical monitoring. Oral betaine at 150 mg/kg/day (in two divided doses) is effective in lowering homocysteine levels. Vitamin C supplementation (1 g/day) ameliorates endothelial dysfunction.

Alkaptonuria

This was the first inborn error of metabolism described by Garrod in 1902 and is caused by defect of the enzyme homogentisate 1,2-dioxygenase (homogentisic acid oxidase). The most prominent symptoms are related to connective tissues and joints. These manifestations are rarely noticed before the age of 20 to 30 yr.

Clinical features. The disorder comes to attention due to change in color of urine to brownish black or staining of diapers. Pigment deposits irritate the articular cartilage, resulting in degeneration and osteoarthritis like changes. Intervertebral disks are degenerated, spaces are narrowed and calcification occurs. Ochronotic arthritis commonly involves shoulders and hips. Pigment deposits in the kidney manifest as renal stones. A grayish discoloration of sclera and the ear and nose cartilage (ochronosis) usually occurs after 30 yr. The pigment in ochronosis is a polymer of homogentisic acid.

Diagnosis. The urine becomes dark on standing, especially if the pH of urine is alkaline. Excessive urine homogentisate results in positive reducing substances. Organic acid analysis by GCMS can identify and quantify homogentisic acid.

Treatment. No specific therapy is known. Administration of vitamin C prevents deposits of the ochronotic material in cartilage but has no effect on the basic metabolic defect. Nitisinone inhibits the enzyme that produces homogentisic acid and may prove useful.

Urea Cycle Defects

The urea cycle is the main pathway for the removal of highly toxic ammonia, derived from the catabolism of

amino acids, in the form of urea. It is basically composed of six enzymes as demonstrated in Fig. 23.4. Defects of any of these enzymes are characterized by hyperammonemia and deranged amino acid metabolism.

Clinical Features

Presentation is highly variable. In the classical forms, neonates present within first few days of life with poor feeding, recurrent vomiting, tachypnea, hypothermia, irritability, seizures and lethargy progressing to coma. Partial deficiencies of these enzymes represent milder forms and have symptoms that are often subtle and may not occur for months or years. These are usually diagnosed by hyperammonemic episodes manifesting as poor appetite, vomiting, lethargy and behavioral problems and are often triggered by stress or illness. These patients are intolerant to and dislike protein food. Arginase deficiency has more specific symptoms such as spastic diplegia, dystonia and ataxia.

Diagnosis

The diagnosis of a urea cycle disorder is based on clinical suspicion and biochemical screening. Presence of hyperammonemia (plasma ammonia >80 µg/dl after neonatal period) associated with normal anion gap and normal glucose level suggests a urea cycle defect. Plasma amino acid analysis and urinary orotic acid can distinguish the specific defects (Fig. 23.5). A definitive diagnosis of a urea cycle defect depends on either DNA analysis or measurement of enzyme activity.

Management

Treatment is based on the principles highlighted in the section on management of acute presentation and includes rapid removal of ammonia and inhibition of its production along with treatment of any intercurrent illness and correction of dehydration or electrolyte imbalance. Maintenance therapy includes nutritional management with restriction of protein, pharmacological therapy with sodium benzoate/phenylacetate (250–500 mg/kg/day), essential amino acids (0.25 g/kg/day) and arginine (200–600 mg/kg/day).

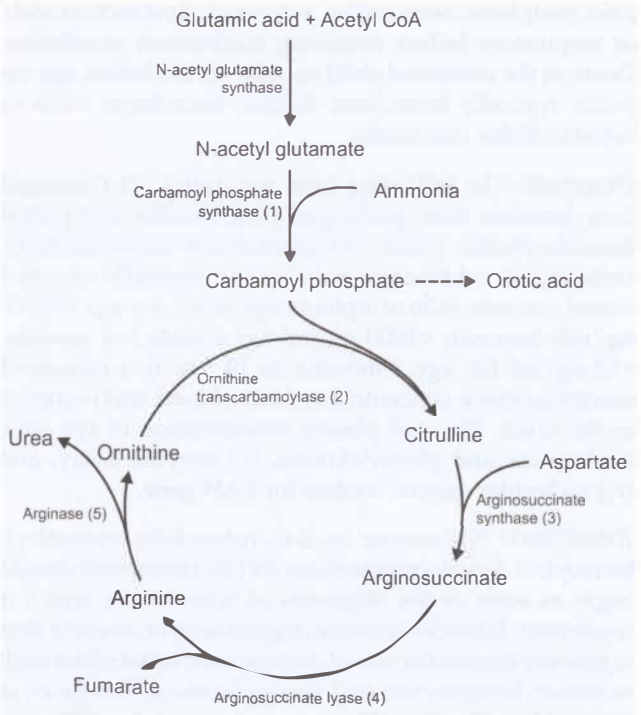


Fig. 23.4: Pathways for ammonia disposal and ornithine metabolism. Deficiency of enzymes results in the following: (1) CPS deficiency, (2) OTC deficiency, (3) citrullinemia, (4) arginosuccinic aciduria and (5) argininemia

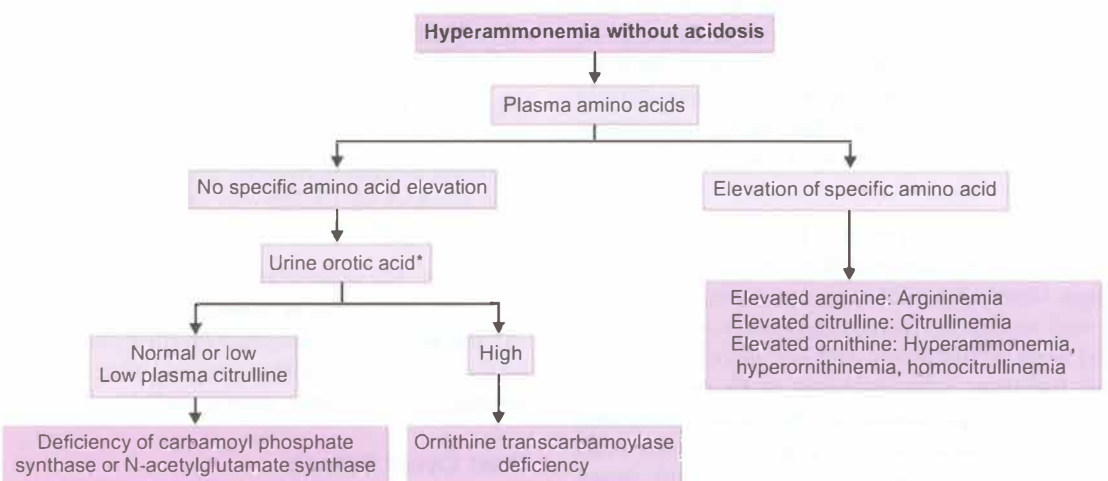


Fig. 23.5: Algorithm to distinguish different urea cycle defects

* Transient hyperammonemia of the newborn is characterized by hyperammonemia, normal levels of urine orotic and normal or high plasma citrulline

Organic Acidurias

The term "organic acidemia" or "organic aciduria" (OA) applies to a group of disorders characterized by the excretion of nonamino organic acids in urine. This group of disorders results from enzyme deficiencies in pathways of amino acid degradation. Defects in the metabolism of the branched-chain amino acids (leucine, isoleucine, valine) as well as tyrosine, homocysteine, methionine, threonine, lysine, hydroxylysine and tryptophan are responsible for most of these disorders. They have two types of clinical presentations: an insidious onset with few to no acute crises and an acute metabolic encephalopathy that is precipitated by illness and increased catabolism.

Clinical Features

Neonates with OA are well at birth and for the first few days of life. The presenting features are that of toxic encephalopathy and includes vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. An early diagnosis and treatment results in improved outcome. In the older child or adolescent, OA present with loss of intellectual function, ataxia or focal neurologic signs, Reye like syndrome, recurrent ketoacidosis or psychiatric symptoms. Specific features of some OA are listed below.

Cutaneous abnormalities. Perioral eruption (multiple carboxylase deficiency).

Abnormal urinary or body odor. Maple syrup/burnt sugar (maple syrup urine disease), sweaty feet (isovaleric acidemia, glutaric aciduria type 2), cat urine (multiple carboxylase deficiency).

Hair abnormalities. Alopecia or sparse hair suggests biotinidase deficiency (Fig. 23.6).

Dysmorphic features. Mevalonic aciduria, glutaric aciduria type 2,3(OH)isobutyric aciduria.

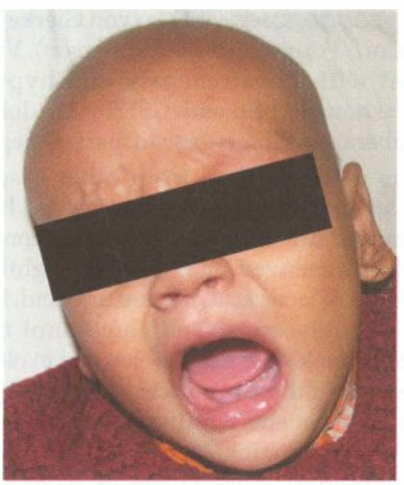


Fig. 23.6: Alopecia in a child with biotinidase deficiency

Hypoglycemia and neurological symptoms. Organic acidurias, including late onset MSUD.

Acute ataxia. Late onset MSUD, methylmalonic acidemia, isovaleric acidemia, multiple carboxylase deficiency.

Acute metabolic encephalopathies. Glutaryl-CoA dehydrogenase deficiency, isovaleric acidemia, MSUD, methylmalonic acidemia, multiple carboxylase deficiency and propionic acidurias.

Acute hemiplegia and metabolic stroke. Methylmalonic acidemia and propionic acidemia, glutaric aciduria type 1, methylcrotonyl-CoA carboxylase deficiency.

Diagnosis

Patients with OA can have acidosis, ketosis, hyperammonemia, abnormal liver function tests, hypoglycemia and neutropenia. Analysis of urine for organic acids using gas chromatography with mass spectrometry (GCMS) enables diagnosis and plasma or serum acylcarnitine prole tested by TMS is often helpful. The urinary organic acid profile is nearly always abnormal in the presence of acute illness with decompensation. However, it may be normal when the affected individual is not acutely ill; in certain disorders, the analytes are present in small amounts.

Urine samples should be obtained during the acute phase of illness and frozen at –20°C. Confirmation of diagnosis is possible by measuring the activity of the deficient enzyme in lymphocytes or cultured fibroblasts and/or DNA analysis.

Management

The management of OA during acute crises follows abovementioned principles. Adjunctive therapy with cofactors or vitamins, such as thiamine to treat thiamine-responsive MSUD and hydroxycobalamin to treat methylmalonic acidemia is useful. For disorders of propionate metabolism, intermittent administration of metronidazole (10–15 mg/kg/day for 10–15 days) reduces the production of propionate by gut bacteria. Various cofactors and adjunctive therapy are detailed in Table 23.4.

Defects of Carbohydrate Metabolism

Galactosemia

There are three disorders of galactose metabolism (Fig. 23.7), but it is the deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT), that is referred to as galactosemia. Deficiency of GALT results in accumulation of galactose-1-phosphate and metabolites (e.g. galactitol) that might have toxic effect on the, e.g. liver and other organs.

Clinical features Patients appear normal at birth, but by 3–4 days of breast milk or formula feeding show life-threatening disease with vomiting, diarrhea, poor weight gain, predominant hepatic and renal manifestations and

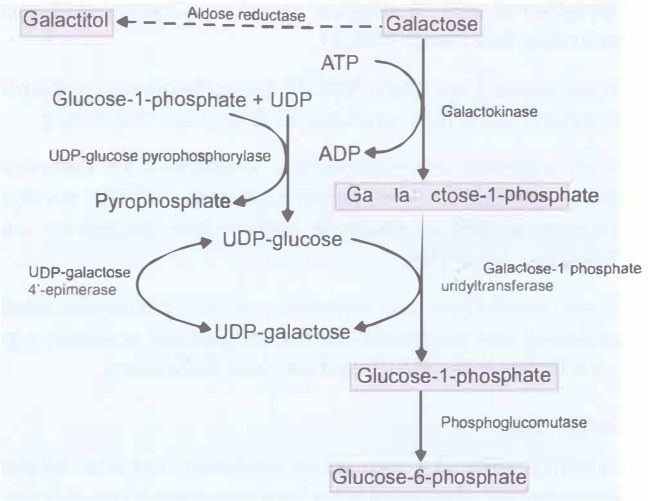


Fig. 23.7: Disorders of galactose metabolism

cataract. Jaundice and liver dysfunction are progressive and appear at the end of first or during second week of life. The disease may present initially with indirect hyperbilirubinemia due to hemolysis secondary to high levels of galactose-1-phosphate in erythrocytes. Many affected infants die of *Escherichia coli* sepsis in the neonatal period. Untreated infants, if surviving the neonatal period, have persistent liver disease, cataracts and severe mental retardation. Alternatively, the effects of acute galactose toxicity may rarely cause predominant neurologic symptoms. Renal tubular disease presents with metabolic acidosis, galactosuria, glucosuria and aminoaciduria (Fanconi syndrome).

Diagnosis The diagnosis is confirmed by either enzyme or specific mutational analysis. In case of suspected galactosemia, the urine should be tested simultaneously with Benedict reagent and by glucose oxidase method. A negative dipstick by glucose oxidase method with positive Benedict reaction indicates nonglucose reducing substances, e.g. galactose or fructose. A negative test does not eliminate the possibility of these disorders, especially if the patient has received intravenous glucose for more than a few hours. If the diagnosis of galactosemia is suspected, whether or not urinary reducing substances are found, galactose-containing feedings should be discontinued and replaced by soy based or lactose free formula pending results of confirmatory enzyme assay or genetic studies.

Galactokinase deficiency Galactosemia due to galactokinase deficiency is rare and has mild manifestations. The only significant abnormality is cataract due to accumulation of galactitol. Liver, kidney and brain damage are not seen. Galactose free diet, if started early, leads to clinical improvement and prevents further damage. Mental retardation, if already present does not improve with therapy. Galactose restricted diet is required throughout life.

Hereditary Fructose Intolerance

The condition occurs due to deficiency of the enzyme, aldolase B. Symptoms occur following ingestion of fructose or sucrose and present with intractable vomiting and symptomatic hypoglycemia. Prolonged exposure results in failure to thrive, irritability, hepatomegaly, abdominal distension, edema and jaundice. Milder variants are common and present with bloating, abdominal distension and diarrhea. Investigations show hypoglycemia, marked lactic acidosis, hyperuricemia, hypophosphatemia, hyperchloremic metabolic acidosis, generalized aminoaciduria and deranged prothrombin and partial thromboplastin time and liver function tests. Confirmation is done by demonstration of deficiency of aldolase B in fresh liver biopsy sample. Fructose free diet is therapeutic.

Glycogen Storage Diseases

Glycogen is an extensively branched polysaccharide macromolecule formed by thousands of glucose units joined into chains by α-1-4 and α-1–6 bond. Ingested carbohydrate is absorbed as glucose *via* the portal system. The glucose is phosphorylated to intermediate compounds (glucose-6-phosphate and glucose-1-phosphate) and is stored as glycogen. Glycogen is the main glucose reservoir in the liver and provides energy between meals or during fasting. In muscle, it provides energy for contraction. When peripheral glucose is utilized and glucose levels fall, glycogen is depolymerized, bonds at branch points are split and free glucose is released into blood by hydrolytic dephosphorylation. The final reaction is mediated by the enzyme glucose-6-phosphatase. The series of reactions causing release of glucose are called glycogenolysis (Fig. 23.8). Any defect in the synthesis and degradation of glycogen causes glycogen storage disease (GSD). Several disorders of glycogen metabolism are described; these are subdivided into liver and muscle glycogenoses (Table 23.6).

Hepatic glycogenoses GSD Ia (von Gierke disease), Ib, type IIIa (Cori/Forbes), IIIb, IV (Anderson), VI (Hers) and IX present with hepatomegaly and hypoglycemia. Figure 23.9 shows a child with GSD I with 'doll like facies' with protuberant abdomen due to marked hepatomegaly.

GSD I is distinguished from other disorders that primarily affect liver by markedly elevated lactic acid as well as elevated uric acid and cholesterol concentrations. GSD III is characterized by normal or slightly increased concentrations of lactic acid, normal uric acid, but a greater elevation of triglycerides and cholesterol than GSD I. Creatine phosphokinase may be elevated in older children and adolescents if there is muscle involvement. GSD III is subdivided into patients who have no muscle involvement (IIIb) and those who develop muscle weakness by their teenage years (IIIa). GSD VI and IX have more benign courses than GSD I and III. Hypoglycemia is less severe,

Table 23.6: Enzymatic deficiencies in common glycogenoses

Type	*Enzyme defect*	*Common name*
Liver glycogenoses		
Ia	Glucose-6-phosphatase	von Gierke
Ib	Glucose-6-phosphate translocase	
IIIa	Liver and muscle debrancher deficiency (amylo-1, 6-glucosidase)	Cori/Forbes
IIIb	Liver debrancher deficiency only	
IV	Brancher enzyme (α-1, 4 glucan: α-1, 4 glucan-6-α glucosyl transferase)	Anderson
VI	Liver phosphorylase	Hers
IX	Phosphorylase kinase	
Muscle glycogenoses		
II	Lysosomal alpha-1, 4-glucosidase (acid maltase)	Pompe
V	Muscle phosphorylase	McArdle
VII	Phosphofructokinase	Tarui

and hepatomegaly resolves after puberty. GSD IV (Anderson amylopectinosis-brancher enzyme deficiency) leads to formation of an abnormal glycogen that appears to be noxious to the liver. Severe liver disease develops in the Ist few months afterbirth, leading to cirrhosis. Unlike the other primarily liver disorders, it often causes severe liver failure. Liver failure with portal hypertension suggests GSD IV.

Work up should be done in patients with hypoglycemia and hepatomegaly. Concentrations of glucose, uric acid, lactic acid, liver transaminases and lipids (cholesterol and triglycerides) are helpful in differentiating type I and III. Enzyme assay in fresh liver tissue confirms the diagnosis of the liver GSD. DNA testing is increasingly available for these disorders, alleviating the need for liver biopsy.

Muscle glycogenoses GSD V (McArdle disease), VII (Tarui) and II (Pompe) primarily involve muscle. GSD V and VII often present in adolescence with exercise intolerance and myoglobinuria. These patients may have muscular hypotonia, weakness, easy fatigability and muscle cramps. A muscle biopsy may be necessary to confirm the diagnosis. DNA testing now offers an alternative and helps to distinguish between type V and type VII.

Type II (Pompe), disease results from lysosomal storage of glycogen in skeletal muscles, cardiac muscles and central nervous system. There is progressive cardiomyopathy. Electrocardiogram shows left axis deviation, short PR interval and large QRS. Heart failure with dyspnea and cyanosis may occur. Skeletal muscles show hypotonia and marked weakness (Figs 23.10A to D). The tongue is large and protruding. Death usually occurs before the age of 1 yr. The diagnosis is suggested by low levels of the enzyme *acid maltase* in leukocytes, liver, muscles and fibroblasts.

Treatment Therapy of hepatic glycogenoses is targeted to maintain normoglycemia and is achieved by continuous nasogastric infusion of glucose or uncooked starch. Depending on response, frequent daytime feeds and continuous nasogastric feeding at night may be given. Uncooked starch acts as a slow release form of glucose. This is especially useful in type I, III and IV but most demanding in type I. The intake of lactose, fructose and sucrose should be restricted, except fruits, vegetables and small amounts of milk products. Enough nutrients, vitamins and minerals should be given. If despite optimizing dietary treatment, serum triglyceride levels remain above 900 mg/dl, triglyceride-lowering drugs (nicotinic acid, fibrates) should be recommended to reduce risk of cholelithiasis and pancreatitis. Allopurinol (10 mg/kg per day, divided into 3 dosages) should be given for hyperuricemia. Enzyme replacement therapy (ERT) is available and very effective for type II GSD but the cost is prohibitive.

Mitochondrial Fatty Acid Oxidation Defects

Pathogenesis

Fatty acid oxidation plays a major role in energy production during fasting or periods of high-energy demand leading to glycogen depletion. It involves three processes:

a. *Mobilization of fatty acids into mitochondria.* Long chain fatty acids (C14–20) undergo active transport through carnitine shuttle; whereas short (C4 to 6) and medium chain (C12) fatty acids enters independently of carnitine and are activated to coenzyme A (CoA) esters. Disorders of carnitine cycle includes carnitine palmitoyl transferase I and II deficiency.
b. *β oxidation.* This involves removal of 2-carbon fragments (i.e. acetyl-CoA) from the transported saturated fatty acids *via* a four-step enzymatic reaction. Each enzyme has different chain length specificity. Deficiency of various acyl-CoA dehydrogenases (AD) results in short chain AD (SCAD) deficiency, medium chain AD (MCAD) deficiency, long chain AD (LCHAD) and very long chain AD (VLCAD) deficiency.
c. *Electron transfer to the respiratory chain.* Acetyl-CoA is utilized as energy substrate in muscle and liver. Example glutaric acidurias type II (multiple acyl-CoA dehydrogenase or MAD deficiency).

Clinical Features

Features may have varying severity and present at any age. Symptoms are precipitated by fasting, exercise or intercurrent illness leading to episodes of metabolic decompensation.

i. Presence of acute hypoketotic hypoglycemia and encephalopathy, associated with Reye like illness, hepatomegaly and liver dysfunction.

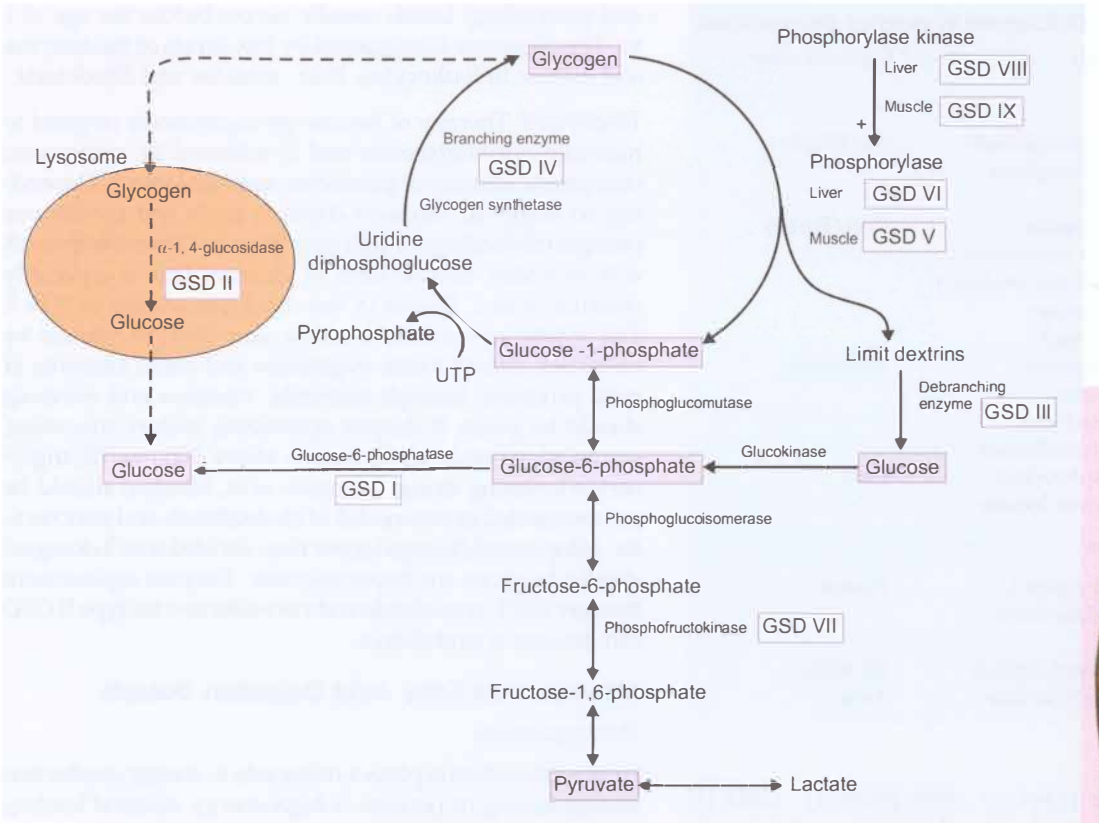


Fig. 23.8: Glycogen storage disorders: Schematic glucose and glycogen metabolism in the liver and lysosome

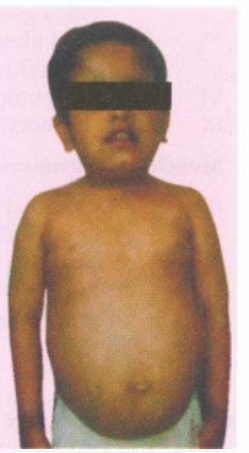
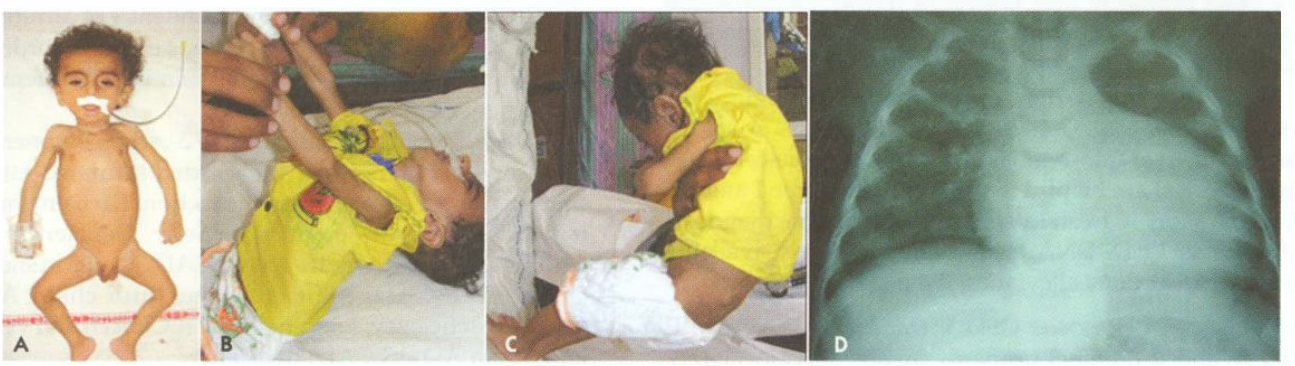


Fig. 23.9: A child with glycogen storage disease type I. Note the doll like facies and protuberant abdomen)



Figs 23.10A to D: A child with Pompe disease showing (A to C) signs of marked hypotonia and (D) cardiomegaly

ii. Cardiomyopathy (hypertrophic more common than dilated) and conduction defects including arrhythmias causing sudden early death.

iii. Myopathy

Diagnosis

This is usually made by performing organic acid analysis on urine and plasma acylcarnitine prole, which is later confirmed by enzyme assay, or mutation analysis.

Treatment

Acute decompensation is managed as mentioned in the above section. Prolonged fasting should be avoided. Medium chain triglyceride (MCT) rich formula can be given in VLCAD, LCHAD and CPT I and II deficiency, but not in MCAD and MAD deficiency.

Mitochondrial Disorders

Mitochondria are mainly involved in the energy production pathway of oxidative phosphorylation (OXPHOS).

Mitochondrial disorders refer to defects in the OXPHOS pathway. Mitochondria are mainly derived from the ovum;hence, mitochondrial DNA (mtDNA) disorders are maternally inherited. Tissues such as brain, liver and kidney have high-energy requirements and are susceptible to injury.

Mitochondrial disorders can occur due to either alterations in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) mutations. The mutant mtDNA produce less energy; symptoms are apparent when energy production is less than energy requirements. Disorders that are due to nDNA mutations are autosomal recessive, autosomal dominant or X-linked. A mitochondrial disorder is often suspected with multisystem involvement such as stroke, hearing loss, muscle weakness, cardiomyopathy and/or endocrine dysfunction. The disorders due to mtDNA deletion/duplication mutations are chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome, Pearson syndrome. Disorders caused by mtDNA point mutations include (Leber hereditary optic neuropathy LHON), (maternally inherited Leigh syndrome MILS), (mitochondrial encephalopathy, lactic acidosis and stroke MELAS), (myoclonic epilepsy with ragged red fibres MERRF), (neurogenic weakness, ataxia and retinitis pigmentosa NARP), hypertrophic cardiomyopathy, mitochondrial myopathy and (nonsyndromic aminoglycoside-induced sensory neural hearing loss SNHL).

Diagnosis

A markedly elevated lactate level raises the possibility of a mitochondrial disorder. An elevated lactate-to-pyruvate ratio of greater than 30 suggests an OXPHOS defect. CSF lactate and pyruvate values also are helpful in some patients. The definite method is muscle biopsy where presence of ragged red bers as well as subsarcolemmal accumulation of mitochondria confirms mitochondropathy. Staining for succinate dehydrogenase and cytochrome C oxidase is useful.

Treatment

No specific therapy is available. Supportive treatment includes symptomatic therapy, supplementation with cofactors such as riboflavin, Co-Q, folinic acid, vitamin E, vitamin C, carnitine, high lipid, low carbohydrate diet and avoiding mitochondrial toxins such as sodium valproate and statins.

Lysosomal Storage Disorders

Lysosomes are one of the important cellular organelles responsible for degradation of complex cellular molecules using various acid hydrolases. Deficiency of these enzymes results in the accumulation or storage of an intermediate compound. Deposition of this stored material in several body tissues leads to cellular damage and disease symptoms. Common categories of lysosomal storage disorders are discussed below.

Enzyme deficiencies in the degradation pathway of glycosaminoglycans cause *mucopolysaccharidoses*. In some glycolipid storage disorders, neurological functions are impaired due to abnormal deposition in the brain. The second category of o*ligosaccharidoses* is the result of deficiencies of enzymes responsible for degradation of glycoproteins with a less complex polysaccharide (oligosaccharides) than glycosaminoglycans. The third category, *sphingolipidoses* is caused by deficiency of sphingolipid degrading enzymes. Accumulation of lipid inside the cells gives them a foamy appearance. Foamy cells appear in liver, spleen, lungs and marrow, resulting in enlargement of these organs. All conditions have autosomal recessive inheritance except mucopolysaccharidosis II and Fabry disease which are (X-linked). Common disorders are discussed below and summarized in Table 23.7.

Mucopolysaccharidoses

Mucopolysaccharides constitute a major part of connective tissue and consist of units of disaccharides, nitrogen and esters. In mucopolysaccharidoses, acid mucopoly-

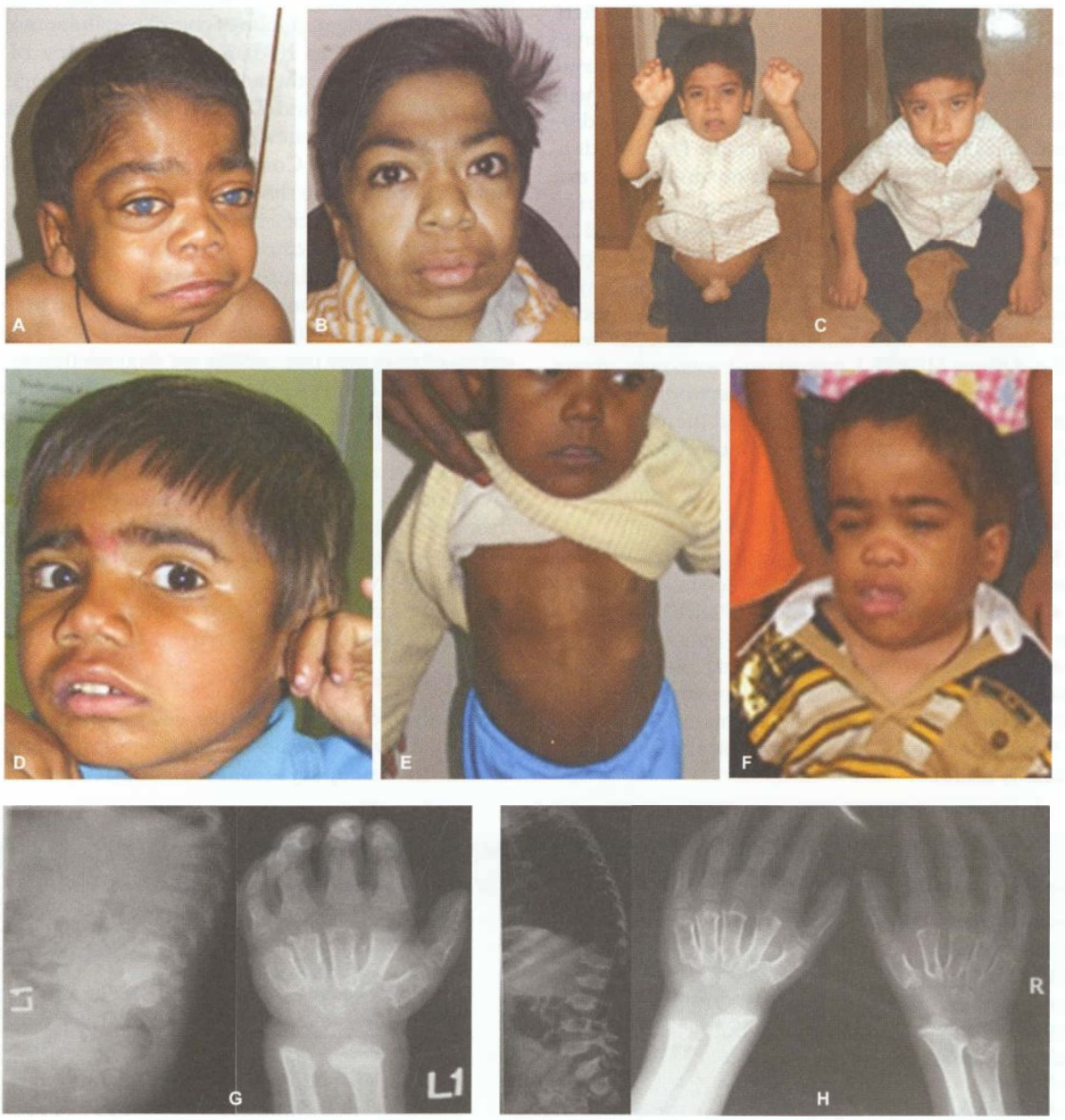
Table 23.7: Clinical features of common lysosomal storage disorders

Disorder	*Cherry-red spot*	*Visceromegaly*	*Skeletal changes*	*Mental retardation*	*Bulbar signs*
Gangliosidosis GM1	+	+	+ (Variable)	+	–
Gaucher disease	–	+	+	+	+ (in types II, III)
Krabbe disease	–	–	–	+	–
Metachromatic leukodystrophy	Rare	–	–	+	–
Multiple sulfatase deficiency	+	+	+	+	–
Niemann-Pick disease	+	+	–	+ (Type A, C)	–
Sandhoff disease	+	+	+ (Variable)	+	+ (in late stages of infantile forms)
Tay-Sachs disease	+	–	–	+	+ (in late stages of infantile forms)

saccharides are deposited in the tissues and excreted in the urine. Due to lack of degradation, mucopolysaccharides accumulate in the lysosomes causing disorganization of the cell structure and function. Partially degraded mucopolysaccharides are excreted in urine. At least 8 genetic variants of mucopolysaccharidoses are recognized (Table 23.8) with phenotypic differences (Figs 23.11A to H).

Mental retardation is severe in type III (Sanfilippo) and VII (Sly), moderate in type I (Hurler, IH), mild in type II (Hunter), rare in type IV (Morquio) and type I (Scheie, IS) and not seen in type VI (Maroteaux Lamy).

Cloudy cornea is observed in types I, IS and VI but it may occur in some cases of type IV, cloudiness of cornea is minimal in type III and is not seen in type II.



Figs 23.11A to H: Mucopolysaccharidoses. (A) Patient with type IH disease showing corneal clouding and coarse facial features; (B) patient with MPS type II without corneal clouding but with facial coarseness; (C) patient with MPS IHS (milder phenotype) demonstrating restriction of joint movements; (D) mild facial coarseness in a child with MPS III; (E) chest deformity in a patient with MPS IV (Morquio disease); (F) patient with MPS VI (Maroteux-Lamy) with abnormal skull and facial coarseness; (G) beaking of the inferior margins of vertebrae and proximal pointing of metacarpals in MPS type I; (H) central beaking of the lumber vertebrae along with proximally pointed metacarpals and short ulnae in MPS IV

Table 23.8: Clinical features of mucopolysaccharidoses

MPS type	*Mental retardation*	*Coarse facies*	*Visceromegaly*	*Joint contractures*	*Dysostosis multiplex*	*Corneal clouding*
Hurler/IH	+	+	+	+	+	+
Scheie/IS	–	+ (Mild)	–	+	±	+
Hunter/II	+	+	+	+	+	–
Sanfilippo/III	+	+ (Mild)	±	–	±	–
Morquio/IV	–	+ (Mild)	–	– (Laxity)	+	+
Maroteaux-Lamy/VI	–	+	+	+	+	+
Sly/VII	+	+	+	+	+	±

Skeletal changes are most marked in type IV, marked in type I, II, VI and VII but are mild in types III and IS. Skeletal changes observed include thickening of the skull, marked deformity of sella turcica, broad spatula like ribs, beak shaped vertebrae (around L1 vertebra) and proximal tapering of metacarpals; these abnormalities are referred to as dysostosis multiplex. In Morquio disease (type IV) the trunk is short with flattened narrow vertebrae, barrel shaped chest with sternum protruding forwards. Other features include short neck, broad mouth, widely spaced teeth, prominent maxilla and joint laxity.

Facies are coarse in type IH. Lips are thick, tongue is enlarged and teeth are peg-like and separated; nasal bridge is depressed. The features are coarse and often mistaken for cretinism.

Hepatosplenomegaly is present in types I, II, VI and VII and multiple sulfatase deficiency.

Diagnosis Urinary excretion of glycosaminoglycans (GAG) by 2D electrophoresis is a useful screening test. Specific enzyme assays and DNA analyses confirm the diagnosis.

i. Accumulation of dermatan sulfate and heparan sulfate in tissues and their urinary excretion occurs in Hurler syndrome (type IH), Scheie syndrome (type IS), Hunter syndrome (type II) and type VII.
ii. Heparan sulfate accumulates in tissues and is excreted in urine in Sanfilippo disease (all varieties of MPS III).
iii. Keratan sulfate and chondroitin sulfate are excreted in Morquio syndrome (type IV).
iv. Dermatan sulfate is excreted in the urine in Maroteaux-Lamy syndrome (type VI).
v. Keratan sulfate like material accumulates in tissue and is excreted in urine in type VIII.

Treatment Palliative care and multidisciplinary management are important. Enzyme replacement therapy is available for type I, II and type VI but the cost is prohibitive. Trials are underway for other types of MPS. Bone marrow transplantation has been found to be effective in MPS I.

Oligosaccharidoses

This group is characterized by developmental delay with or without regression, facial coarsening, enlarged liver and spleen, and ocular (cherry-red spot, corneal clouding) changes. Oligosaccharidoses include-pyknodysostosis, β, β mannosidosis, fucosidosis, aspartyl glucosaminuria, Schindler disease and sialidosis I and II. Urine screening for oligosaccharides provides clue for diagnosis. Radiological evidence of dysostosis multiplex may be present. Enzyme assay and DNA analysis is confirmatory.

Sphingolipidoses

These are clinically heterogeneous disorders and include GM1 and GM2 gangliosidoses, Gaucher disease, Niemann-Pick diseases, Fabry disease, Farber disease, and Krabbe and metachromatic leukodystrophies. The most consistent feature is enlarged liver and spleen, with or without neurological involvement (Gaucher disease I and III, Niemann-Pick disease A and B, and GM1 gangliosidosis). Metachromatic leukodystrophy and Krabbe disease are characterized by white matter involvement and demyelination.

Gaucher disease Gaucher disease is the commonest lysosomal storage disease. Inherited in an autosomal recessive manner, there is deficiency of the tissue enzyme *glucocerebrosidase* that splits glucose from glucosylceramide, resulting in accumulation of the latter in cells of the reticuloendothelial system. The cerebroside-laden cells are large and have eccentric nuclei with vacuolated cytoplasm and 'wrinkled tissue paper' appearance (Gaucher cells).

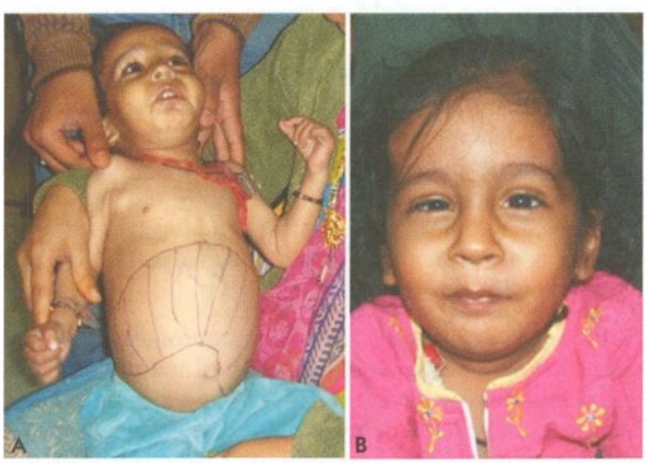
The spleen is markedly enlarged and there are signs of hypersplenism, e.g. leukopenia and thrombocytopenia. The liver is enlarged and the marrow cavity is widened, due to deposits of Gaucher cells. Expansion of the bone is prominent, especially at the lower end of the femur and humerus. It manifests as a spectrum and has two variants: non-neuronopathic (type I) and neuronopathic (type II: acute; type III: chronic form).

Non-neuronopathic (type I) is the commonest form and characterized by absence of neurological symptoms. Signs and symptoms can develop at any age and include anemia, fatigue, poor growth, delayed puberty, easy bleeding and bruising, weak bones, bone and joint pain, fractures and enlarged liver and spleen (Fig. 23.12A). The earlier the onset of first symptoms, the more severe is the disease and rapid progression if left untreated.

Neuronopathic forms show involvement of the central nervous system. Two types are distinguished by the rate of neurological progression. Type II (acute neuronopathic) presents early in fetal life as hydrops (excess accumulation of fluid in subcutaneous tissue and other cavities) or in early infancy. Infants are normal during first few months of life before showing neurological signs and involvement of spleen and liver. They can also have skin involvement. Course is rapidly progressive leading to early death by 2–4 yr. Type III Gaucher disease (chronic neuronopathic, Fig. 23.12B) represents a chronic form with a more indolent course and manifestations in early childhood before the age of 2 yr. Signs and symptoms are the same as in type 1 except that neurological involvement is slowly progressive and leads to death by 2nd or 3rd decade. Neurological symptoms include developmental delay, stridor, squint and swallowing difficulty, opisthotonus, head retroflexion, spasticity and trismus, abnormal eye movements, oculomotor apraxia (trouble in moving eyes to look side-to-side, need to turn head to see things on the side), saccadic initiation failure (failure in starting fast eye movements) and optokinetic nystagmus, dementia and ataxia, generalized tonic-clonic seizures and progressive myoclonic epilepsy.

Diagnosis is made by measuring glucocerebrosidase levels in leukocytes or skin fibroblasts. Serum chitotriosidase levels are elevated. Volume assessment of liver and spleen by MRI or ultrasound is advised. Neuro-ophthalmological investigations, hearing assessment by brain evoked response audiometry, EEG and neuropsychometry tests are required. DNA analysis is helpful in assessment of phenotype and prenatal diagnosis.

Treatment. This was the first storage disorder for which treatment was available. Options include: enzyme replacement therapy (ERT) and substrate reduction therapy.



Figs 23.12A and B: (A) Gaucher Type 1: Note protuberant abdomen due to hepatosplenomegaly; (B) Gaucher Type III. Note trismus and ophthalmoplegia

ERT means providing deficient enzyme through IV route to allow breakdown of fat in cerebroside laden cells, so that they function normally and size of spleen and liver is restored, with improved quality of life. While ERT does not have much effect on neurons, it is efficacious first line of therapy for the hematological, visceral and skeletal manifestations. The dose of ERT is 60 IU/kg/every 2 weeks, but dose is individualized depending upon the clinical status. Substrate reduction therapy (SRT) means reducing the production of fatty material, thereby avoiding cellular accumulation. Miglustat is oral treatment for adult patients with type I Gaucher disease with mild to moderate manifestations for which enzyme therapy is not an option. Both forms of treatment are expensive. Splenectomy increases the risk of progressive skeletal and pulmonary disease. Stem cell transplantation is another option.

Metachromatic leukodystrophy Sulfated glycosphingolipids accumulate in white matter of the central nervous system, peripheral nerves, liver and kidney. The myelin degenerates but neuronal cells are affected to lesser degree. Granular masses accumulate in the white matter of the brain. Acidified cresyl violet stains them purple with a brown background, resulting in metachromatic staining.

Clinical features. This disorder has infantile and juvenile forms. Early manifestations including disturbances of gait, incoordination and progressive mental deterioration appear in the second year of life. Knee jerk is brisk but ankle reflex and plantar response may be absent because of involvement of peripheral nerves. Death occurs before the age of 10 yr. Diagnosis is confirmed by level of the enzyme, arylsulphatase A in white cells.

Treatment. There is no effective treatment; bone marrow transplantation has been used.

GM_1 gangliosidosis In type I, the onset is at birth. There is severe cerebral degeneration. Facial features resemble mucopolysaccharidosis type IH. Hepatosplenomegaly and cherry red spot on the macular region are present. X-ray of the bones show mild dysostosis. These children die of respiratory infections before the age of 2 yr. In type II, the onset of illness is between 1 and 2 yr and death occurs before the age of 10 yr. Liver and spleen are not enlarged. Radiological abnormalities are minimal but psychiatric and motor disturbances are severe.

GM_2 gangliosidosis Inborn errors of GM_2 ganglioside metabolism result in accumulation of the metabolite within lysosomes of nerve cells. Most infants with *Tay-Sachs* form (type I) of the disease have severe deficiency of β-N-acetylhexosaminidase A (hexosaminidase A). Hexosaminidase A and B are deficient in *Sandhoff disease* (type II).

Tay-Sachs disease is an autosomal recessively inherited defect, common in Ashkenazi Jews, but reported from all

over the world including India. A history of consanguinity is obtained. Deficiency of hexosaminidase leads to accumulation of ganglioside GM_2 within ganglion cells of the nervous system; myelin is degenerated. The disorder manifests by 6 months. Apathy, hypotonia, visual defects and developmental retardation occur early. The child progressively becomes spastic, blind and demented. Fundus shows cherry-red spot over the macular region. Death occurs within 3–4 yr. In Sandhoff disease, visceral involvement is present in addition to features of Tay-Sachs disease.

Niemann-Pick disease This is an autosomal recessive disorder of sphingomyelin and cholesterol in the lysosomes. In the classical form (type A), clinical features begin in early life with feeding difficulties, failure to thrive and developmental delay and later neuroregression. There is protuberant abdomen with hepatosplenomegaly. Cherry-red spot on fundus examination is seen in about half the cases. Diagnosis is confirmed by measurement of sphingomyelinase levels. Type B disease is a milder form with hepatosplenomegaly but no neurological involvement. Late onset variants (type C) are associated with extrapyramidal manifestations. There is no specific treatment. Table 23.7 summarizes the clinical features of common sphingolipidosis.

Neuronal ceroid lipofuscinosis (NCL) These are one of the most frequent and progressive neurodegenerative disorders of childhood. It is characterized by progressive psychomotor retardation, seizures, visual loss and early death. Depending upon the age of onset and severity, it can be divided into infantile, late infantile, juvenile and adult NCL. Confirmation is done by enzyme assay and mutation analysis. No specific therapy is available at present. Antiepileptic such as lamotrigine and levetiracetam are preferred.

Peroxisomal Disorders

Peroxisomes are involved in the oxidation (β-oxidation of phytanic acid and β oxidation of very long-chain fatty acids, VLCFAs) as well as synthesis of plasmalogens. Based upon their functioning, peroxisomal disorders can be divided into two major groups.

Disorders of peroxisomal biogenesis or importation are caused by defects in the transfer of proteins produced in the cytosol into the peroxisomes. This includes Zellweger syndrome, neonatal adrenoleukodystrophy and infantile Refsum disease and rhizomelic chondrodysplasia punctata. These disorders have autosomal recessive inheritance and are caused by defects in genes coding for peroxins (PEX). Defects in these genes interfere with peroxisomal biogenesis and import of proteins into peroxisome. Approximately 65% of the patients harbor mutations in *PEX1* gene.

Zellweger syndrome (Fig. 23.13), also known as cerebrohepatorenal syndrome is characterized by dysmorphic facies (high forehead, large anterior fontanelle, at occiput, hypoplastic supraorbital ridges, broad nasal bridge, epicanthal folds, anteverted nostrils, micrognathia), central nervous system defects (neuronal migration defect, dysmyelination, seizures), hepatic dysfunction and cirrhosis, adrenal insufficiency and renal microcysts. Prognosis is poor and patients usually die in infancy. Diagnosis is suggested by high plasma levels of very long chain fatty acids (VLCFA) and phytanic acid, and low erythrocyte plasmalogen levels.

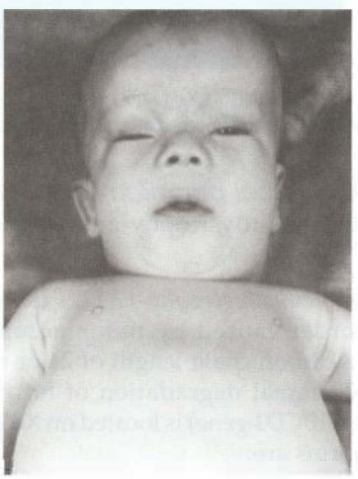
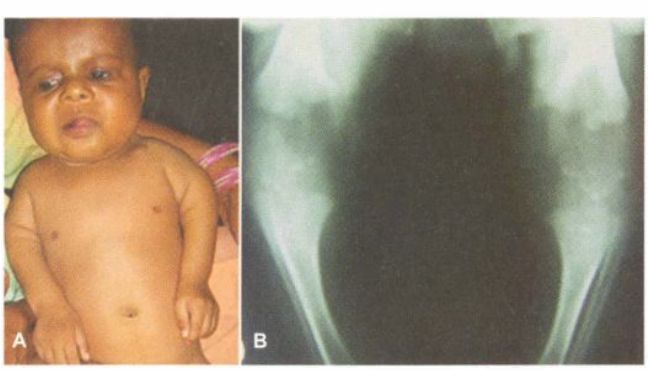


Fig. 23.13: An infant with Zellweger syndrome. Note flat facial profile

Rhizomelic chondrodysplasia punctata is characterized by altered phytanic acid α-oxidation and plasmalogen synthesis. Type 1 is a peroxisomal biogenesis defect, while types 2 and 3 are disorders of individual peroxisomal enzymes. Patients show rhizomelia and joint contractures along with extensive epiphyseal stippling of long bones (Figs 23.14A and B). They have congenital cataract, developmental delay and growth failure. In contrast to Zellweger syndrome, patients with this disorder have normal VLCFA concentrations and low red blood cell plasmalogens. Phytanic acid concentrations are either elevated (in type 1) or normal (type 2 or 3).



Figs 23.14A and B: (A) Child with rhizomelic chondrodysplasia punctata; (B) epiphyseal stippling

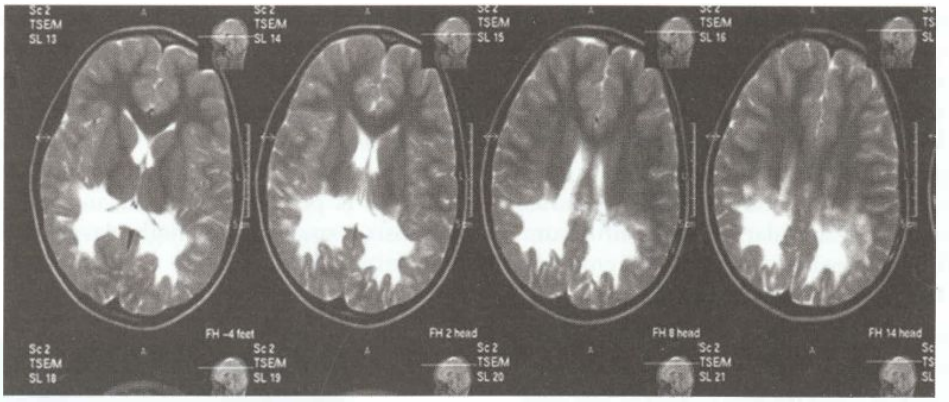


Fig. 23.15: Brain MRI findings in X-linked adrenoleukodystrophy. T2 weighted axial images show symmetrical hyperintense signal changes in the bilateral parieto-occipital white matter and splenium of corpus callosum (*Courtesy*: Dr. Atin Kumar, Deptt. of Radiodiagnosis, AIIMS, New Delhi)

Disorders of individual peroxisomal enzymes include X-linked adrenoleukodystrophy and classical Refsum disease.

X-linked adrenoleukodystrophy (ALD) is an X-linked recessive disorder caused by tissue accumulation of VLCFA with a carbon chain length of 24 or more due to deficient peroxisomal degradation of fatty acids. The defective gene (*ABCD1* gene) is located on Xq28. The three neurological forms are:

The *childhood cerebral form* usually manifests between 4 and 8 yr of age with subtle initial manifestations of worsening school performance and behavioral problems such as hyperactivity and emotional lability. Auditory and visual disturbances may be associated. Seizures are often the initial manifestation. In most patients, adrenal dysfunction is noticed after the cerebral symptoms. Soon rapid neurological progression ensues causing increasing spasticity, visual and hearing impairment. Progression is due to an inflammatory response, which is most intense in the parieto-occipital areas. MRI brain typically shows demyelination in these areas (Fig. 23.15). In *adolescents*, the usual age of manifestation is between 10 and 21 yr and progression is much slower than the above form. *Adrenomyeloneuropathy* is a milder form with onset in late adolescence or adulthood and is characterized by progressive paraparesis due to long tract degeneration in the spinal cord.

Elevated plasma levels of VLCFA can identify patients and 85% of female carriers of X-adrenoleukodystrophy. Mutation analysis is the most reliable method to identify carriers. Corticosteroid replacement should be given for adrenal insufficiency. Bone marrow transplantation can be considered in neurologically asymptomatic or mildly involved patients. Lorenzo oil is recommended in neurologically asymptomatic and boys who are less than 8-yr-old with normal MRI.

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Eye Disorders 24

Radhika Tandon

Children may present to pediatricians with various primary eye problems. Several systemic diseases have ocular manifestations, some of which are very useful in making the correct diagnosis and instituting appropriate management. Finally, therapies for some diseases are known to have ocular side effects which need to be recognized.

PEDIATRIC EYE SCREENING

The concept of screening children for eye diseases is based on the awareness that infants and young children cannot communicate their symptoms and visual difficulties. In addition, several potentially blinding diseases manifest in this age group; their early detection and treatment can limit ocular morbidity and prevent irreversible blindness.

The goal of pediatric eye screening is to detect eye and visual disorders in children or identify their risk factors so that the child can be referred for detailed ophthalmic evaluation, confirmation of diagnosis and appropriate medical management.

Comprehensive Pediatric Eye Evaluation

Presence of any of the following risk factors is an indication for referral for comprehensive ophthalmic evaluation.

I. *General health condition, systemic disease or use of medications associated with eye disease*
- Extreme prematurity (gestational age ≤30 weeks); suspected retinopathy of prematurity
- Intrauterine growth retardation
- Perinatal complications
- Neurological disorders
- Juvenile rheumatoid arthritis
- Thyroid disease
- Craniofacial abnormalities
- Diabetes mellitus
- Syndromes with known ocular manifestations
- Chronic steroid therapy; use of hydroxychloroquine or other medications known to affect eyes
- Suspected child abuse

II. *Family history of any of the following*
- Retinoblastoma
- Childhood cataract
- Childhood glaucoma
- Refractive errors in early childhood
- Retinal dystrophy or degeneration
- Strabismus and/or amblyopia
- Sickle cell disease
- Syndromes with ocular manifestations
- Nontraumatic childhood blindness

III. *Signs or symptoms reported by the family, health care provider or school teacher*
- Defective ocular fixation or visual interactions
- Abnormal appearance of the eye(s)
- Squinting or tendency to close one eye in certain situations
- Any obvious ocular alignment, movement abnormality, head tilt or nystagmus
- Large and/or cloudy eye(s)
- Drooping of the eyelid(s)
- Lumps or swelling around the eye(s)
- Persistent or recurrent tearing, sticky discharge, redness, itching or photophobia
- Learning disabilities or dyslexia

Guidelines for Examination

Children are best examined in a comfortable and friendly environment. Very young children can remain in the lap of their mother while older children can be distracted with toys and colorful objects. When the child first enters the room, simple observation of behavior, fixation, movement and general awareness of the surroundings are good indicators of the child's visual status, and gross abnormalities can be detected.

Steady fixation and uniform steady alignment of the eyes develop in the first 4–6 weeks. Visual acuity assessment in children less than 6 months of age is limited to seeing if the child attempts to fix and follow light. A child 6–12 months

of age can follow and even reach out towards colorful objects, and this permits a very crude assessment of gross visual ability. A more objective assessment can be made with electrophysiological tests using a pattern-induced visual evoked response (pattern VER) using chequered patterns of varying degrees of resolution or by observing the optokinetic response or nystagmus induced by the child's attempt to view a striped pattern on a moving drum (OKN). Both these tests are an assessment of the resolution acuity or power of the eye to distinguish patterns of varying degrees of separation or width. These tests are expensive and not readily available in routine clinics. For most preverbal children up to the age of 3 yr, a simple observation of fixation pattern and behavior, ability to see, follow or pick-up small objects like toys or candy beads, preferential looking tests using Teller acuity cards or preferential looking cards are used to estimate the visual status. Unilateral loss is also tested for by observing if the child resists closure or occlusion of one eye over the other.

Vision of children 3–5 yr of age can be assessed using picture tests and symbols with matching cards such as the Kays symbols, tumbling E or HOTV card tests where one relies on the child's ability to recognize the shape and match the shape with a similar one on a card. Children 5 yr or older can be tested with more conventional vision testing methods using a Snellen visual acuity chart with either alphabets or tumbling E or Landoldts C symbols.

Ocular movements and external examination of the eye can be performed by using adequate illumination with a torch and aided by toys or colorful pictures to capture the child's attention and interest to cooperate with the examiner. Pupillary reactions must be tested and fundus examination should be attempted with a direct ophthalmoscope through the undilated pupil to view the disc and macula. In case required, more detailed examination of the fundus and retinal periphery can be carried out after dilating the pupils with mydriatic eye drops such as 2.5% phenylephrine or short-acting cycloplegic-mydriatic drops such as 0.5% tropicamide or 1% cyclopentolate eye drops. The retina is best viewed with an indirect ophthalmoscope as this gives the maximum field of view and the examination can be completed efficiently. In general, as far as possible, most of the examination should be completed without touching or going too close to the child so that the child is comfortable and does not feel intimidated. Digital assessment of the intraocular pressure, eversion of the lids and slit lamp examination are occasionally required. In certain situations, an examination under anesthesia is required and should be done only after obtaining the parents' informed consent.

CONGENITAL AND DEVELOPMENTAL ABNORMALITIES

This group of diseases may or may not manifest at birth. If the disease is detected at birth, it is 'congenital' such as lid coloboma, severe corneal opacity or total cataract with a white opaque lens. Sometimes the disease is present at birth, but is detected later on, for example, a partial cataract or mild congenital glaucoma. Sometimes the disease is a defect of development but manifests later, such as developmental cataract or juvenile glaucoma.

Disorders in Development of the Whole Eyeball (Globe Abnormalities)

A child may be born with a small eye (microphthalmos or nanophthalmos), absent eyeball (anophthalmos) with or without an orbital cyst, or more complex abnormalities associated with craniofacial dysgenesis.

Abnormalities of Development of the Orbit, Eyelids and Adnexa (Lacrimal Drainage System and Glands)

Children are sometimes born with the eyes completely covered by the eyelids so that the globe is not apparent or visible (cryptophthalmos). A blocked nasolacrimal duct may manifest at birth as a dacryocystocele, or later as dacryocystitis. Lacrimal diverticulae or fistula are other abnormalities which may or may not be apparent at birth. Telangiectasias and vascular abnormalities such as capillary or cavernous hemangioma, lymph hemangioma, arteriovenous malformations and orbital varices may be present as isolated abnormalities or as part of syndromes such as the phakomatoses.

Other abnormalities of the lids include abnormal shape and position such as blepharophimosis, ptosis, prominent epicanthic folds, lid coloboma, congenital ichthyosis, entropion and ectropion. Early oculoplastic reconstruction needs to be undertaken if the visual axis is covered or the cornea is at risk of exposure keratopathy due to lagophthalmos or inadequate lid closure.

Diseases Affecting the Conjunctiva and Anterior Segment

Some of the important conditions that may be seen include conjunctival telangiectasia, hazy or opaque cornea (causes of which can be memorized using the mnemonic STUMPED, i.e. **s**clerocornea, birth **t**rauma, **u**lcer, **m**ucopolysaccharidosis, **P**eter anomaly, **e**ndothelial dystrophy or **e**ndothelial dysfunction secondary to congenital glaucoma, and **d**ermoid); flat cornea (cornea plana), anterior segment dysgenesis, aniridia, iris coloboma, primary congenital or juvenile developmental glaucoma, lens opacity or cataract, lens coloboma, displaced or subluxated lens or ectopia lentis, abnormal shape of lens such as microspherophakia, lens coloboma, lenticonus and persistent hyperplastic primary vitreous (Fig. 24.1).

Retinopathy of Prematurity

This condition is seen in preterm babies due to early exposure to oxygen and other environmental factors by a premature, underdeveloped retinal vascular system. The chief risk factors are prematurity, especially birth before 32 weeks of gestation, birth weight less than 1500 g and presence of other contributory risk factors such as

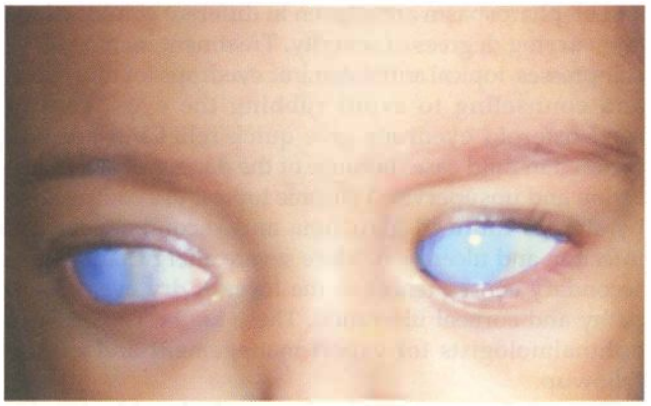


Fig. 24.1: Child with bilateral congenital corneal opacity. Differential diagnoses include all causes of congenital corneal opacity, congenital glaucoma with buphthalmos and corneal edema due to raised intraocular pressure

supplemental oxygen therapy, hypoxemia, hypercarbia and concurrent illnesses like septicemia. The clinical features are graded in stages of severity depending on the retinal signs and the zone of retina involved. Children at risk should be screened periodically to look for evidence of developing what is considered as 'threshold' disease, i.e. requiring ablative laser treatment of the avascular zone of the retina to check further progression and prevent blinding stages of the disease which would then require surgical intervention to treat the ensuing retinal detachment and other complications.

ACQUIRED EYE DISEASES

Nutritional Disorders

The most important condition in this category is vitamin A deficiency which can be catastrophic in young children if severe enough to produce keratomalacia. Up to the age of six months, children have adequate hepatic reserves of vitamin A. However, if the mother's nutrition is poor or the infant is not properly fed afterbirth, severe vitamin A deficiency may be precipitated by an attack of acute respiratory infection such as measles, pneumonia or acute gastroenteritis, which could lead to bilateral blindness due to severe keratomalacia. Milder forms of vitamin A deficiency may manifest with xerosis of the conjunctiva, Bitot spot and nyctalopia or night blindness. Adequate nutritional advice to the pregnant and lactating mother and proper weaning with vitamin A rich fruits and vegetables is advised. Keratomalacia is treated with oral vitamin A 200,000 IU stat followed by a second dose after 24 hr and a third dose after 2 weeks. In case the child is vomiting and cannot retain oral supplement, an intramuscular injection of vitamin A may be given instead. For children less than 1 yr of age and those weighing less than 10 kg, half the dose is given to avoid vitamin A toxicity and vitamin A induced intracranial hypertension.

Infections

Preseptal cellulitis and orbital cellulitis manifest as swelling and inflammation of the eyelids, are differentiated clinically, and often occur due to spread of infection from the lids, adnexa or paranasal sinuses or following trauma. These are potentially dangerous infections as they involve the anatomical 'dangerous area of the face' and if not treated promptly and adequately, can spread intracranially, resulting in meningitis or cavernous sinus thrombosis. Ultrasonography is required to detect an orbital abscess, which has to be drained. CT scan or MRI is required if involvement of adjacent paranasal sinuses or intracranial involvement is suspected. Treatment requires systemic antibiotics and anti-inflammatory agents, supplementation with topical antibiotics, and supportive measures, including lubricating eyedrops to prevent corneal damage.

Other infections involving the eyelids include blepharitis, hordeolum externum (stye), hordeolum internum (infected chalazion), molluscum contagiosum and phthiriasis of the eyelashes. Lid hygiene, hot fomentation and local antibiotic ointments are useful along with instructions for personal hygiene. Phthiriasis will require mechanical removal of nits adhering to the eyelashes, local application of 20% fluorescein sodium to the lid margins and systemic ivermectin therapy for recalcitrant cases, along with advice on hygiene and treatment of other affected family members.

Common infections of the ocular surface include conjunctivitis which could be bacterial, viral or chlamydial. Conjunctivitis occurring within the first month after birth is called *ophthalmia neonatorum*. Every effort should be made to identify the etiologic agent, especially in cases of *ophthalmia neonatorum*, since gonococcal conjunctivitis can cause loss of vision in the newborn. Conjunctival smears and swabs can be sent for microbiological evaluation. Mucopurulent conjunctivitis is treated with topical antibiotic eyedrops and supportive measures such as cleansing the eye with clean water, lubricating eyedrops and cold compresses.

More severe infections include keratitis and corneal ulcers (Fig. 24.2). Trauma is the most common underlying predisposing factor, but poor hygiene and lowering of local immunity secondary to chronic inflammation, viral infections or use of topical steroids are other risk factors for bacterial and fungal infections of the cornea. Trauma with vegetative matter, such as a thorn, tree branch or wooden broomstick (often used for making 'bows and arrows' for playing), predisposes to fungal infections. Corneal ulcers require an examination under anesthesia for detailed evaluation and corneal scraping for microbiological analysis. Empirical therapy for bacterial corneal ulcers is started with a combination of freshly prepared fortified topical antibiotics such as 5% cephazolin and 1.3% tobramycin eye drops hourly and half hourly alternately round the clock for the first 48 hr. After 48 hr, the culture report and clinical response are reviewed. If there is no

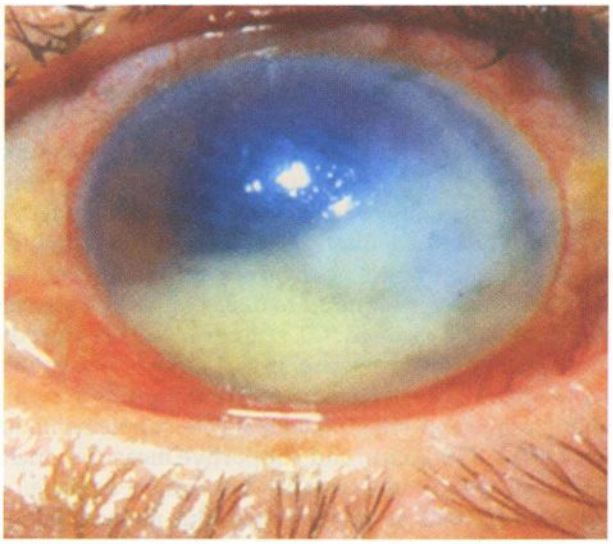


Fig. 24.2: A partially treated hypopyon corneal ulcer. The overlying epithelial defect has healed, but there is a deep corneal abscess, corneal edema and purulent fluid, i.e. hypopyon in the anterior chamber

substantial clinical improvement, the antibiotic is changed based on microbiology results. If clinically responding to therapy, the frequency of antibiotics can be reduced to use during waking hours only, followed two days later by two hourly application, then reduced to 4 hourly or 6 hourly, and discontinued a week after the ulcer has healed. Supportive measures include topical cycloplegics, hot fomentation, analgesics, antiglaucoma medication if secondary glaucoma is present, and antibiotic ointment at night. Fungal keratitis is treated with topical natamycin (5%) 1 hourly with supportive measures. Herpes simplex viral keratitis is treated with topical acyclovir 3% eye ointment for epithelial involvement and systemic acyclovir for herpetic keratouveitis or recurrent disease.

Other infections include endophthalmitis (traumatic, metastatic, or iatrogenic following intraocular surgery) and parasitic infestations, such as toxoplasmosis, toxocariasis, and cysticercosis of the eye, extraocular muscles or orbit.

Allergic and Inflammatory Diseases

Children may develop allergic diseases of the skin around the eye and the ocular surface and conjunctiva. Dermatitis may be an allergic reaction to local ophthalmic medication or sometimes secondary to insect bite, application of traditional eye medicines or herbal remedies and use of local creams or lotions. In addition, a variety of environmental and hereditary factors may interplay to produce a variety of allergic conjunctival manifestations such as seasonal allergic conjunctivitis, hay fever conjunctivitis, perennial or chronic allergic conjunctivitis, atopic allergic conjunctivitis and vernal keratoconjunctivitis. Itching, redness, discomfort, gritty or foreign body sensation, watering, mucoid or thick ropy discharge, photophobia and blepharospasm are all seen in different combinations and varying degrees of severity. Treatment includes cold compresses, topical antihistaminic eyedrops for mild cases and counseling to avoid rubbing the eyes. Topical corticosteroid eyedrops give quick relief but are best avoided in mild cases because of the danger of self-medication and unsupervised chronic topical use complicated by steroid induced glaucoma and secondary corneal infection and ulceration. More severe allergies may have secondary consequences in the form of dry eye, keratopathy and corneal ulceration. These are best referred to ophthalmologists for expert management and careful followup.

Other inflammatory diseases include phlyctenular conjunctivitis or keratoconjunctivitis (believed to be an 'allergic' immunological reaction to tubercular antigen); interstitial keratitis secondary to infections like rubella, syphilis, leprosy and tuberculosis; and uveitis, either idiopathic or associated with juvenile chronic arthritis, psoriasis, tuberculosis, sarcoidosis and toxoplasmosis. Acute anterior uveitis (iritis, cyclitis and iridocyclitis) usually presents with a red inflamed eye with photophobia and diminution of vision. Chronic uveitis may be less symptomatic with decreased vision due to complicated cataract. Intermediate and posterior uveitis (pars planitis, vitritis, retinitis, choroiditis and retinochoroiditis) are usually painless with symptoms of decreased vision (due to hazy media and retinal or optic nerve swelling and inflammation) and floaters (due to inflammatory cells in the vitreous). Treatment is with topical cycloplegic agents and steroids, supplemented with systemic steroids and specific therapy for any underlying disease, such as tuberculosis. Patients with uveitis need detailed examination with a slit lamp biomicroscope to identify the inflammatory response, ophthalmoscopy to view the fundus and specialist ophthalmic care and followup to control the inflammation and minimize the morbidity related to the disease and its treatment.

Intraocular (retinoblastoma or juvenile xanthogranuloma) or systemic malignant disorders may sometimes mimic uveitis syndrome due to malignant cells in the eye and vascular uveal tracts.

Optic neuritis is another important inflammatory disease which could be idiopathic, secondary to infections or associated with demyelinating disorders. Classical features include a rapid drop in vision, usually in one eye, which is accompanied by a relative afferent pupillary defect and normal fundus (retrobulbar neuritis) or inflammatory swelling of the optic disc (papillitis) and retinal edema and/or exudates (neuroretinitis). Patients need to be treated in consultation with a neuroophthalmologist after investigations to identify the cause.

Metabolic and Endocrine Disorders

Homocystinuria is associated with subluxation of the lens, and secondary glaucoma can be seen as a complication.

The lens is usually subluxated downwards which causes poor vision due to displacement and astigmatism. Surgical lens removal has to be done under general anesthesia taking suitable precautions, as the patients are prone to thromboembolism. Optical rehabilitation is usually done with spectacles or contact lenses, though in some cases intraocular lenses can be fitted using scleral or bag fixation augmented with bag fixation devices.

Various storage disorders such as cerebral storage disease, lipidosis and gangliosidosis may be associated with a 'cherry red spot' due to abnormal deposition in the retina, corneal clouding as in some of the mucopolysaccharidoses, and Kayser-Fleischer ring in peripheral cornea in Wilson disease. Juvenile diabetes mellitus may be associated with cataract and diabetic retinopathy and thyroid dysfunction with dysthyroid eye disease. Tyrosinase deficiency might be associated with ocular albinism with foveal hypoplasia and poor vision.

Musculoskeletal and Neurodegenerative Diseases and Phakomatoses

Marfan and Ehlers Danlos syndromes may be associated with subluxated lens and consequent secondary glaucoma. Marfan syndrome is usually associated with upward and outward displacement of the lenses and myopia with blurred vision. Retinal detachment is not connected also common. Surgical lens removal becomes necessary if the vision is not corrected with spectacles or contact lenses. Leukodystrophies and demyelinating diseases may be associated with extraocular muscle weakness, ptosis and optic neuropathy. Phakomatoses like neurofibromatosis, Sturge-Weber syndrome and nevus of Ota may be associated with café au lait spots, plexiform neurofibromas of the lids and orbit and Lisch nodules on the iris and glaucoma.

Muscular dystrophies or degenerations such as chronic progressive external ophthalmoplegia result in ptosis and restriction of eye movements. Duchenne muscular dystrophy may be associated with cataracts.

Tumors and Neoplastic Diseases

Benign tumors include dermoids of orbit, lids or on cornea, hamartomas, osteoma, vascular malformations or hemangiomas of various types and neurofibromas. Malignant intraocular tumors are confined to retinoblastoma (Fig. 24.3), juvenile xanthogranuloma, medulloepithelioma and metastatic lesions from neuroblastomas, Ewing sarcoma, leukemias and lymphomas. Orbital tumors include rhabdomyosarcoma, Langerhans cell histiocytosis, extraocular spread of retinoblastoma, metastatic spread of Ewing sarcoma, neuroblastoma, leukemia and lymphoma.

Refractive Errors

An abnormality in the refractive and focusing apparatus makes it difficult for parallel rays of light from the distance

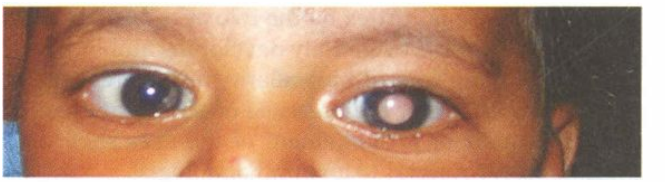


Fig. 24.3: 'Leukocoria' or white pupil in an infant secondary to retinoblastoma. Note the white appearance that appears to be from a structure located more posteriorly, has a slight yellowish pinkish tinge due to vascularization and has an appearance that is unlike that seen with to a cataract. Ultrasonography of the orbits helps confirm the diagnosis

to be accurately focused on the retina. This deviation from the normal emmetropic state is termed as 'ametropia' or refractive error. This manifests as poor or blurred vision which may be noticed by parents, relatives, friends, school teachers or reported by the child as a difficulty in viewing clearly. Sometimes, indirect evidence is reported as eye rubbing, 'squinting', 'going too close to the television' or holding objects too close to the eyes. An assessment of visual acuity is followed by cycloplegic refraction; fundus evaluation is required in addition to routine ophthalmic evaluation. Refractive errors include myopia, hypermetropia and astigmatism, and spectacles must be prescribed accordingly. Associated amblyopia or strabismus must be taken care of and any additional features like nystagmus or extraocular muscle imbalance ruled out. Patients need to be carefully counseled with respect to improvement of vision with spectacles and need for compliance with followup. Failure to show an improvement of vision warrants investigations to rule out any associated subtle pathology such as microstrabismus, retinal macular degeneration, retinitis pigmentosa, congenital hereditary cone dystrophy, delayed visual maturation, dyslexia or Leber amaurosis.

Strabismus and Amblyopia

Strabismus is defined as the condition when the visual axes of the two eyes do not meet at the point of regard. In other words, the motor and sensory alignment of the two eyes and their images in the brain are not synchronized. The cause may be a basic abnormality of development as in essential esotropia or exotropia (concomitant squint when the angle of deviation or separation of the two eyes is uniform, irrespective of the direction or position of gaze) or secondary to extraocular muscle paralysis, e.g. paralytic squint, orbital space occupying lesion, myositis or orbital inflammation as in orbital pseudotumor syndrome, orbital musculofascial abnormality like Duane retraction syndrome or Brown's superior oblique tendon sheath syndrome (causing an incomitant or nonconcomitant squint, where the deviation is more in certain positions and less or even absent in some positions of gaze).

An inward deviation of the eye is termed esotropia and outward deviation is termed exotropia. The child initially suffers diplopia due to the different images being pre-

sented to the visual cortex by the two eyes, but learns to suppress one image, eventually developing amblyopia or a 'lazy eye' with loss of binocularity and stereopsis. In very young children, the presence of an intermittent or constant squint or misalignment of the eyes should be indications for referral to an ophthalmologist.

Amblyopia or 'lazy eye' is a condition of subnormal vision defined as two lines less than normal or less than the fellow eye on the visual acuity chart with no anatomical cause detectable on examination, i.e. no media opacity and a normal fundus. Amblyogenic factors have their maximum impact on the immature developing visual system, i.e. during the first 6 yr of life and include sensory deprivation or abnormal binocular interaction. The former would refer to a corneal opacity or cataract which, even if taken care of surgically, do not indicate good chances of restoration of normal vision. Similarly, abnormal binocular interaction occurs in the presence of strabismus or anisometropia (difference in the refractive power of the two eyes), in which case one eye takes over and the visual cortical neurons meant to receive stimuli from the other eye are unable to develop normally, leading to a 'lazy eye'. These changes are potentially reversible with appropriate therapy in the first decade, but become irreversible and permanent later. Treatment involves restoration of vision with correction of refractive error, removal of media opacity if present (such as corneal opacity or cataract), patching therapy by part time patching of the 'good' eye to enable the 'lazy' eye to catch up, and strabismus surgery to restore ocular alignment if required.

Cataract

A visible lenticular opacity in the eye is termed as a cataract. It is congenital if present since birth, developmental if appearing later on, and traumatic if occuring after an episode of eye trauma. A central opacity is considered visually significant if it impairs visual acuity, and on clinical assessment obstructs a clear view of the fundus. A cataract may be unilateral or bilateral and symmetric or asymmetric. In view of the risk of sensory deprivation amblyopia, visually significant cataract should be treated surgically as soon as possible after birth. Functional success is highest if operated within the first few weeks after birth, provided the child is medically fit to undergo general anesthesia. Unilateral cataracts must be supplemented with postoperative patching therapy to take care of any amblyopic effect. Optical and visual rehabilitation for the aphakic state resulting from lens removal includes the implantation of an intraocular lens (IOL) for children above two years of age. Generally, intraocular lenses are avoided for children less than two years old as there are significant problems of change in lens power requirements as the maximum growth of the eyeball takes place during the first two years of life and the risk of complications of glaucoma and intraocular inflammation and fibrosis are higher. In very young children, therefore, a capsule rim is left for subsequent secondary IOL implantation, and temporary optical rehabilitation is provided with spectacles or contact lenses supplemented with patching for amblyopia in unilateral cases (Fig. 24.4).

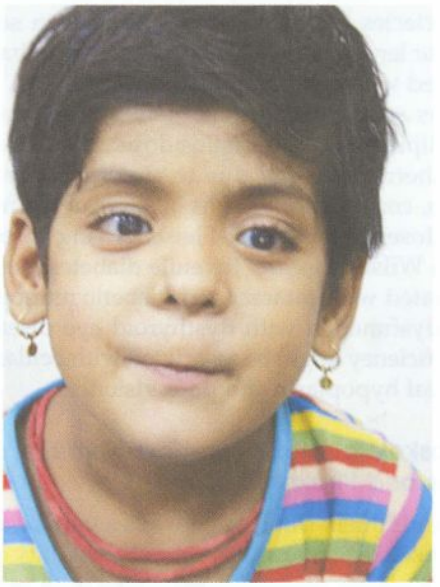


Fig. 24.4: A child with bilateral developmental cataract. The cataract is partial and the condition was detected late. Also note that the child has a convergent squint. The child also has impaired hearing and congenital heart disease, suspected to be due to congenital rubella syndrome

Glaucoma

Primary congenital and developmental juvenile glaucoma are now recognized to be inherited diseases. Primary congenital glaucoma is associated with *CYP1B1* gene, (2p21) with a predominantly autosomal recessive mode of inheritance, and mutations in the myocillin (*MYOC*) gene. Photophobia, blepharospasm, watering and an enlarged eyeball are classic symptoms. Suspicion of glaucoma or buphthalmos warrants urgent referral to an ophthalmologist. An examination under anesthesia is required to measure the corneal diameter and intraocular pressure, and to visualize the optic disc. Once glaucoma is confirmed, medical therapy is started to lower the pressure and patient prepared for surgery. If the cornea is clear enough to allow visualization of the angle structures, a goniotomy is attempted. If the glaucoma is more severe or the cornea very edematous, a drainage procedure is undertaken to open alternative aqueous drainage channels such as trabeculectomy and trabeculotomy. If the cornea fails to clear after adequate control of the intraocular pressure, corneal transplantation is required to restore vision and prevent irreversible sensory deprivation amblyopia.

Children can also develop secondary glaucoma due to chronic use of topical corticosteroid eyedrops, following eye trauma particularly if associated with traumatic hyphema (blood in the anterior chamber) or angle

recession, after surgery for developmental cataract and after chronic uveitis.

Eye Trauma and Related Problems

Eye injuries are common in children (Figs 24.5A and B). Eye injuries are considered to be an important cause of preventable blindness. Effort must be made to educate the community in general, and mothers in particular, about the importance of not allowing children to play with sharp pointed toys like bows and arrows, firecrackers, chemicals including colors during Holi festival or other chemicals like edible 'chuna'. Sharp and dangerous household objects like knives, scissors and needles, and chemicals like cleaning liquid, acid, whitewash paint and edible 'chuna' should be kept out of reach of children.

In case an injury is sustained, the eyes should be immediately washed thoroughly with locally available drinkable water, and the child should be rushed to the nearest hospital.

Perforating injuries of the globe require surgical repair under general anesthesia along with administration of systemic and topical antibiotics and tetanus prophylaxis. The child should be told not to rub the eyes and given only fluids while rushing the child to hospital so that there is no unnecessary delay in preparing the patient for general anesthesia and planning surgery. Meticulous repair of the wounds is undertaken as soon as possible to minimize the risk of secondary complications such as endophthalmitis, expulsion of intraocular contents and later risk of sympathetic ophthalmitis or an inflammatory panuveitis in the normal eye due to sensitization of the immune system to the sequestered antigens in the exposed uveal tissue.

Retinal Diseases

Children may be affected by a wide variety of retinal diseases. Retinal detachment can occur secondary to trauma or spontaneously in cases with high or pathological myopia. Classical symptoms such as sudden loss of vision with floaters and photopsia may not be reported by children and the detachment may not be detected till much later. Retinal detachment requires surgical treatment and the sooner the surgery is performed, the greater are the chances of functional recovery of vision. Other diseases that can affect the retina in childhood include degenerative and hereditary conditions like retinitis pigmentosa and different forms of macular degeneration such as Stargardt disease. These diseases lead to gradual, painless, bilateral diminution of vision in the first or second decade of life which may be accompanied by defective dark adaptation or abnormal color vision. No specific treatment modalities are available, but refractive correction, low vision aids, visual rehabilitation and genetic counseling are ancillary measures.

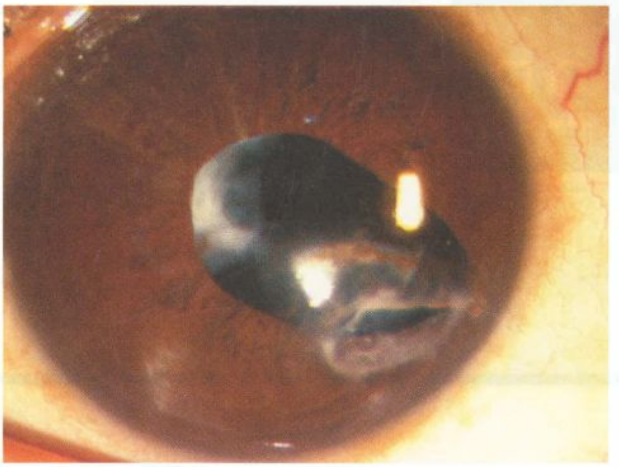


Fig. 24.5A: The sequelae of ocular trauma. Following injury with a wooden stick, the child had corneal perforation, which was repaired. Traumatic cataract was surgically removed. Note the irreversible anatomical damage with corneal scar, distorted iris and pupil and lens capsular opacification

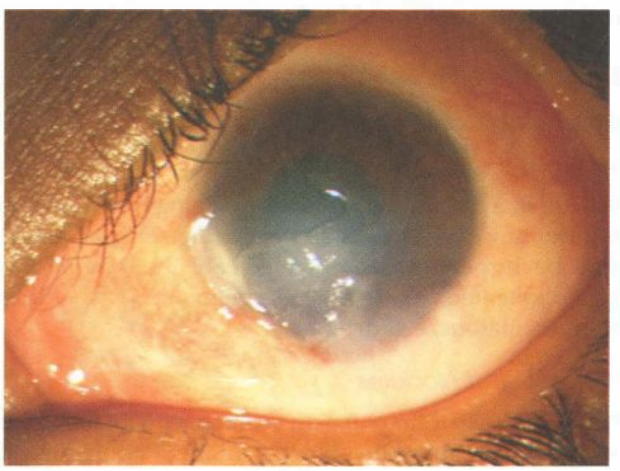


Fig. 24.5B: The sequelae of chemical injury, due to edible 'chuna'. Despite aggressive management, longterm sequelae include residual conjunctival inflammation with limbal stem cell deficiency and a scarred, irregular and opacified corneal surface

Vascular abnormalities of the retina such as hemangiomas, arteriovenous malformations and exudative vitreoretinopathies like Coats disease may be seen. Retinal vasculitis may be seen in Eales disease and other inflammatory disorders. Diabetic retinopathy and hypertensive retinopathy can occur if these systemic disorders are present in sufficient grade of severity and for an adequate duration of time.

Suggested Reading

Sihota R, Tandon R. Parsons' diseases of the eye, 21st edn, 2011 Elsevier India, Delhi.

25 Skin Disorders

Neena Khanna, Seemab Rasool

Skin disorders account for nearly one-third of ailments in children. The prerequisite for dermatological diagnosis is identification of the different skin lesions as well as the various patterns formed by them.

BASIC PRINCIPLES

Morphology of Lesions

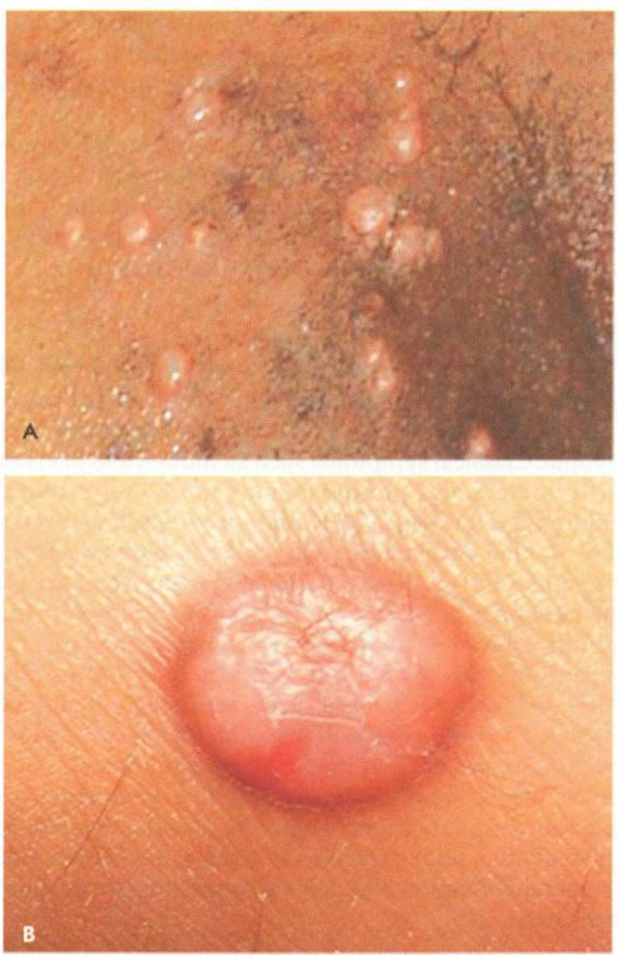
Macules

Macule is a circumscribed area of change in skin color without any change in consistency (Fig. 25.1). A macule may be hyperpigmented, e.g. café au lait macule, hypopigmented, e.g. leprosy, depigmented, e.g. vitiligo or erythematous, e.g. drug rash.

Papules and Nodules

Papule is a solid lesion < 0.5 cm in diameter with major part of it projecting above the skin (Fig. 25.2A). Papules may be dome shaped (e.g. trichoepithelioma), flat topped (e.g. verruca plana), conical (e.g. condyloma acuminata), filiform (e.g. filiform warts) or umblicated (with crater on surface, e.g. molluscum contagiosum) or verrucous (with multiple closely packed firm elevations, e.g. verrucous warts). A papule which is >0.5 cm in size and with the major part in the skin is called a nodule (Fig. 25.2B).

Fig. 25.1: Macule: Circumscribed area of change in skin color without any change in consistency



Figs 25.2A and B: (A) Papule: Solid lesion, <0.5 cm; (B) Nodule: Solid lesion, >0.5 cm

Plaque

Plaque is an area of altered skin consistency, the surface area of which is greater than its depth (Fig. 25.3). A plaque can be elevated, depressed or flat.

Wheal

Wheal, the characteristic lesion in urticaria, is an evanescent, pale or erythematous raised lesion which disappears within 24–48 hr (Fig. 25.4). Wheals are due to dermal edema, and when the edema extends into subcutis, they are called *angioedema*. When the wheals are linear, the phenomenon is called *dermographism*.

Blisters

Blister is a circumscribed elevated, superficial fluid filled cavity (Fig. 25.5). If <0.5 cm, it is a vesicle and if >0.5 cm, a bulla.

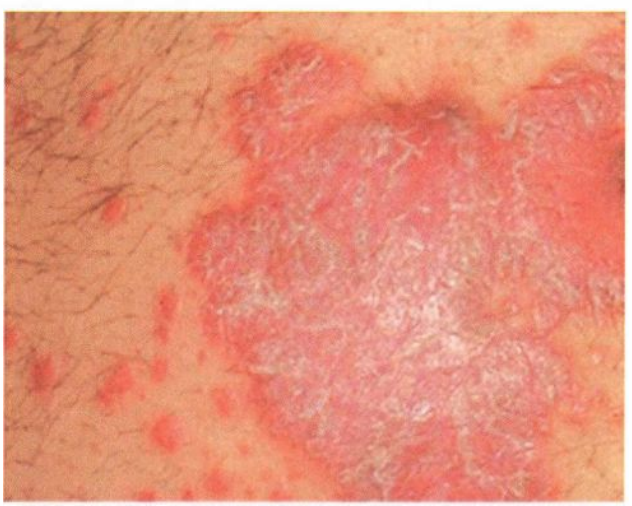


Fig. 25.3: Plaque: Area of altered skin consistency with a surface area of which is greater than its depth

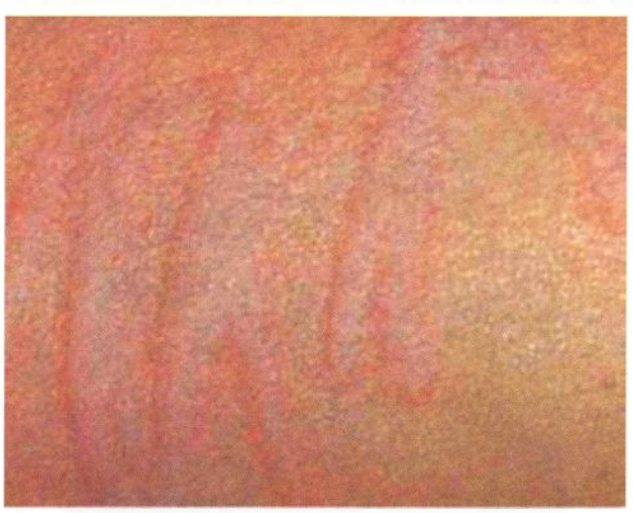


Fig. 25.4: Wheal: Evanescent, pale erythematous raised lesion which disappears within 24–48 hr

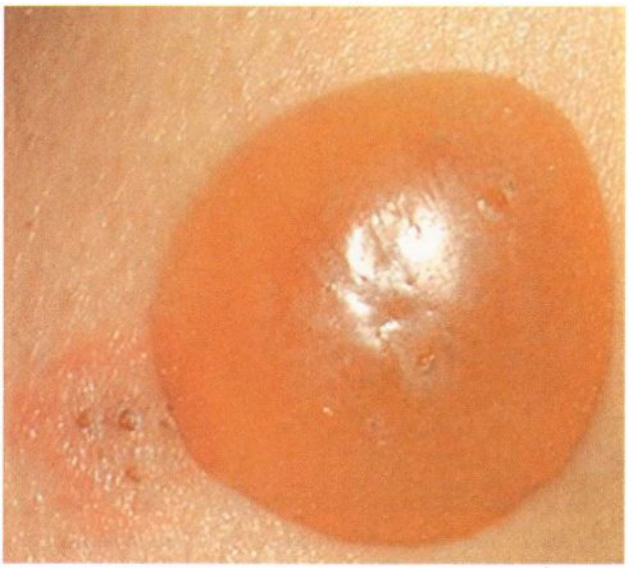


Fig. 25.5: Blister: Circumscribed, elevated, superficial fluid filled lesion

Scales

Scales are flakes of stratum corneum (Fig. 25.6) and are diagnostic in certain dermatoses, e.g. silver easily detachable flakes (psoriasis), branny (pityriasis versicolor) and fish-like scales ichthyosis).

Crusts

Crusts are formed when serum, blood or pus dries on the skin surface (Fig. 25.7).

Erosions and Ulcers

A defect, which involves only the epidermis and heals without a scar (Fig. 25.8A) is called an erosion, while an ulcer is a defect in the skin which extends into the dermis or deeper, and heals with scarring (Fig. 25.8B).

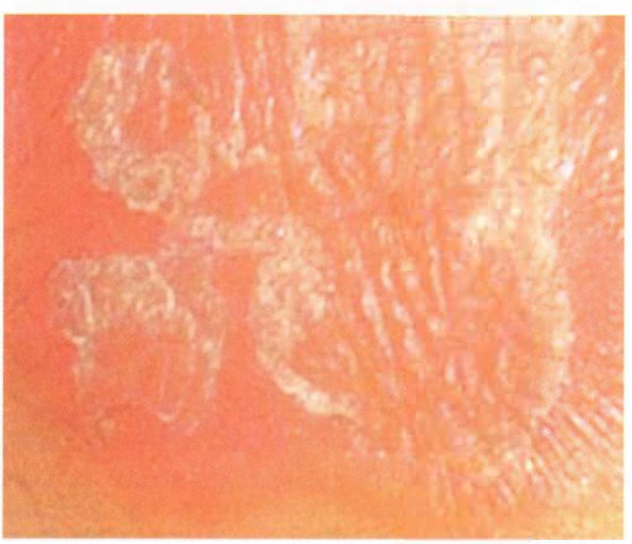


Fig. 25.6: Scale: Flakes of stratum corneum

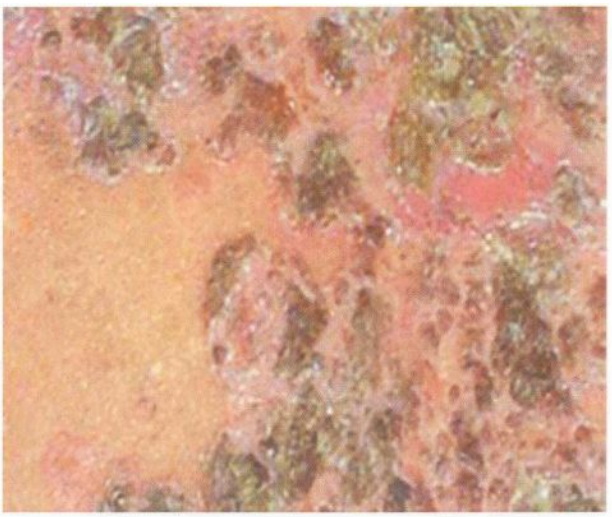
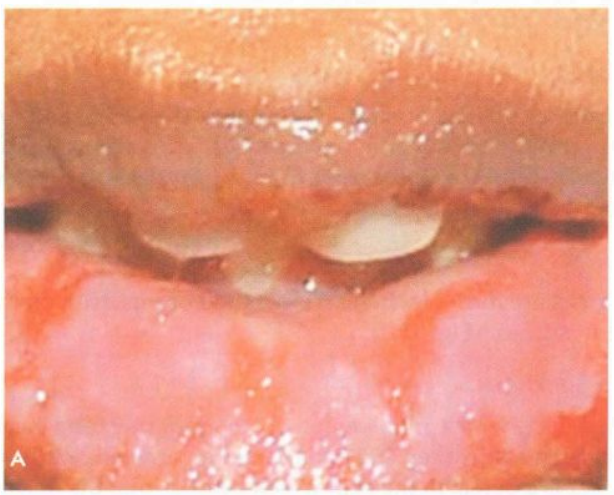
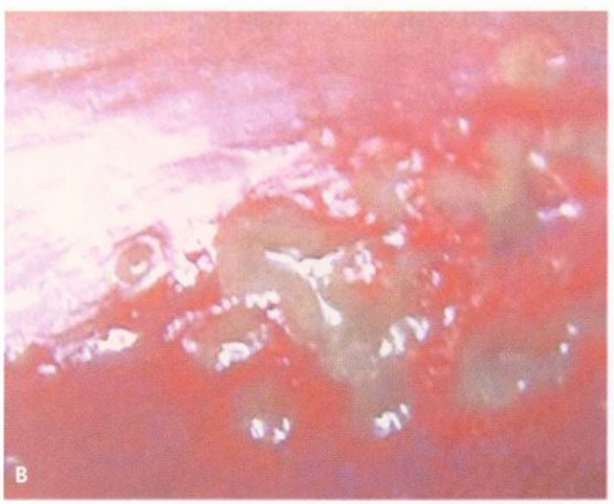


Fig. 25.7: Crust: Yellow brown collection of keratin and serum





Figs 25.8A and B: Erosions and ulcers: (A) Erosions are due to complete or partial loss of epidermis with no loss of dermis; (B) ulcer is a defect in the skin which extends into the dermis or deeper and heals with scarring

Atrophy

Atrophy is the reduction of some or all layers of skin. In epidermal atrophy, thinning of the epidermis leads to loss of skin texture and cigarette-paper like wrinkling without depression. In dermal atrophy, loss of connective tissue of the dermis leads to depression of the lesion.

Lichenification

Lichenification consists of a triad of skin thickening, hyperpigmentation and increased skin markings (Fig. 25.9). It is caused by repeated scratching.

Burrow

Burrow is a dark serpentine, curvilinear lesion with a minute papule at one end and is diagnostic of scabies (Fig. 25.10).

Comedones

Comedones are due to keratin plugs that form within follicular ostia and they can be open or closed (Fig. 25.11).

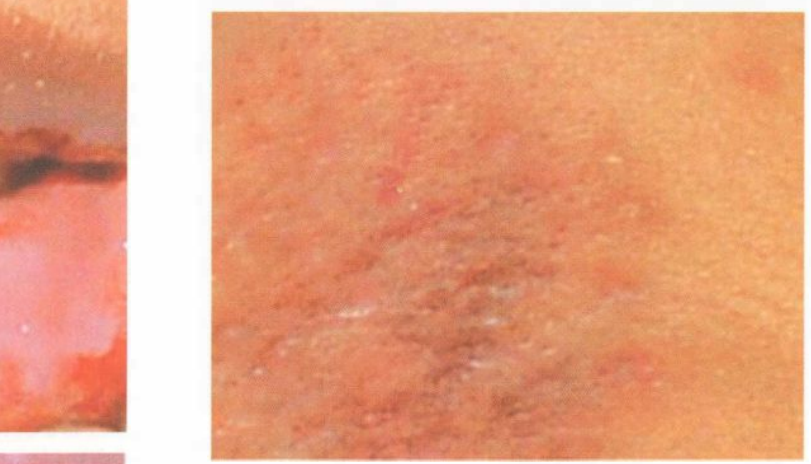


Fig. 25.9: Lichenification: Thickening and hyperpigmentation of skin with increased skin markings

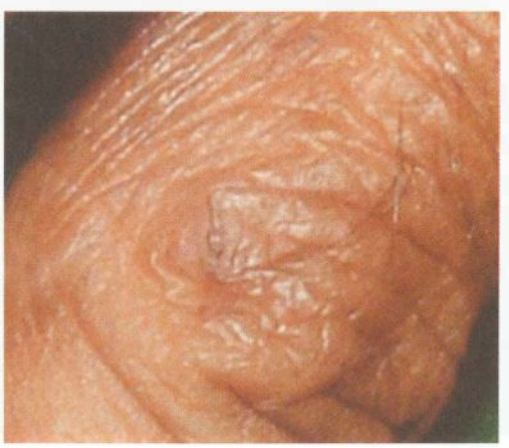


Fig. 25.10: Burrow: Serpentine, thread-like, grayish curvilinear lesion, diagnostic of scabies

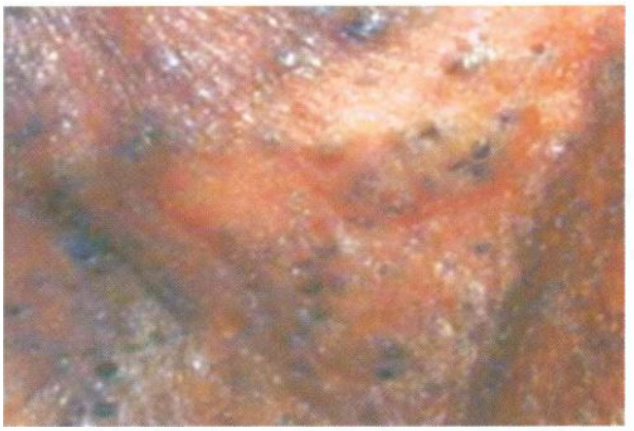


Fig. 25.11: Comedones: Keratin plugs that form within follicular ostia

Arrangement and Configuration of Lesions

Arrangement and configuration of skin lesions can help in diagnosis (Table 25.1).

Table 25.1: Arrangement and configuration of skin lesions

Arrangement	*Example*
Linear	Verrucous epidermal nevus
Grouped	Herpes simplex
Dermatomal	Herpes zoster
Arcuate	Granuloma annulare

Sites of Predilection

Sites of predilection are important for dermatological diagnosis (Fig. 25.12).

GENODERMATOSES

Genodermatoses are a group of inherited single gene cutaneous disorders that manifest themselves wholly or in part in the skin, mucous membranes, hair and nails.

Ichthyoses

Ichthyoses are a heterogeneous group of disorders characterized by the presence of fish-like scales. The etiology is heterogeneous (Table 25.2). They are classified as follows:

i. Ichthyosis vulgaris
ii. X-linked ichthyosis
iii. Autosomal recessive ichthyosis
   a. Lamellar ichthyosis
   b. Nonbullous ichthyosiform erythroderma
iv. Keratinopathic ichthyosis

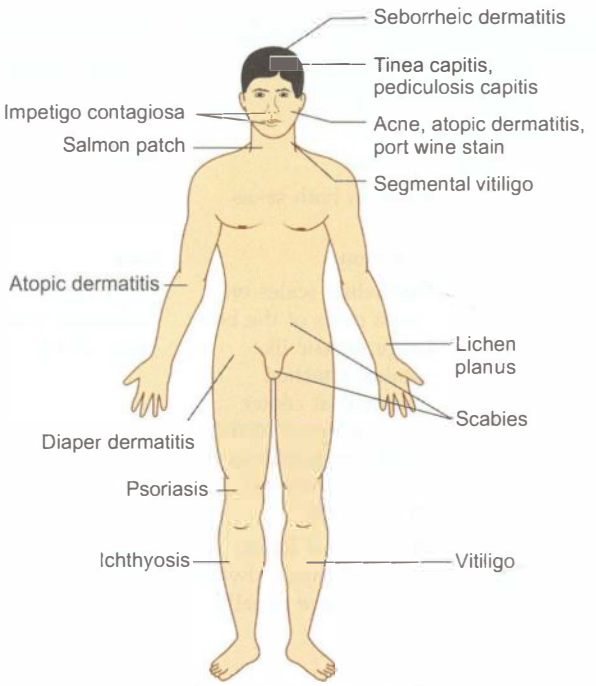


Fig. 25.12: Sites of predilection of common skin disease

The chief clinical features of icthyosis are listed in Table 25.3 and Figs 25.13 to 25.18.

Treatment

Hydration (by immersing in water) and immediate lubrication with petroleum jelly or urea containing creams and lotions are useful.

Keratolytic agents (hydroxyacids, propylene glycol and salicylic acid) are used when lesions are moderately severe. Oral retinoids (acitretin) are administered in collodion baby, severe cases of lamellar ichthyosis and in keratinopathic ichthyosis. A short course of topical steroid and antibiotic combination is used in eczematized skin.

Palmoplantar Keratoderma

This condition may be inherited or acquired. The hereditary keratodermas are caused by a gene abnormality

Table 25.2: Inheritance and etiology of ichthyoses

Type	*Inheritance*	*Defect*
Ichthyosis vulgaris	Autosomal dominant	Reduced or absent filagrin (helps form keratin filaments)
X-linked ichthyosis	X-linked	Deficiency of steroid sulfatase enzyme
Autosomal recessive ichthyosis*	Autosomal recessive	Abnormality of gene encoding transglutaminase; several defects identified
Keratinopathic ichthyosis	Autosomal dominant	Defect in keratin synthesis or degradation

*Heterogeneous group of disorders that includes many clinical phenotypes including lamellar ichthyosis and nonbullous ichthyosiform erythroderma

Table 25.3: Clinical features of ichthyoses

	Ichthyosis vulgaris	*X-linked ichthyosis*	*Lamellar ichthyosis*	*Nonbullous ichthyosiform erythroderma*	*Keratinopathic ichthyosis*
Age of onset	3–12 mo	Birth	Birth	Birth	Birth
Sex	Equal in both sexes	Only males	Equal in both sexes	Equal in both sexes	Equal in both sexes
Incidence	Common	Rare	Very rare	Rare	Rare
Clinical features	Fine white scales on most parts of the body Large mosaic-like scales, attached (pasted) at center and upturned at the edges on extensors of lower extremities (Fig. 25.13)	Large dark brown adherent scales (Fig. 25.14)	Collodion baby, ensheathed in shiny lacquer-like membrane at birth (Fig. 25.15); diffuse large thick brown plate-like scales (Fig. 25.16) which persist for life; erythema minimal	Collodion baby at birth; followed by fine branny scales and marked erythema (Fig. 25.17)	Generalized erythema with blistering at birth; followed by brown, warty, broad linear plaques (Fig. 25.18); scales may fall off leaving skip areas
Sites of predilection	Extensors of limbs; major flexures always spared; face usually spared	Generalized involvement; encroachment of flexures; palms and soles spared	Generalized involvement; accentuation on lower limbs and flexures	Generalized erythema and scaling	Generalized involvements; accentuation in flexures
Associated features	Hyperlinear palms and soles; keratosis pilaris; atopic diathesis	Corneal opacities; cryptorchidism	Ectropion and eclabium; crumpled ears; palmar and plantar keratoderma	Palmar and plantar keratoderma are less frequent	Palmar and plantar keratoderma in >60%

Fig. 25.13: Ichthyosis vulgaris: Large scales on extremities that are attached at the center and turned up at the edge

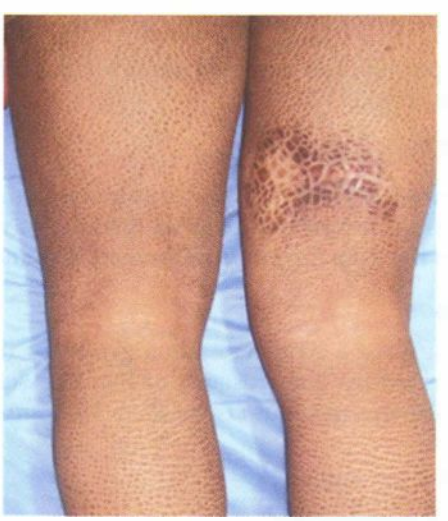


Fig. 25.14: X-linked ichthyosis: Large dark brown adherent scales without sparing of flexure

that results in abnormal keratin. Inheritance is either autosomal dominant or autosomal recessive (Table 25.4).

The condition is characterized by thickening of skin of palms and soles (Fig. 25.19), which usually manifests at birth or in the first few months of life. Mutilating variants are characterized by massive thickening and mutilation (Fig. 25.20). Sometimes keratoderma extends onto the dorsae of hands and feet (*keratoderma transgrediens*).

Therapy for keratoderma includes the topical use of emollients, keratolytics (salicylic acid 6–12%, urea 30–40%), retinoids and vitamin D (calcitriol). Systemic retinoids (acitretin) are used in mutilating variants.

Epidermolysis Bullosa

These are a heterogeneous group of disorders defined by a tendency to develop blisters even on trivial trauma. The common clinical features are listed in Table 25.5. EB

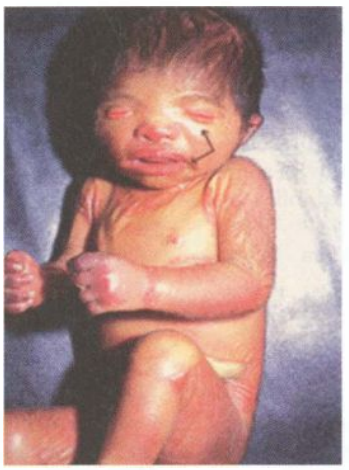


Fig. 25.15: Collodion baby: Baby is ensheathed in a shiny lacquer-like membrane

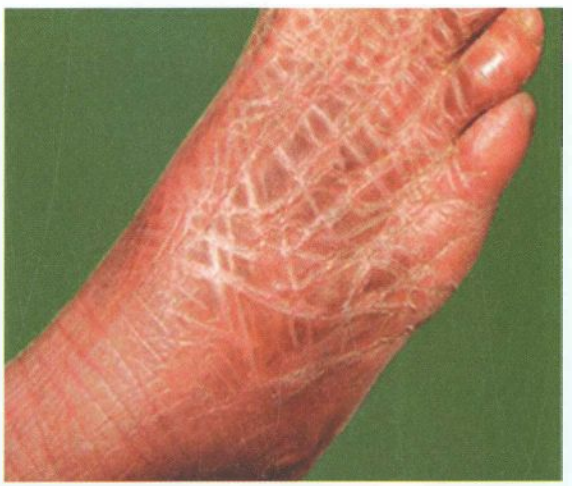


Fig. 25.16: Lamellar ichthyosis: Large pasted scales with continuous rippling around ankle

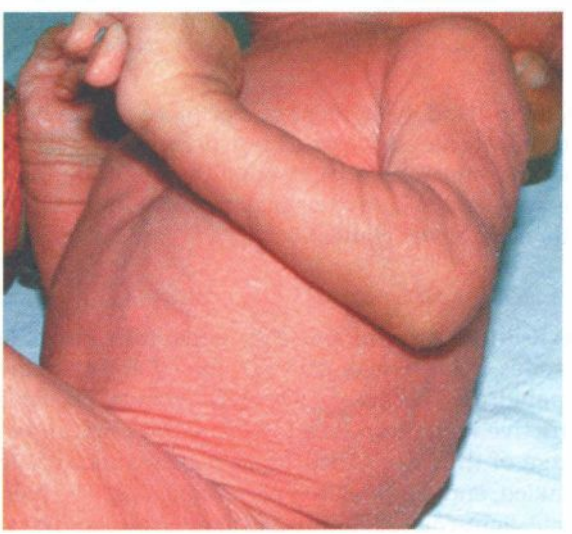


Fig. 25.17: Nonbullous ichthyotic erythroderma: Diffuse erythema, with fine scales

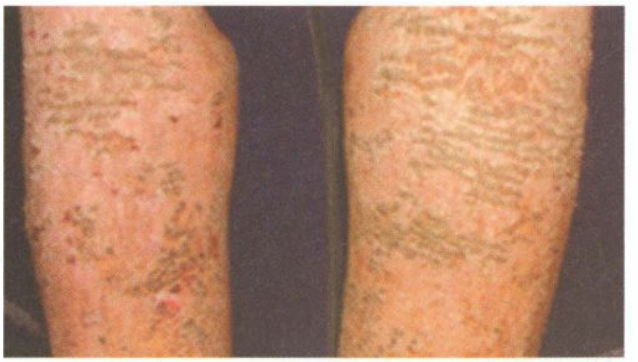


Fig. 25.18: Keratinopathic ichthyosis: Brownish, warty, broad linear plaques

Table 25.4: Classification of hereditary palmar and plantar keratoderma

Type	*Inheritance*
Diffuse	Autosomal dominant
Focal	Autosomal dominant
Mutilating	Autosomal recessive
Transgrediens	Autosomal recessive

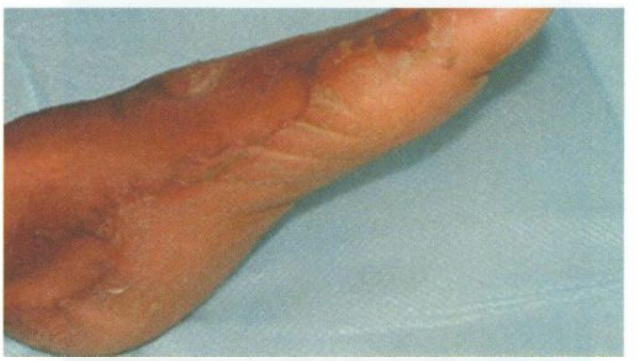


Fig. 25.19: Palmoplantar keratoderma: Autosomal dominant variant thickening of skin of soles

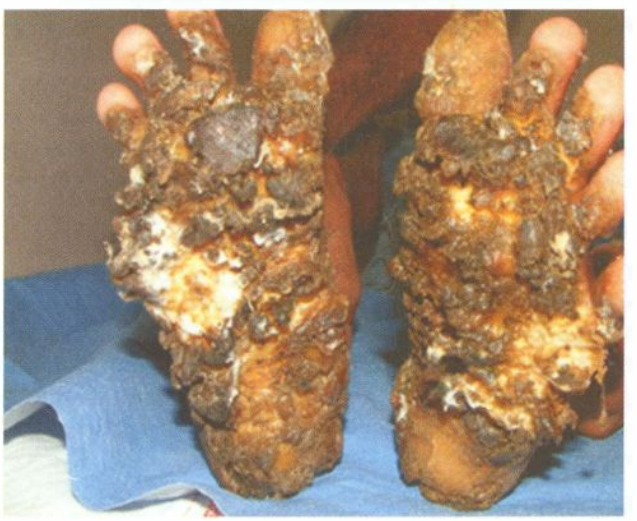


Fig. 25.20: Palmoplantar keratoderma: Autosomal recessive massive thickening and mutilation

Table 25.5: Clinical features of epidermolysis bullosa (EB)

	EB simplex	*Junctional EB*	*Dominant dystrophic EB*	*Recessive dystrophic EB*
Age of onset	Early childhood	At birth	At birth, infancy	At birth
Skin lesions	Nonhemorrhagic bullae which heal without scarring	Large flaccid bullae which heal slowly	Hemorrhagic blisters which heal with some scarring and milia (Fig. 25.21)	Hemorrhagic blisters which heal with scarring (Fig. 25.22)
Sites	Hands and feet	Perioral and perianal areas; sites of trauma (knees, elbows, fingers)	Sites of trauma	Generalized
Mucosal lesions	None	Involved	Minimal	Severe
Nail involvement	Absent	Present	Present	Present
Complications	Heal without scarring	One variant is lethal	Scarring and milia formation	Severe scarring; esophageal strictures
Variants	Herpetiformis or Dowling-Meara Localized or Ogna syndrome	Gravis Mitis	Cockayne-Touraine Pasini syndrome	Mitis Hallopeau-Siemens Bart syndrome Kindler syndrome

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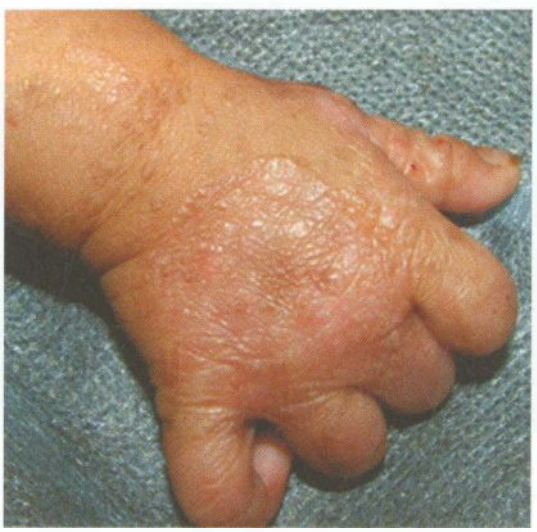

Fig. 25.21: Epidermolysis bullosa dominant dystrophic: Bullae heal with minimal scarring and milia formation

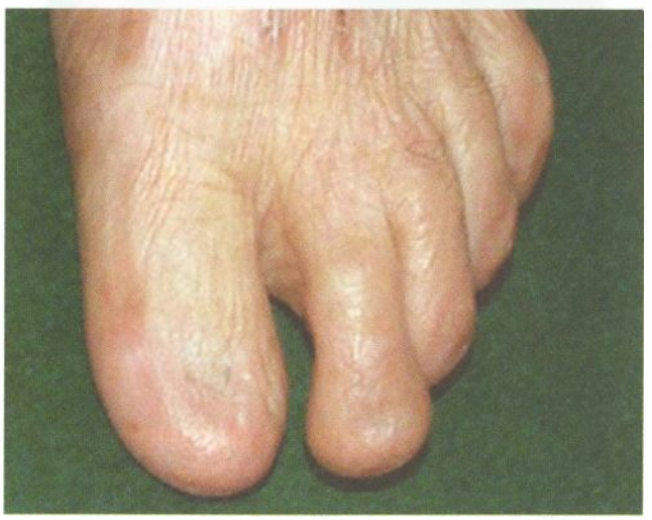

Fig. 25.22: Recessive dystrophic epidermolysis bullosa: Bullae heal with scarring and there is loss of nails

simplex and dominant dystrophic EB are inherited in an autosomal dominant manner. Junctional EB and recessive dystrophic EB are inherited as autosomal recessive.

Treatment

General measures include avoiding friction and trauma, wearing soft well ventilated shoes and gentle handling. Prompt and appropriate use of antibiotics for injuries and infected lesions is necessary. The role of vitamin E and phenytoin is doubtful. Surgery may be required for release of fused digits, correction of limb contractures and esophageal strictures.

Ectodermal Dysplasias

Ectodermal dysplasias comprise a large, heterogeneous group of inherited disorders that are defined by primary defects in the development of 2 or more tissues derived from embryonic ectoderm. The disorders can be classified based on inheritance (autosomal dominant, autosomal recessive, and X-linked) or by structures involved (hair, teeth, nails, sweat glands).

Anhidrotic Ectodermal Hypoplasia

This X-linked disorder presents with intolerance to heat, episodes of high fever due to reduced ability to sweat (hypohidrosis) because of few sweat glands. The facies is districtive with prominent forehead, thick lips and a flat bridge of the nose. Additional features include thin, wrinkled, and dark-colored periorbital skin. The hair are sparse, light-colored, brittle and slow-growing. The teeth may be absent (hypodontia) or malformed (small, conical) (Fig. 25.23).

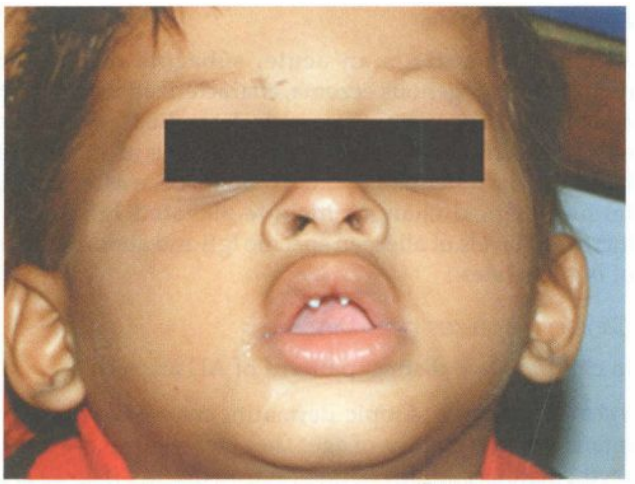

Fig. 25.23: Anhidrotic ectodermal hypoplasia: Sparse scalp hair, small pointed teeth

There is no specific treatment, but the quality of life can be improved by maintenance of cool ambient temperature and managing fever by tepid sponging. Dental restoration and use of artificial tears to prevent drying of the eyes is often necessary.

Hidrotic Ectodermal Dysplasia

This autosomal dominant disorder presents with patchy alopecia with sparse wiry hair, progressive palmar and plantar hyperkeratosis and dystrophic nails. Sweating and teeth are normal.

NEVI

Nevus is a developmental disorder characterized by hyperplasia of epidermal or dermal structure in a circumscribed area of skin.

Melanocytic Nevi

Melanocytic nevi are circumscribed pigmented lesions composed of groups of melanocytic nevus cells. Their clinical features are listed in Table 25.6. *Congenital nevi*, especially those larger than 20 cm, need to be observed for malignant transformation. *Acquired nevi* can be left alone.

Dermal Melanocytosis

Mongolian Spot

These present at birth as grey blue macules commonly in the lumbosacral region. These spots, that occur due to ectopic melanocytes in dermis, disappear spontaneously by early childhood.

Nevus of Ota

These lesions present at birth or infancy and consist of mottled slate gray and brown hyperpigmented macules in the distribution of the maxillary division of trigeminal nerve. Pigmentation of sclera (slate gray) and conjunctiva (brown) is common. The nevi persist for life but can be treated with Nd: YAG lasers.

Epidermal Nevi

These nevi usually present at birth, as multiple brown papular lesions arranged linearly (Fig. 25.24). Several variants are described, including verrucous epidermal nevus, inflammatory linear verrucous epidermal nevus, nevus comedonicus, nevus sebaceous. Topical retinoic acid and dermabrasion are helpful.

Vascular Birthmarks

Two types of lesions are seen in Table 25.7. Clinical features of common vascular birthmarks are summarized in Table 25.8.

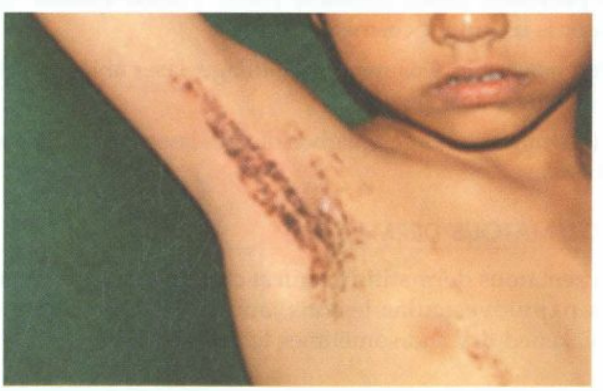

Fig. 25.24: Verrucous epidermal nevus: Multiple brown papular lesions arranged linearly

Table 25.6: Clinical features of melanocytic nevi

	Congenital nevus	*Junctional nevus*	*Compound nevus*
Age of onset	Birth	Early childhood	Childhood
Morphology	Macules, papulonodules or plaques at birth; dark brown or black lesions	Macules; brown to dark brown with color variation; smooth margin	Dome shaped smooth papules; brown or black with color variation
Hair	Usually have coarse hair	No hair	May have hair
Site	Anywhere on the body; giant lesions on trunk	Palms, soles or genitals	Face
Complications	Malignant transformation in giant lesions; meningeal involvement; spina bifida	Malignant transformation is rare	Inflammation; malignant transformation is rare

Table 25.7: Classification of vascular birthmarks

	Vascular tumors	*Malformations*
Types	Infantile hemangioma Congenital hemangiomas Angiokeratoma	*High flow* Arteriovenous malformations *Low flow* Capillary Port wine stain Salmon patch Venous Lymphatic
Age of onset	Usually begin after birth	Always present at birth
Evolution	Initial growth followed by involution (in infantile hemangioma)	Growth proportionate to body growth; then persists (except salmon patch)
Underlying skeletal defects	Infrequent	Frequent

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Treatment

Salmon patch. No treatment required.

Infantile hemangioma. Small lesions resolve spontaneously. Large symptomatic lesions need treatment with systemic steroids in the proliferative phase. Propranolol used under supervision shows dramatic result. Pulsed–tunable dye laser is useful for cosmetic results.

Port wine stain: Cosmetic camouflage; laser ablation with pulsed–tunable dye laser.

Lymphangioma: Surgery, carbon dioxide laser, radiofrequency ablation

ECZEMATOUS DERMATITIS

Eczematous dermatitis manifest clinically in acute phase as papulovesicular lesions, and in chronic phase as thickened dry and sometimes lichenified skin.

Atopic Dermatitis

Atopic dermatitis is an acute, subacute or chronic relapsing, endogenous eczema, characterized by dry skin and pruritic, recurrent, symmetric dermatitic lesions. The etiology is unclear. Genetic predisposition is an important factor but the inheritance pattern has not been ascertained. Immunological changes include elevated IgE levels, increased levels of allergen specific IgE and abnormalities of lymphocytes.

Clinical Features and Diagnosis

In children, two distinct patterns of AD are seen.

Infantile pattern Atopic dermatitis may have onset in infancy, after 3 months of age. The chief features are itchy, erythematous papulovesicles, seen on the face (Fig. 25.27), but may become generalized. The lesions clear by 18 months of age in 40% and evolves into the childhood pattern in the rest.

Childhood pattern The childhood pattern is characterized by dry lichenified and crusted plaques, seen mainly on antecubital (Fig. 25.28) and popliteal fossa, the neck and face. Most (70%) clear by 10 yr of age. Common complications include the occurrence of superimposed bacteria or viral (herpes simplex, molluscum contagiosum) and fungal infections.

The diagnosis of atopic dermatitis is facilitated by diagnostic criteria (Table 25.9).

Treatment

Parents and the child should be educated about the disease and its chronic course. There is limited role for dietary restriction. Breastfeeding decreases the chance of developing atopic dermatitis.

Patients are educated to avoid scratching, avoid contact with irritants, like woolens and chemicals. Mild soaps and cleansing lotions are used. Measures to reduce exposure to house dust mite, e.g. using barriers on pillows and mattresses, regular vacuuming of rooms may help. There

Table 25.8: Clinical features of vascular birthmarks

	Infantile hemangioma	*Salmon patch*	*Port wine stain*	*Lymphangioma*
Onset	After birth	At birth	At birth	At birth
Morphology	Soft, bright nodule with pale stippling (Fig. 25.25)	Telangiectatic macules	Light pink, red macules (Fig. 25.26); bosselated with age	Cluster of thin-walled vesicles
Site	Face and neck	Nape of neck, forehead, eyelids	Face	Trunk
Complications	Interfere with function; bleeding or ulceration	None	Sturge-Weber syndrome associated with hamartomas; seizures, eye deficits	
Course	Grows for few mo; later regression	Involutes by 1 yr	Persists throughout life	Persists

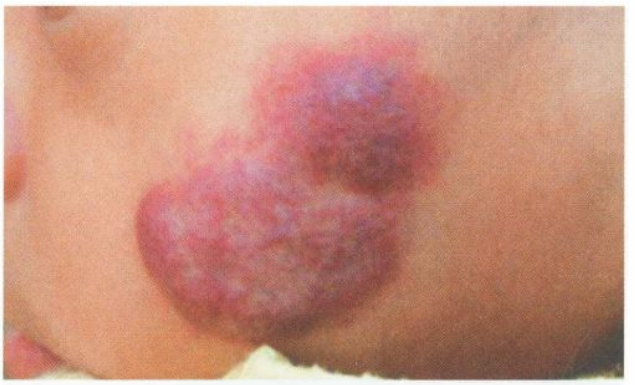

Fig. 25.25: Infantile hemangioma: Soft bright red nodule with pale stippling

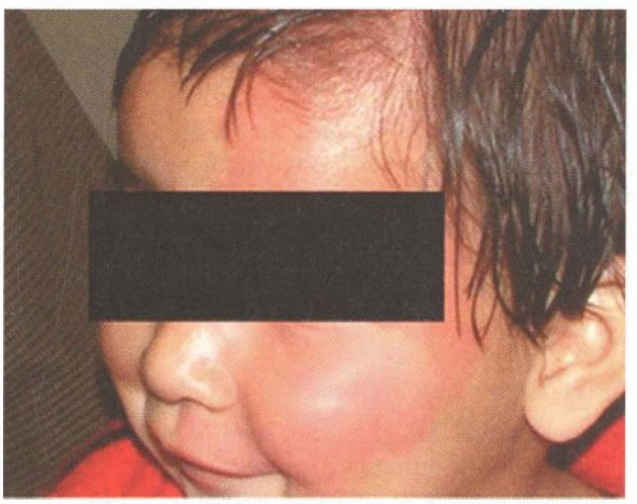

Fig. 25.26: Port wine stain: Light pink to deep red macule

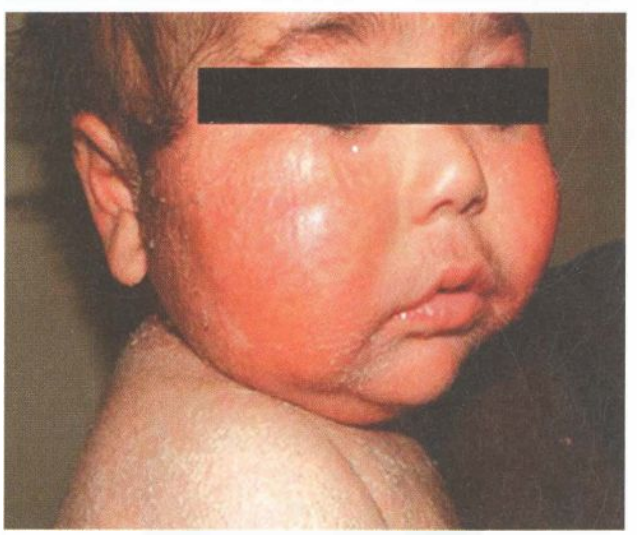

Fig. 25.27: Infantile eczema: Papulovesicular lesions on the face

is no contraindication to vaccination except in children specifically allergic to eggs, in whom influenza and yellow fever vaccines are avoided.

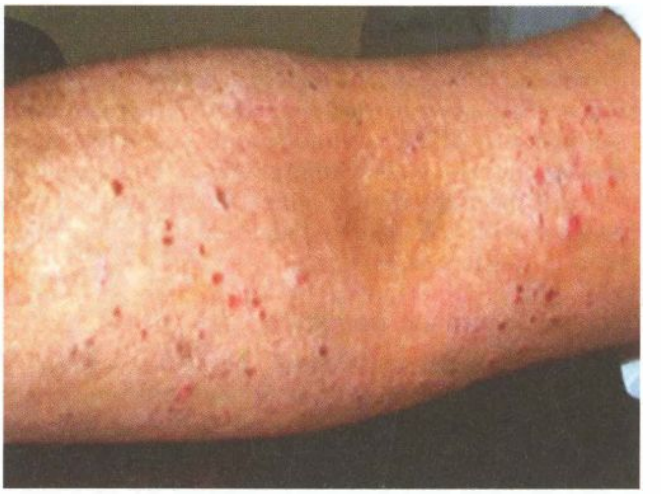

Fig. 25.28: Atopic dermatitis in childhood: Dry plaques in the flexures

Table 25.9: Hanifin and Rajkar's criteria for atopic dermatitis

Major features (must have 3 or more)
Pruritis
Typical morphology and distribution (facial and extensor involvement in infants and children; flexural lichenification in adults)
Dermatitis, chronic or chronically relapsing
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Minor features (must have 3 or more)
Cataracts (anterior subcapsular)
Cheilitis
Conjunctivitis, recurrent
Facial pallor or erythema
Food intolerance
Hand dermatitis: nonallergic, irritant
Ichthyosis
Elevated levels of IgE
Immediate (type I) skin test reactivity
Infections
Itching, when sweating
Keratoconus
Keratosis pilaris
Nipple dermatitis
Orbital darkening
Palmar hyperlinearity
Perifollicular accentuation
Pityriasis alba
White dermographism
Wool intolerance
Xerosis

Acute eczema is treated with wet dressing; topical steroids and topical and oral antibiotics, are used when indicated. The role of oral antihistaminics is controversial.

Chronic eczema is managed by hydration followed by application of emollients like petrolatum. Topical steroids are sometimes combined with keratolytic agents like

salicylic acid (in lichenified lesions). It is preferred to use the least potent steroid, which reduces symptoms. Potent steroids should be avoided on face and genitalia. Topical immunomodulators like tacrolimus and pimecrolimus are useful because of their steroid sparing action and rapid reduction in itching. Oral antihistaminics might be used to break the itch-scratch cycle. Narrow band UVB, psoralens with UVA (PUVA) and oral cyclosporine are useful in resistant cases.

Infantile Seborrheic Dermatitis

The onset of symptoms is usually in the first 4 weeks of life, with erythema with yellow-orange scales and crusts (Fig. 25.29) on the scalp (cradle cap). Eczematous lesions may be present in the major flexures and trunk. The illness is self limiting and generally resolves by 12 weeks. *Malassezia furfur* is incriminated in pathogenesis. The crusts of cradle cap should be removed and this can be facilitated by pretreatment with an oil. Application of 2% ketaconazole shampoo, mild topical steroid or 1% pimecrolimus cream hastens subsidence.

25

Diaper Dermatitis

This is irritant dermatitis in infants due to prolonged contact with feces and ammonia (produced by the action of urea splitting organisms in urine). The area in contact with diapers (the convexity of buttocks) shows moist, glazed erythematous lesions with sparing of depth of flexures (Fig. 25.30). Diaper dermatitis is prevented by keeping area clean and dry and avoiding the use of disposable absorbent diapers. The washed cotton diapers should be rinsed in dilute lemon juice. Emollients and mild topical steroids with antifungal agents are useful in the acute phase.

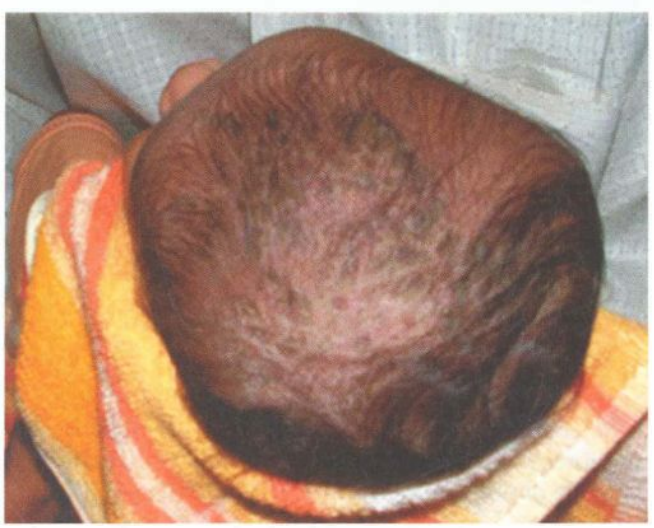

Fig. 25.29: Infantile seborrheic dermatitis: Erythema with yellow-orange scales and crust on the scalp

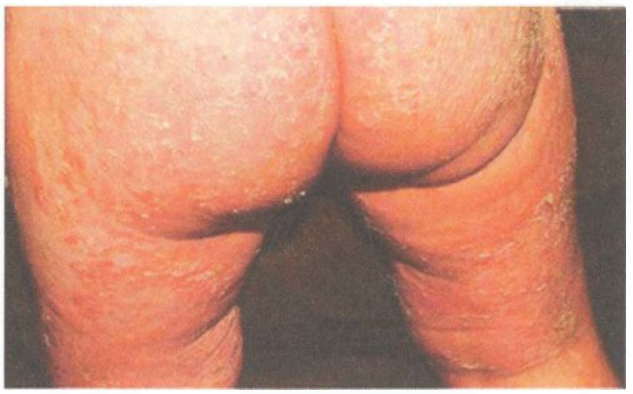

Fig. 25.30: Diaper dermatitis: Moist, glazed erythematous lesions with sparing of depth of folds

DISORDERS OF SKIN APPENDAGES

Acne Vulgaris

Acne vulgaris is a polymorphic eruption due to inflammation of the pilosebaceous units. This is a common illness, affecting 80% adolescents who present with a polymorphic eruption of open and closed comedones, papules, pustules, nodules and cysts on a background of oily skin (Fig. 25.31). The lesions usually heal with pitted scars.

Etiology

The etiology is multifactorial and includes:

Increased sebum secretion. Sebaceous glands in these patients show enhanced sensitivity to circulating androgens leading to increased sebum secretion.

Microbial colonization. Propionibacterium acnes (a normal commensal) is most commonly implicated.

Occlusion of pilosebaceous orifice. Pilosebaceous orifice is occluded by keratin plugs leading to retention of sebum and consequent growth of microbes, setting up a vicious cycle.

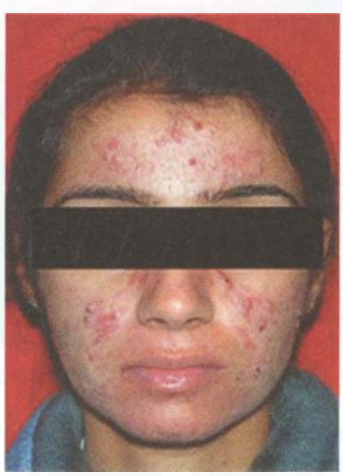

Fig. 25.31: Acne vulgaris: Polymorphic eruptions with comedones

Variants

Infantile acne is caused by maternal hormones and presents at birth, lasting for up to 3 yr. It is more common in males and lesions are similar to adolescent acne.

Acne conglobata is a severe form of acne characterized by abscesses, cysts and intercommunicating sinuses.

Drug induced acne. Drugs causing acne include steroids, androgens, antituberculous and anticonvulsant drugs. The eruption consists of monomorphic lesions of papules or pustules.

Therapy

Therapy of acne is summarized in Table 25.10. In addition, oil and oil based skin care products should be avoided. There is no restriction with regard to use of soaps and cleansers. No dietary restrictions are usually needed.

Table 25.10: Management of acne

Severity	*Subtype*	*Drug of choice*
Mild	Comedonal	Topical retinoids
	Papulopustular	Topical retinoids and oral antibiotics or benzoyl peroxide
Moderate	Papulopustular	Oral antibiotics, topical retinoids and benzoyl peroxide
	Nodular	Oral antibiotics, topical retinoids and benzoyl peroxide In girls: Oral antiandrogens and topical retinoids*
Severe	Nodular; conglobata	Oral retinoids In girls: Oral antiandrogens and topical retinoids*

* Oral retinoids may be used in females with moderate or severe lesions under supervision

Alopecia Areata

The condition affects children and young adults, who present with discoid areas of noncicatricial alopecia with exclamation mark hair at periphery (Fig. 25.32). The common sites are scalp, eye lashes and eye brows. In alopecia totalis there is total absence of terminal hair on scalp, while alopecia universalis is characterized by total loss of terminal hair from scalp and body (Fig. 25.33). Ophiasis is a band like pattern of hair loss from periphery of the scalp. Nails may occasionally show fine pitting and thinning of the nail plate.

Spontaneous remission is common. Initially, the regrowing hairs are grey, but regain color over period of time. Poor prognostic features include onset in childhood, ophiasis, association with atopy and widespread alopecia. The principles of treatment are outlined in Table 25.11.

Miliaria

Miliaria is due to obstruction and rupture of eccrine sweat ducts resulting in spillage of sweat into adjacent tissue. Its clinical features depend the level of rupture.

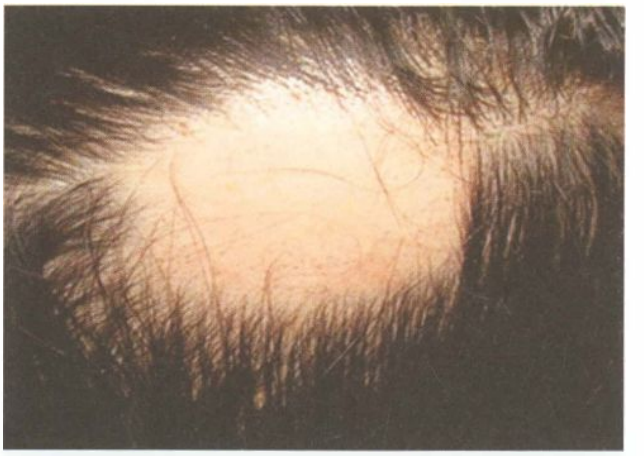

Fig. 25.32: Alopecia areata: Noncicatricial, noninflammatory discoid lesions with exclamation mark hair at periphery

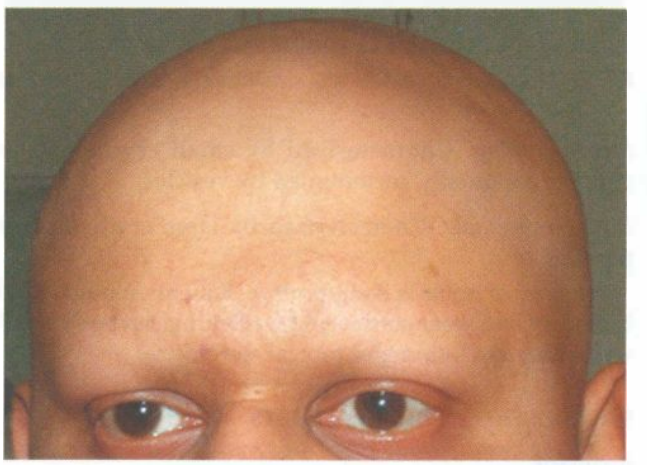

Fig. 25.33: Alopecia totalis: Total loss of terminal hair from scalp and body

Table 25.11: Treatment of alopecia areata

Description	*Management*
Single or few lesions of <6 mo duration	Observe; spontaneous recovery common
Single or few lesions of >6 mo duration; rapid progression	Topical corticosteroids Intralesional triamcinolone or acetonide Topical minoxidil Topical psoralens and ultraviolet A sunlight
Extensive lesions	Oral corticosteroids Oral psoralens with ultraviolet A sunlight Induction of allergic contact dermatitis with diphencyclopropenone

Miliaria crystallina. Usually seen during high fever. Is characterized by tiny, noninflamed superficial vesicles (Fig. 25.34).

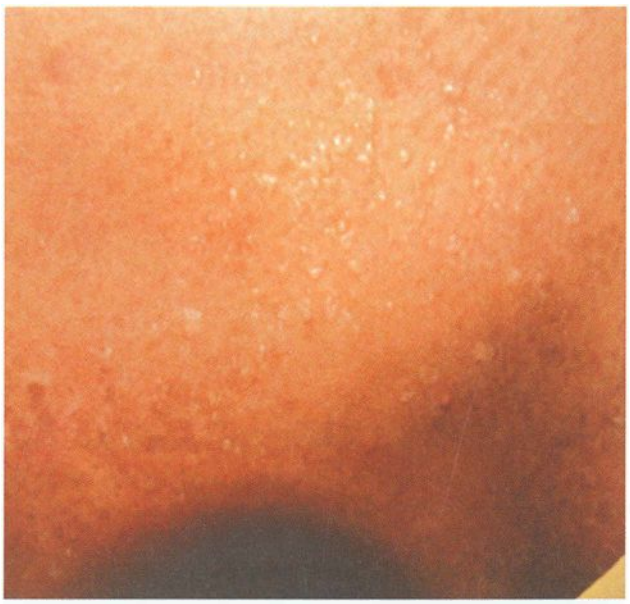

Fig. 25.34: Miliaria crystallina: Tiny, noninflamed superficial vesicles

Miliaria rubra. Characterized by small erythematous papules commonly surmounted by vesicles.

Miliaria profunda. Characterized by large erythematous papules.

Therapy of miliaria is supportive. Patients should avoid humidity and wear cotton clothes. Itching can be avoided with calamine lotion and topical steroids.

PAPULOSQUAMOUS DISORDERS

Psoriasis

Psoriasis is a chronic, recurring dermatosis which may have onset in childhood or adolescence (type I psoriasis) and in adults (type II psoriasis). Type I psoriasis is usually characterized by a positive family history, severe disease, prominent Koebner phenomenon, association with HLA cw6 and prolonged course, requiring aggressive therapy.

Psoriasis is a polygenic trait. At least 9 different psoriasis susceptibility loci (*PSORS 1–9*) have been identified in genome linkage studies. The condition is often triggered by physical trauma, infections (β hemolytic streptococci, HIV infection) and drugs (lithium, NSAIDs, antimalarials). T lymphocytes are believed to be important in the pathogenesis.

Psoriasis vulgaris is characterized by well demarcated, indurated, erythematous scaly lesions. Lesions become polycyclic due to confluence and annular because of central clearing. Symmetrical involvement of knees, elbows and extensors, lower back, scalp and sites of trauma (*Koebner* or isomorphic phenomenon) is seen. Face and photoexposed areas are generally spared. The scales are accentuated on grating the lesion with a glass slide (*Grattage* test). Removal of the scales by scraping with a glass slide reveals a glistening white membrane and on removing the membrane, punctate bleeding points become visible (*Auspitz* sign).

Guttate psoriasis is defined by crops of small erythematous scaly papules, predominantly on trunk. The conditions may follow an episode of streptococcal tonsillitis.

Pustular psoriasis is rare in children. Annular pustular psoriasis is characterized by sudden onset of fiery red erythema rapidly covered by cluster of very superficial creamy white pustules, which form circinate or annular lesions (Fig. 25.35). Infantile and juvenile pustular psoriasis is seen in infants (Fig. 25.36) and has a benign course; it is often confused with seborrheic and napkin dermatitis.

Associated Findings

Nail changes. Include pitting, thickening, subungual hyperkeratosis, onycholysis, discoloration and oil spots or staining of nail bed.

Joints 10% patients have joint involvement.

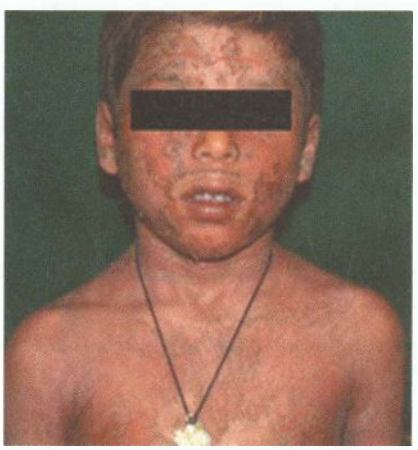

Fig. 25.35: Pustular psoriasis: Superficial pustules which coalesce to form circinate lesions

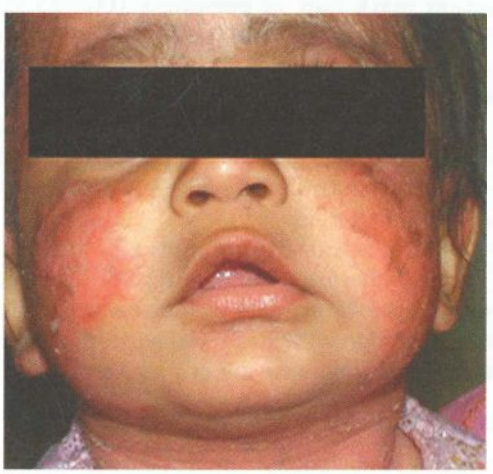

Fig. 25.36: Juvenile psoriasis: Annular or circinate lesions seen in infants

Treatment

It is important to counsel the parents and the child about the chronic nature of the disease and the likelihood of relapses. Several options are available for treatment depending on the type and extent of disease (Table 25.12).

Table 25.12: Treatment of psoriasis

	Treatment of choice	*Alternative modalities*
Psoriasis vulgaris		
Localised (<10% body surface area)	Coal tar	Topical steroids and salicylic acid
Extensive (>10% body surface area)	Narrow band UVB or PUVA*	Methotrexate, acitretin, cyclosporin A
Facial lesions	Topical steroids	
Guttate psoriasis	Antibiotics and emollients Narrow band UVB PUVA*	Coal tar, tacrolimus, mild topical steroids
Pustular psoriasis	Methotrexate, cyclosporin	Acitretin

*PUVA: Psoralen and ultraviolet A (UVA). Two hours after ingestion of 0.6 mg/kg of 8-methoxypsoralen, and after application of an emollient on the lesions, the patient is exposed to gradually increasing doses of UVA, provided either from an artificial source or from sunlight. The therapy should not be used in children <6 yr of age

Lichen Planus

It is an acute or chronic dermatosis involving skin, mucous membranes and nails. The etiology is unknown. A lichenoid eruption is seen after intake of drugs like chloroquin and as a manifestation of graft *vs.* host disease.

The lesions are pruritic, polygonal, violaceous and flat topped papules (Fig. 25.37) with white streaks (Wickham striae) on the surface. They are seen on wrists, around ankles and may appear at sites of trauma (Koebner phenomenon). Mucosal involvement is seen in 25% patients in form of reticulate lacey pattern on buccal mucosa, tongue and gingiva or superficial erosions on tongue and buccal mucosa. Annular lesions are seen on genitalia. Rarely scarring alopecia is present; nail changes are infrequent in children. The therapy of lichen planus is outlined in Table 25.13.

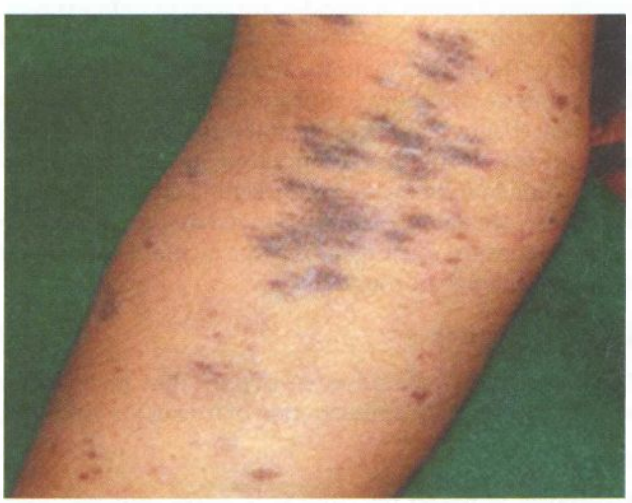

Fig. 25.37: Lichen planus: Plane polygonal, violaceous papules

Table 25.13: Treatment of lichen planus

Type of disease	*Therapy*
Localized	Topical steroids Oral antihistamines
Extensive	Narrow band UV B, PUVA* Oral steroids Acitretin
Lichen planus of scalp	Oral steroids
Mucosal lichen planus	Dapsone and steroids in orabase Oral steroids Acitretin

* PUVA: Psoralen and ultraviolet A (UVA); not to be used in children of <6 yr of age. Ultraviolet B (UV B)

Pityriasis Rosea

Pityriasis Rosea is a common self limiting papulosquamous disorder, associated with infection with human herpes viruses (HHV-7, HHV-6). The illness, usually between 10 and 35 yr, begins with a 'herald patch' in 80% cases. Lesion is characteristically oval, wrinkled with a collarette of scales at the periphery. This is followed by multiple oval to round smaller scaly secondary eruptions. Their arrangement is characteristic lesions run downwards and outwards from the spine (Christmas tree appearance) along lines of cleavage. The condition resolves spontaneously within 2–10 weeks. No treatment is usually required. Oral antihistamines, calamine lotion and topical steroids may be used to decrease itching. Exposure to sunlight makes the lesions resolve more quickly. Recalcitrant lesions may be treated with ultraviolet light.

Pemphigus Vulgaris

This is the most common variant of pemphigus, accounting for over 80% cases. The condition is characterized by IgG antibodies against desmogleins 3 and 1, which are cell-to-cell adhesion molecules. Patients show flaccid bullae on normal looking skin, which rupture early to form crusted erosions. The usual sites are scalp, face, flexures and trunk. Oral lesions might antedate skin lesions in 50% of patients and eventually 80–90% of patients develop oral lesions. Mucosal lesions are characteristically painful erosions with ragged margins.

The therapy of pemphigus vulgaris is supportive, including maintaining water and electrolyte balance and controlling systemic infections. Treatment with corticosteroids, either as daily dose or monthly bolus is recommended. Occasionally therapy with azathioprine, methotrexate and cyclophosphamide is required.

Chronic Bullous Disease of Childhood

This blistering disorder is characterized by linear deposition of IgA in the basement membrane. The condition is seen in children less than 5 yr of age with slight female preponderance. The lesions are itchy, tense bullae on an erythematous base. New lesions appears around previous lesions resulting in a 'string of pearl' appearance. The lesions are usually grouped around the orifices (perioral, perinasal, perigenital or perianal). They are also frequently seen on lower abdomen, buttocks, knees and elbows. The oral mucosa is involved in one-half cases. The illness resolves within 2 yr of onset in most cases. Patients with mild disease are treated with dapsone (1–2 mg/kg), while those with extensive disease required combined therapy with dapsone and oral corticosteroids.

DISORDERS OF PIGMENTATION

Vitiligo

It affects both sexes equally and peak incidence is between 10 and 30 yr. A positive family history is present in 20–30% patients. Vitiligo is associated with other autoimmune disorders, e.g. thyroid disorders and alopecia areata, suggesting an autoimmune etiology.

The lesions are characterized by depigmented (chalky white or pale white) macules with sharp scalloped margins, which might coalesce to form geographical patterns. Lesional hair may be depigmented (leukotrichia). Lesions may be present anywhere on the body, but areas prone to trauma are most susceptible. The lesion may be focal (≥1 macules at a single site), segmental (unilateral, dermatomal usually along distribution of mandibular division of the facial nerve), acrofacial (periorificial and acral) (Fig. 25.38) and universalis (extensive, generalized due to confluence of patches).

The course is slowly progressive, though can sometimes progress rapidly. Spontaneous pigmentation is seen in 10% of patients. Segmental vitiligo has a stable course. Patients with vitiligo should be examined for cutaneous associations (alopecia areata, atopic dermatitis), endocrine disorders (diabetes mellitus, Addison disease, hypo-parathyroidism and thyroid disorders) and pernicious anemia.

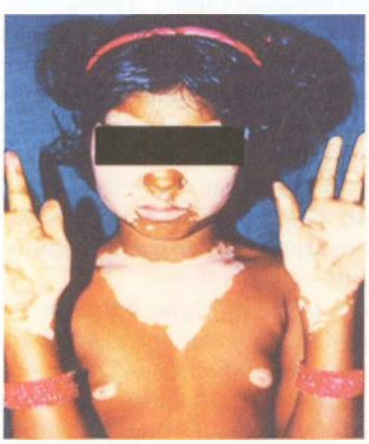

Fig. 25.38: Acrofacial vitiligo: Involvement of face and acral parts

Treatment

Predictors of poor prognosis include long-standing disease, leukotrichia and lesions on resistant areas (bony prominences, nonhairy, nonfleshy areas and mucosae). The patient and family should be reassured. Sunscreens and cosmetic cover up may be needed. The treatment of vitiligo is shown in Table 25.14.

Table 25.14: Treatment of vitiligo

Localized disease	
New lesions	Topical steroids, topical calcineurin inhibitors
Old lesions	Topical PUVA*/PUVA sol
Extensive disease	
New lesions	Oral steroids + PUVA*/PUVA* sol or narrow band UVB
Rapid increase	Oral steroids + PUVA*/PUVA* sol or narrow band UVB
Old lesions	Oral PUVA*/ PUVA* sol or narrow band UVB
Intolerance to PUVA	Oral steroids

*PUVA/PUVA sol: Psoralen and ultraviolet A (UVA) or sunlight; not to be used in children <6 yr of age

In refractory but stable patients of non segmental vitiligo and stable segmental vitiligo surgical techniques like punch grafting, split skin grafting, blister grafting and melanocytes transfer can be tried.

Freckles and Lentigines

Both are characterized by presence of discrete hyper-pigmented macules. Lesions of freckles are seen in red haired, very fair children. Lentigines show no such predilection. Lesions of freckles are seen in light exposed parts of body (face, V of neck and dorsolateral aspect of forearms) with conspicuous absence on covered skin. Lentigines do not show predilection and may be seen on mucosae (Peutz-Jeghers syndrome). Freckles (Fig. 25.39) are lighter, with less delineated edges and show variegation in color including darkening on sun exposure. Lentigines are darker, sharply defined and do not darken on sun exposure. Lentigines may be a cutaneous marker of multisystem syndromes.

DRUG ERUPTIONS

Drug eruptions are adverse events that occur after systemic or topical administration of a drug (Table 25.15).

Diagnosis

Diagnosis is based on clinical features and temporal relation to drug use. Though any drug can cause a reaction

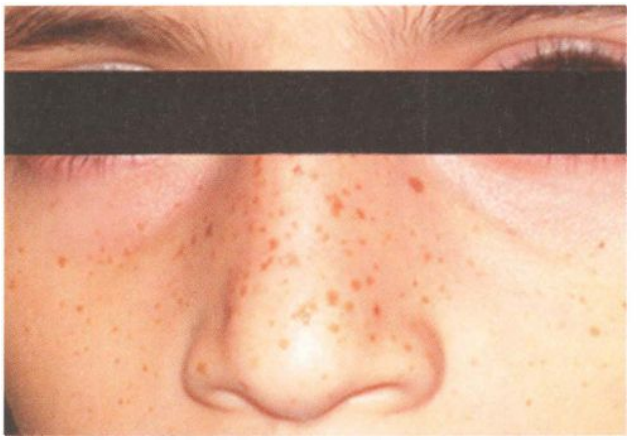

Fig. 25.39: Freckles: Discrete hyperpigmented macules with variegation in color on the face of a fair child

after any length of treatment, some drugs are more suspect and the most recent introduction the most likely cause. The role of drug provocation test is controversial but may be needed to find the culprit drug in patients on multiple drugs as well as to find safe alternative drugs.

Treatment

Withdrawal of drug is most effective approach but is not easy as the child may be taking several drugs or the suspected drug may be difficult to withdraw. A chemically unrelated substitute may not be available.

Symptomatic therapy is provided using antihistaminics. Therapy for anaphylactic reactors might be required. In patients with Stevens-Johnson syndrome—toxic epidermal necrolyses complex, treatment includes maintenance of fluid-electrolyte balance and wound care. The role of systemic steroids is controversial. Intravenous immunoglobulins and cyclosporine have also been used successfully.

INFECTIONS

Skin can be infected with bacteria, virus, and fungi.

Pyodermas

Based on morphology and extent of infections, pyodermas are classified as shown in Table 25.16.

The causative organisms include *S. aureus* or *S. pyogenes* or both. Predisposing factors underlying include skin disease (scabies, atopic dermatitis, pediculosis), poor hygiene, and systemic diseases (diabetes, immune deficiencies). Clinical features of different types of pyodermas are discussed in Tables 25.17 to 25.19.

Table 25.16: Classification of pyodermas

	Superficial	*Deep*
Follicular		
Folliculitis	Superficial	Deep
Perifolliculitis	Furuncle	Carbuncle
Nonfollicular		
Spreading	Erysipelas	Cellulitis
Localized	Impetigo contagiosa	Ecthyma
	Bullous impetigo	

Table 25.15: Common drug eruptions

Pattern	*Morphology*	*Drugs implicated*
Exanthematous eruptions	Symmetric erythematous macules and papules surmounted by scales	Penicillins, sulphonamides, anticonvulsants, antitubercular drugs, gold, gentamicin, cephalosporins, barbiturates
Erythroderma (exfoliative dermatitis)	Entire skin (>90%) is erythematous, scaly and edematous	Penicillins, barbiturates, isoniazid, gold, carbamazepine, isoniazid, griseofulvin
Stevens-Johnson syndrome—toxic epidermal necrolysis (SJS-TEN) complex	Initial lesions often targetoid, followed by diffuse, intense erythema. Flaccid blisters, followed by large areas of skin denudation; mucosae always involved	Sulphonamides, penicillin, quinolones, barbiturates, phenytoin, carbamazepine, lamotrigine, frusemide, hydralazine, oxicam derivatives and COX-2 inhibitors, terbinafine, griseofulvin
Fixed drug eruption	Well demarcated, erythematous plaques; subside with hyperpigmentation; recur at same site each time the implicated drug is taken	Barbiturates, tetracyclines, salicylates, penicillin, erythromycin, griseofulvin, dapsone, paracetamol
Photosensitive eruption	Pruritic papules and plaques on sun-exposed areas	Thiazides, sulphonamides, tetracyclines, quinolones, phenothiazines, psoralens, NSAIDs, amiodarone
Vasculitis	Palpable purpura, urticarial vasculitis, necrotic ulcers, nodular vasculitis	NSAIDs, phenytoin, tetracyclines, ampicillin, carbamazepine, erythromycin, griseofulvin, levamisole
Urticaria and angioedema	Occur independently or along with bronchospasm and circulatory collapse (anaphylaxis)	Aspirin, ACE inhibitors, indomethacin, opiates, penicillin, antifungals, vaccines with egg proteins

Table 25.17: Clinical features of follicular pyodermas

	Folliculitis	*Furuncle*
Clinical features	Erythematous follicular papules, often surmounted by pustules (Fig. 25.40)	Firm red follicular nodules which discharge pus and heal with minimal scarring
Sites of predilection	Face, lower extremities	Buttocks, lower extremities

Table 25.18: Clinical features of spreading pyodermas

	Erysipelas	*Cellulitis*
Clinical features	Tender, warm, erythmatous rapidly spreading plaques; superficial vesiculation; constitutional symptoms	Red, hot, edematous, rapidly spreading, ill defined deep plaques; constitutional symptoms
Sites of predilection	Face	Lower extremities

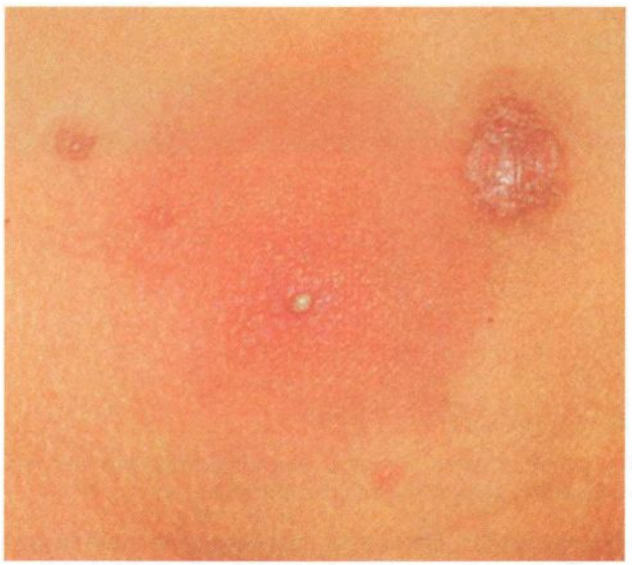

Fig. 25.40: Folliculitis: Erythematous follicular papule, often surmounted by pustules

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Treatment

General measures for treatment include local hygiene, rest and limb elevation in case of spreading pyodermas and NSAIDs, if pain and constitutional symptoms are present. Topical antibiotics like mupirocin, sodium fusidate and nadifloxacin are used for localized lesions. Patients with extensive spreading lesions, in presence of constitutional symptoms require therapy with systemic antibiotics.

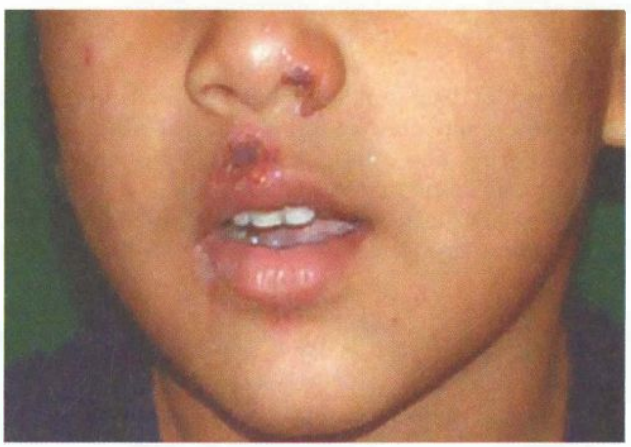


Fig. 25.41: Impetigo contagiosa: Honey colored crusted lesions around mouth

Staphylococcal Scalded Skin Syndrome

The condition is mediated by hematogenously spread exotoxin produced by *S. aureus* present in infected site distant from the involved skin (e.g. otitis media, pneumonitis) and rarely in skin. The disorder usually affects newborns and infants <2 yr of age. Erythema and tenderness is followed by superficial peeling of skin in thin

Table 25.19: Clinical features of nonfollicular pyoderma

	Impetigo contagiosa	*Bullous impetigo*	*Ecthyma*
Age	Children	Infants	Any age
Clinical features	Thin walled blisters with erythematous halo; rupture to form honey colored crusts (Fig. 25.41)	Thick walled, persistent blisters on bland skin; rupture only after a few days to leave thin varnish like crusts (Fig. 25.42)	Crusted, tender erythematous indurated plaque
	Lesions spread without central clearing	Lesions heal in center to form annular plaques	Lesions heal with scarring
	Lymphadenopathy frequent	Lymphadenopathy rare	
Sites of predilection	Face, especially mouth and nose	Face, other parts of body	Glutei, thighs, legs
Complications	Poststreptococcal glomerulonephritis, eczematization	Staphylococcal scalded skin syndrome	Glomerulonephritis, eczematization, scarring

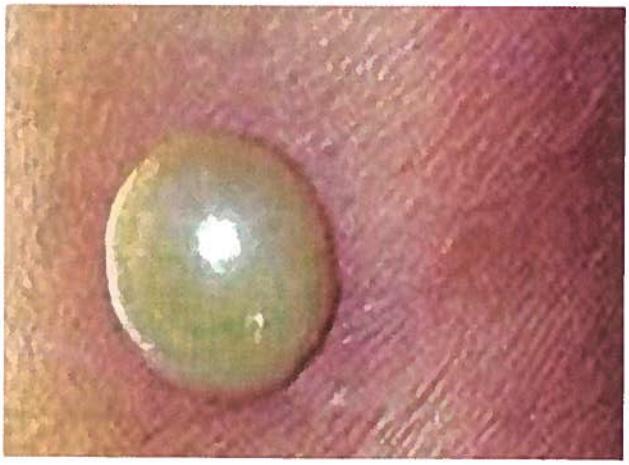


Fig. 25.42: Bullous impetigo: Thick walled, persistent blisters on bland skin

sheets, giving the appearance of scalding (Fig. 25.43). Constitutional symptoms are minimal. Treatment is chiefly supportive. Antistaphylococcal antibiotics are administered initially parenterally then orally.

Cutaneous Tuberculosis

Clinical presentation is highly variable and depends on immunity of the individual as well as route of inoculation of *M. tuberculosis*.

Lupus Vulgaris

Lupus vulgaris is characterized by solitary, well defined, reddish brown plaque on head, neck and glutei, which spreads centrifugally (Fig. 25.44). On diascopy, i.e. pressing the lesion with a clean glass slide, apple jelly nodules are identified. The center becomes atrophic and scarred with time but typically develops nodules.

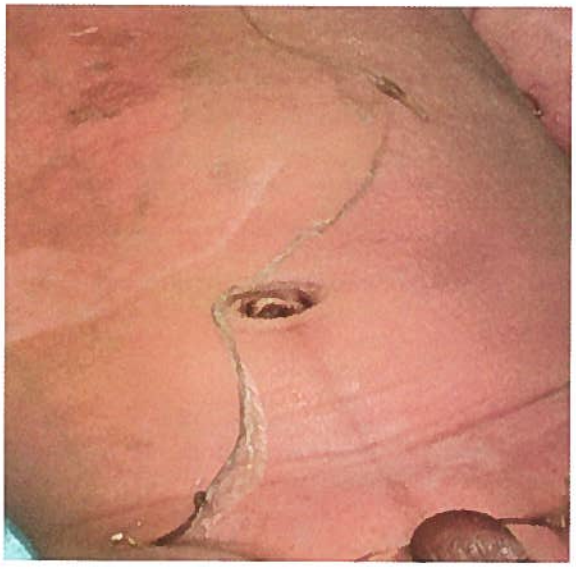


Fig. 25.43: Staphylococcal scalded skin syndrome: Erythema and superficial peeling of skin in thin sheets

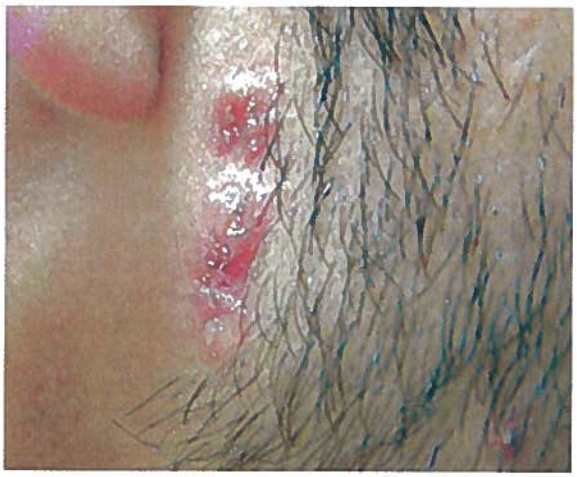


Fig. 25.44: Lupus vulgaris: Solitary, well defined annular plaque with central scarring

Scrofuloderma

Occurs by contiguous spread from tubercular lymph nodes (cervical most frequent), bones (tibia) or joints (sternoclavicular). The condition manifests initially as firm subcutaneous nodules which break open to form sinuses. The mouth of the sinus is serpiginous with undermined edges (Fig. 25.45).

Tuberculosis Verrucosa Cutis

The condition presents as a single warty firm plaque with a violaceous halo. The surface has clefts and fissures that discharge pus. There may be scarring at the center. The diagnosis is confirmed by histopathology. Patients should be evaluated for systemic tuberculosis.

Therapy of cutaneous tuberculosis comprises the use of 4 antitubercular medications (isoniazid, rifampicin,

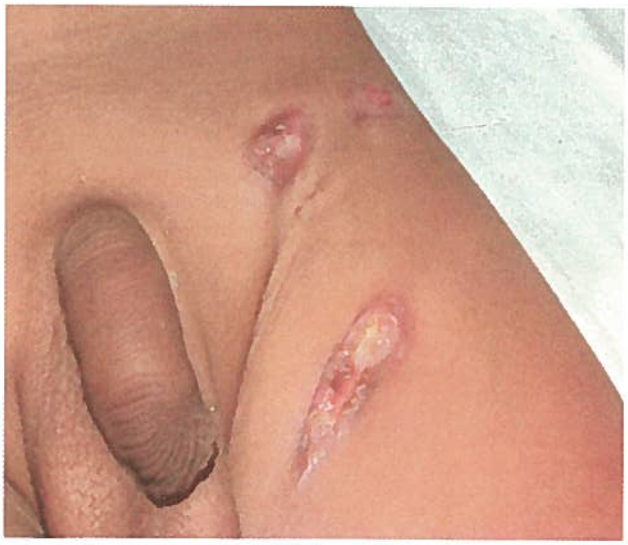


Fig. 25.45: Scrofuloderma: Sinus with mouth showing undermined edge and fixed to underlying lymph node

ethambutol and pyrazinamide) for 8 weeks followed by two agents (isoniazid and rifampicin) for the next 16 weeks.

Leprosy

The mode of transmission of *M. leprae* is uncertain but possibly nasal droplet infection is important. The clinical manifestations depend on the host immunological response. If the host mounts good cell mediated immunity (CMI), the infection is localized while if the CMI is poor, the infection is extensive with visceral involvement.

The Ridley Jopling classification, based on clinico-pathological, immunological and bacteriological parameters, classifies leprosy into indeterminate and determinate forms. The latter is further defined as: (i) polar (stable) leprosy: (a) tuberculoid leprosy (TT); and (b) lepromatous leprosy (LL); (ii) borderline (unstable) leprosy: (a) borderline tuberculoid leprosy (BT); (b) borderline leprosy (BB); (c) borderline lepromatous leprosy (BL).

Skin lesions consist of macules, plaques and nodules which are hypopigmented, erythematous, anaesthetic or hypoesthetic. Skin appendages (hair, sweating) on the lesions are reduced and there is epidermal atrophy. The nerves may be thickened and tender and there may be associated sensory and motor impairment.

Acid-fast bacilli can be demonstrated in some forms (usually LL, BL and less frequently BB). The profile of different clinical types of leprosy is shown in Table 25.20.

Two types of acute episodes (lepra reactions) are seen in course of leprosy. Type 1 lepra reactions characteristically occur in patients with borderline leprosy (BT, BB, BL) following alteration in host CMI. These can thus be an upgrading (reversal reaction) with improvement of CMI or a downgrading reaction (as seen in natural course of disease) when CMI decreases. Patients show edema and erythema of pre-existing lesions and neuritis which may result in sensory and motor impairment.

Type 2 lepra reaction (erythema nodosum leprosum) is an immune complex reaction that occurs in patients with BL and LL. These reactions result in several tender erythematous, transient nodules on face, flexures and legs. Patients may also show neuritis, orchitis, iridocyclitis, arthralgia and fever.

Patients with leprosy may show the following complications:

i. Trophic ulcers
ii. *Deformities:* Claw hand, clawing of toes, foot drop and saddle nose deformity
iii. *Ophthalmologic complications:* Diminished corneal sensation, lagophthalmos, recurrent iridocyclitis
iv. Renal involvement

Table 25.20: Clinical features of leprosy

	Indeterminate	*TT*	*BT*	*BB*	*BL*	*LL*
Skin lesions						
Number	Single	Single/Few	Few	Several	Numerous	Innumerable
Size	Variable	Variable	May be large	Variable	Small	Small
Sensations	Variable	Anesthetic	Hypoesthetic	Hypoesthetic	Hypoesthetic	Normal
Symmetry	Asymmetrical	Asymmetrical	Asymmetrical	Bilateral, asymmetrical	Tendency to symmetry	Symmetrical
Morphology	Hypopigmented macule; usually ill-defined; hypoesthetic; on face (Fig. 25.46)	Macule, plaque; well defined	Plaques; well defined satellite lesions (Fig. 25.47)	Macules, plaque; sloping edge (inverted saucer appearance)	Macules, papules, nodules or plaques; ill-defined	Macules, papules, nodules, plaques; ill-defined; diffuse infiltration of face
Nerves	+/–	Single trunk/ feeder nerve related to lesion; thickened	Asymmetrical; few nerves thickened; anesthesia in its distribution	Asymmetrical; several nerves thickened	Almost symmetrical; several nerves thickened; glove and stocking anesthesia	Symmetrical; several nerves thickened; glove and stocking anesthesia
Systemic involvement	Usually none	None	None	None	Lymphadenopathy, hepatosplenomegaly, ocular and testicular involvement	
Reactions	–	Stable	Type 1	Type 1	Type 1, 2	Type 2
Lepromin	+/–	+	+/–	–	–	–
Acid-fast bacilli	+/–	–	–	+/–	++	+++

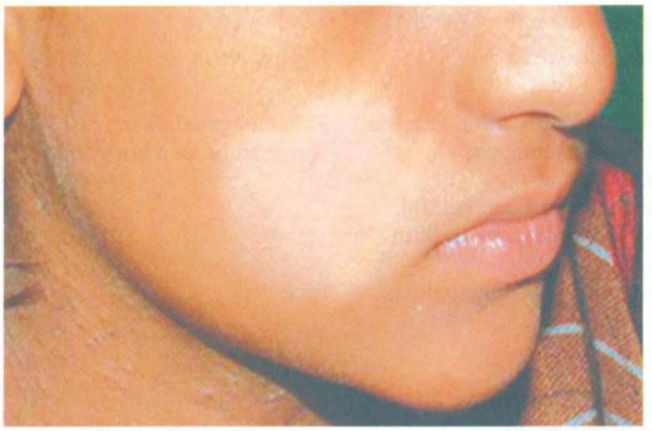


Fig. 25.46: Indeterminate leprosy: Ill-defined hypopigmented, hypoesthetic lesion on the face

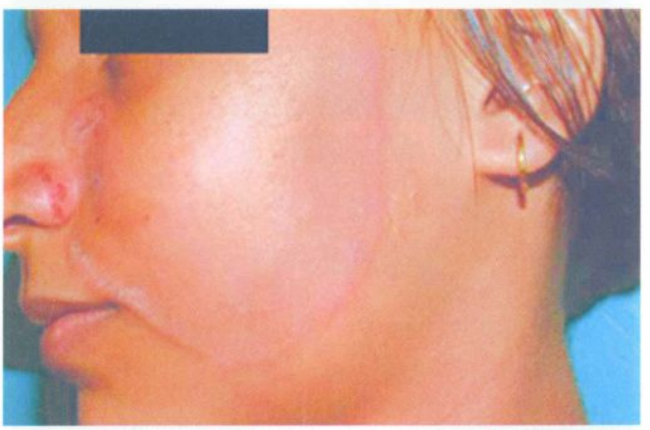


Fig. 25.47: Borderline tuberculoid: Well defined erythematous plaque with satellite lesions

Investigations

Slit skin smears. Slit skin smears, from the lesions and ear lobules, are stained with modified Ziehl-Neelsen method. The smears are usually negative in TT/BT/BB leprosy. The Lepromin test is generally not required for the diagnosis. On histologic examination, perineural granulomas (epitheloid cells in tuberculoid and foamy cells in lepromatous leprosy) are typical, but might not be seen in indeterminate, BL and LL forms.

Treatment

The patient and parentsshould be reassured and counselled regarding treatment compliance and care of hands, feet and eyes. For the purpose of treatment, leprosy is classified into paucibacillary and multibacillary leprosy. Multidrug therapy is instituted based on number of lesions (Table 25.21). Therapy of lepra reactions is shown in Table 25.22.

Table 25.21: WHO recommendations for treatment of leprosy in children aged 10–15 yr

	Paucibacillary	*Multibacillary*
Definition	Five or less lesions	More than 5 lesions
Duration of therapy	6 mo of treatment, to be completed in 9 mo	12 mo, to be completed in 18 mo
Supervised (monthly)	Rifampicin 450 mg	Rifampicin 450 mg and clofazimine 150 mg
Unsupervised (daily)	Dapsone 50 mg	Dapsone 50 mg and clofazimine 25 mg

Doses in children: Rifampicin 10 mg/kg; clofazimine 1 mg/kg daily, 6 mg/kg monthly; dapsone 2 mg/kg

Table 25.22: Treatment of reactions in leprosy

	Type 1 reaction	*Type 2 reaction*
Mild	NSAIDs	NSAIDs
Moderate	NSAIDs Oral corticosteroids	NSAIDs Thalidomide Chloroquine Clofazimine
Severe	NSAIDs Oral corticosteroids	Thalidomide* Corticosteroids Antimony (parenteral)

NSAIDs nonsteroidal anti-inflammatory drugs are avoided
*Thalidomide is a teratogenic agent and avoided in girls in the reproductive age

Verruca (Warts)

Warts are caused by human papilloma virus, of which there are more than 100 types. They are transmitted by close contact and auto-inoculation. In children, nongenital warts are common, with an incidence of up to 10%. The clinical features of various types of warts are listed in Table 25.23.

Molluscum Contagiosum

Patients show multiple pearly white, dome shaped papules with central umbilication (Fig. 25.50). Cheesy material can be expressed from the lesion. The lesions are seen on any part of the body. Widespread lesions are seen in atopic dermatitis and immunocompromised patients. The condition is self limiting, and clears within an one-yr. Therapy comprises Wart paint or mechanical extirpation under cover of a topical anesthetic.

Herpes Simplex Virus (HSV) Infections

HSV infection can be asymptomatic and when symptomatic, the manifestations depend on whether the infection is primary or recurrent. Primary type 1 infection may present as acute gingivostomatitis with closed grouped vesicles on an edematous base which rupture to form polycyclic erosions (Fig. 25.51). There may be associated malaise, fever and lymphadenopathy. Patients with herpes simplex labialis have a prodrome of burning and stinging followed by grouped vesicular lesions with background of slight erythema. These lesions may evolve into erosions

Table 25.23: Clinical features and therapy of warts

	Verruca vulgaris (common warts)	*Verruca plana (plane warts)*	*Palmoplantar warts*	*Filiform warts*
Clinical features	Single or multiple firm papules with hyperkeratotic, clefted surface (Fig. 25.48)	Skin colored, flat smooth palpable papules (Fig. 25.49); Koebner phenomenon due to autoinoculation	Superficial (mosaic): Painless, hyperkeratotic papules and plaques Deep (myrmecia): Painful, deep seated papules with collar	Thin elongated, firm projections on a horny base
Site	Any part of body, most commonly back of hands, fingers and knees	Face and back of hands	Soles and less often palms	Face
Therapy	Cryotherapy, electric cautery and radiofrequency ablation	Trichloroacetic acid touches; retinoic acid (0.025–0.05%) at night	Wart paint; cryotherapy; formalin soaks	Electric cautery; radiofrequency ablation

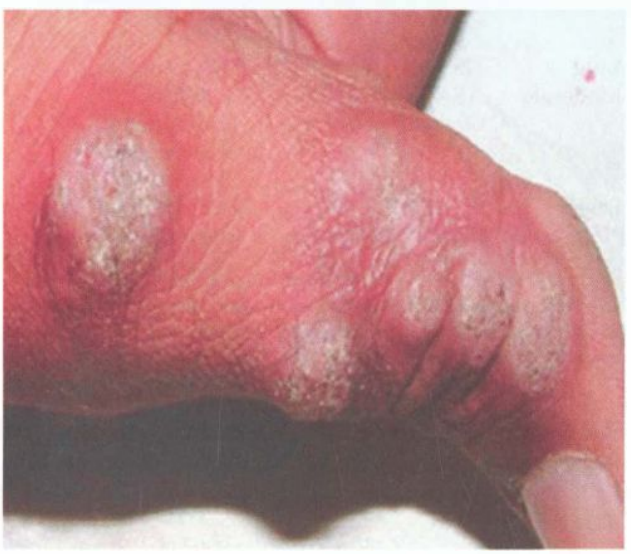


Fig. 25.48: Verruca vulgaris: Firm papules with hyperkeratotic, clefted surface

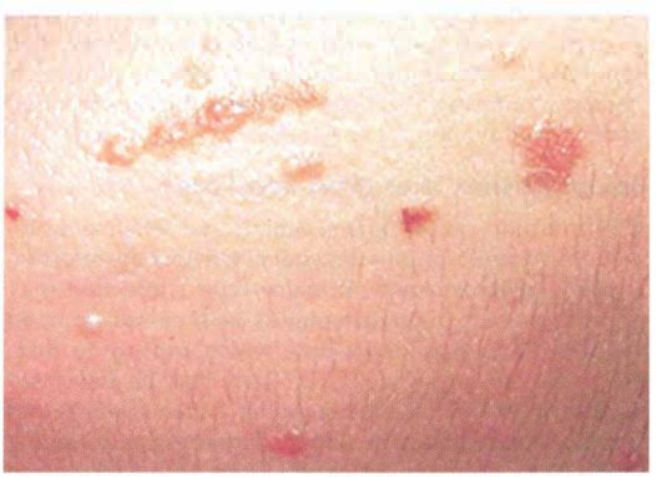


Fig. 25.49: Verruca plana: Multiple skin colored papules

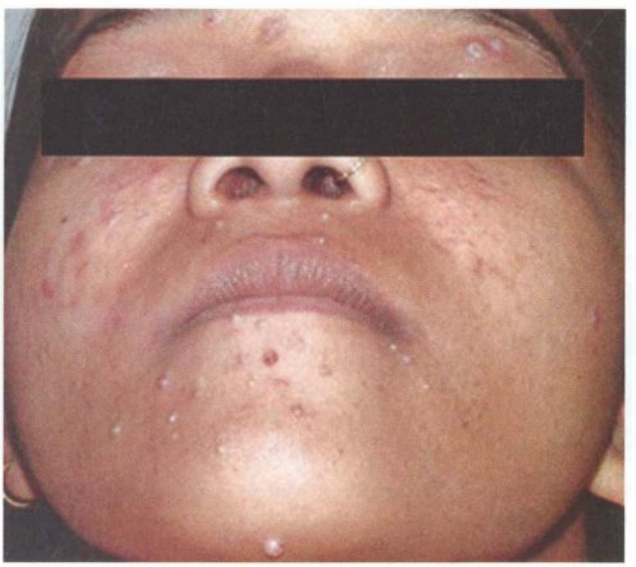


Fig. 25.50: Molluscum contagiosum: Pearly white dome shaped papules with central umbilication

with polycyclic margins, leaving area of depigmentation after healing (Fig. 25.52). No treatment is generally required, except in severe infection or immunocompromised patients where treatment with oral acyclovir may be given for 5–7 days.

Dermatophytoses

Three genera of fungi cause dermatophytoses *Trichophyton, Epidermophyton and Microsporum*. The infection is given different names depending on the site affected. Dermatophyte infection of skin is known as *tinea corporis*, of groin as *tinea cruris*, of hands as *tinea manuum*, of feet as *tinea pedis* and of nails as *tinea unguium*. The classical lesion is an annular or arcuate plaque with a clear center and an active edge showing papulovesiculation and scaling.

Tinea Capitis

Three patterns are commonly seen:

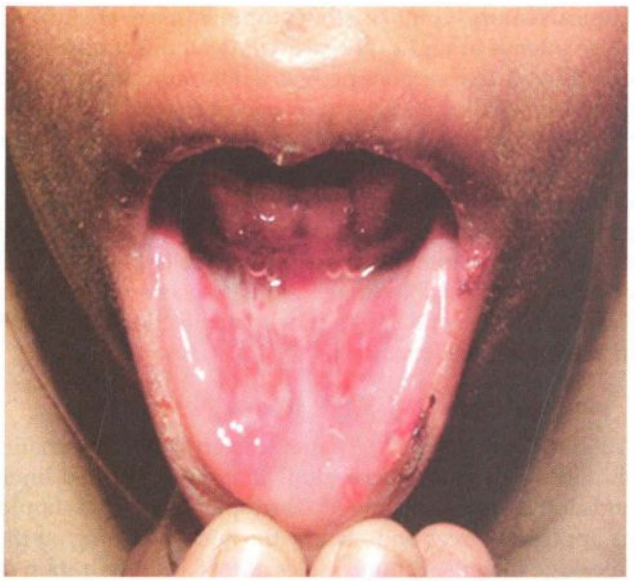


Fig. 25.51: Herpes gingivostomatitis: Closed grouped vesicles on an edematous base which coalesce to form polycyclic erosions

Noninflammatory or epidemic type. Caused by anthropophilic organisms and so is responsible for epidemics. It presents as a patch of alopecia with marked scaling at periphery (Fig. 25.53). Hairs break off easily and inflammation is minimal.

Inflammatory or kerion. Caused by zoophilic organisms and so does not cause epidemics. It presents as a boggy swelling which drains pus from multiple openings (Fig. 25.54). Hair is easily pluckable without pain. Usually associated with occipital lymphadenopathy.

Favus. Caused by *T. schoenleinii*, presents as yellowish, foul smelling cup-shaped crusts with matting of hair.

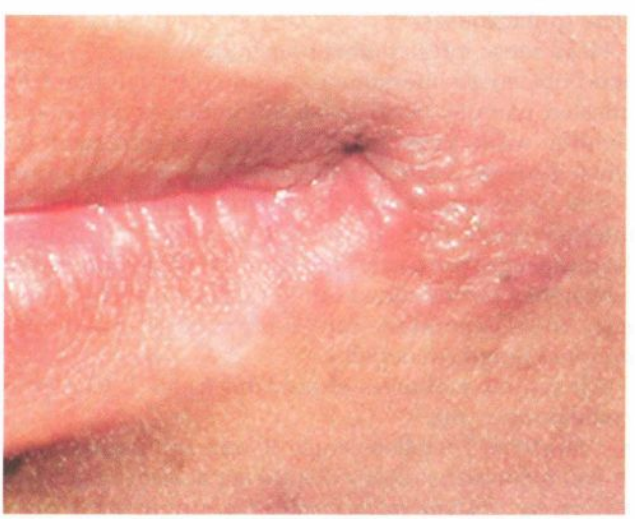


Fig. 25.52: Herpes labialis: Polycyclic area of hypopigmentation and vesicular lesions

Tinea Corporis

Shows classical features of tinea and is most frequent on exposed parts. Infection of face is common in children. The diagnosis is confirmed by the KOH test that shows fungal hyphae. Culture helps in identification of species and this is important in patients with tinea capitis.

The therapy of tinea capitis comprises griseofulvin (15 mg/kg/day of ultramicrosized formulation) for a duration of 8 weeks. Terbinafine (5 mg/kg/day for 4 weeks) is effective in noninflammatory tinea capitis. Longer treatment (8 weeks) is needed for kerion. Use of terbinafine in children is hindered by absence of liquid formulation and an unpleasant aftertaste of the tablet. Washing with ketoconazole shampoo helps to reduce transmission. Sharing of combs and head wear should be avoided.

Localized lesions of tinea corporis are managed by topical therapy (azoles available as clotrimazole,

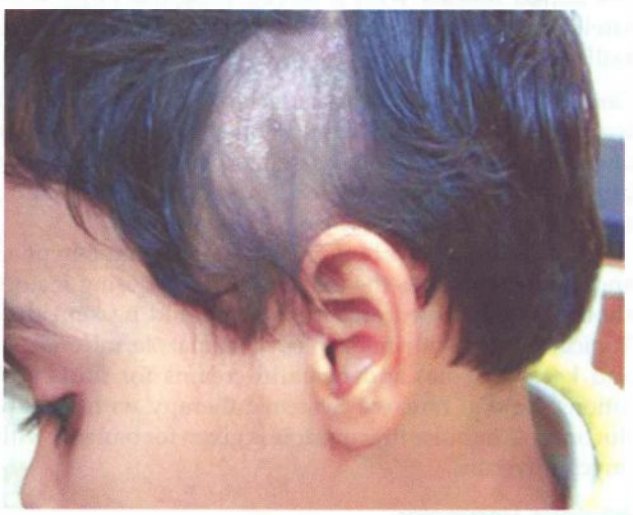


Fig. 25.53: Tinea capitis: Area of nonscarring alopecia with minimal inflammation

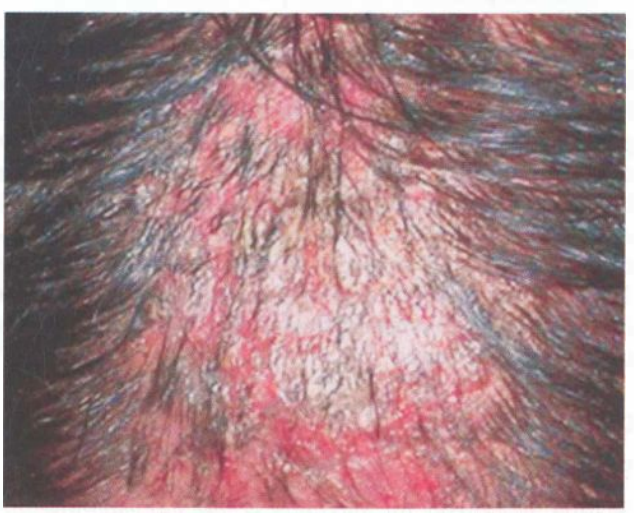


Fig. 25.54: Kerion: Boggy swelling of scalp

miconazole or ketoconazole in lotion, gel and cream formulations). Widespread lesions require systemic antifungal therapy with terbinafine (2 weeks) or griseofulvin (for 4 weeks).

Candidiasis

Candida albicans, a normal commensal becomes pathogenic in the presence of predisposing factors that include obesity, diabetes and immunocompromised states. Less frequently other species like *C. glabrata* may be involved. In children, candidiasis presents as oral thrush, vulvovaginitis, intertrigo, candidal diaper dermatitis or paronychia.

Oral thrush presents as soft, creamy white to yellow, elevated plaques, that are easily wiped off to leave an erythematous, eroded or ulcerated surface. The lesions are seen on buccal mucosa, tongue, palate and gingiva.

Candidal intertrigo presents as erythematous, moist, macerated lesions with a frayed irregular edge with satellite pustules, chiefly present in major skin folds, like axillae, groins and neck.

25

Candidal diaper dermatitis is characterized by well defined weeping eroded lesions with scalloped border and a collar of overhanging scales and satellite pustules. The lesion begins in the perianal region, spreading to perineum, upper thighs, lower abdomen and lower back.

The KOH test shows budding yeasts and pseudohyphae and culture confirms the diagnosis. Predisposing factors should be addressed and the area should be kept dry. Topical therapy with imidazoles (clotrimazole, miconazole and ketoconazole) and nystatin creams for folds and lotions for oral mucosa. Systemic therapy with weekly fluconazole or pulse itraconazole is given for patients with onychomycosis.

Pityriasis Versicolor

This condition is caused by commensal yeast, *M. furfur*. Adolescents present with scaly, perifollicular macules with variable pigmentation (hypopigmented, erythematous or hyperpigmented). The fine branny scales are accentuated by gentle abrasion with a glass slide. The lesions are frequently seen on upper torso (both anterior and posterior), neck and sometimes also on proximal part of upper extremities. KOH mount shows a mixture of short branched hyphae and spores (spaghetti and meatball appearance). Topical therapy with imidazoles (keto-conazole 2%) for 3 consecutive days or selenium sulfide 2.5% lotion applied once a week for 4 weeks is sufficient in most cases. Systemic therapy with fluconazole is occasionally required.

DISEASES CAUSED BY ARTHROPODS

Scabies

Scabies is caused by *Sarcoptes scabei* var *hominis* and transmitted by close contact with infested humans. Clinical features comprise the symptoms of severe itching, more intense at night. The primary lesion is a burrow, a grey thread like serpentine line with a minute papule at the end; papules and papulovesicles may also be seen. Secondary lesions consist of pustules, eczematized lesions and nodules. Lesions are seen in webs of hands, on wrists, ulnar aspects of forearms, elbows, axillae, umbilical area, genitalia, feet and buttocks. Face is usually spared except in infants in whom scalp, palms and soles (Fig. 25.55A) are also involved. Nodular lesions are seen on genitalia (Fig. 25.55B). Secondary streptococcal infection may result in acute glomerulonephritis.

Treatment

All close contacts of the patient, even if asymptomatic, should be treated. Overzealous laundering of bed linen and clothes is not warranted. The topical scabicide should be applied all over body below the neck including on the free edge of nails, genitals, soles of feet after hydration of body with a bath. Scabicides available include:

Permethrin 5%. Overnight single application is treatment of choice beyond 2 months of age.

Crotamiton 10%: Two applications daily for 14 days, is recommended for infants less than 2 months.

Benzyl benzoate 25%. Three applications at 12 hourly intervals.

Ivermectin, single oral dose of 200 µg/kg body weight, in children older than 5 yr is the treatment of choice for epidemics (as in orphanages). Antibiotics are given, if secondary infection is present. Antihistamines are given for 1–2 weeks to reduce pruritus.

Pediculosis

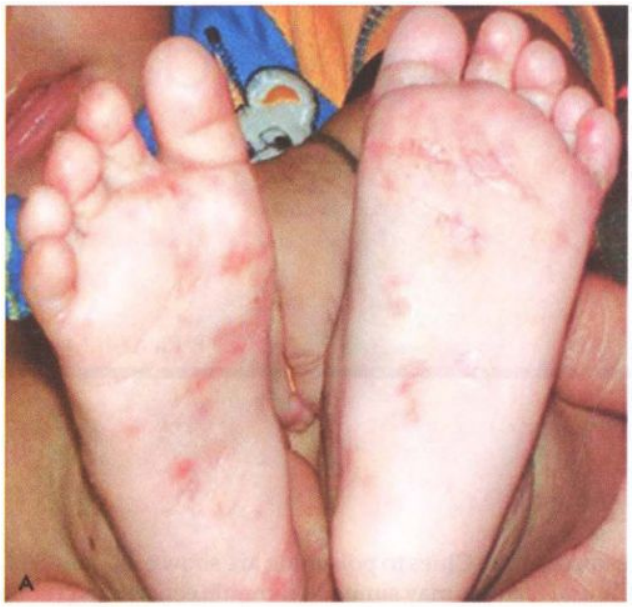
Louse is an obligate ectoparasite and two species infest humans: *Pediculosis humanus* (*P. humanus capitis*, head louse and *P. humanus corporis*, body louse), and *Phthirus pubis* (pubic louse)

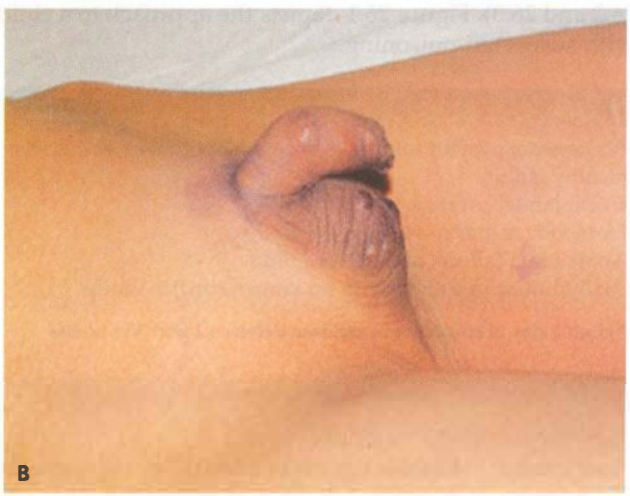
Head louse infestation is transmitted by close contact and pubic louse infestation is acquired by children from infested parents. Head louse infestation is common in children while pubic louse infestation is infrequent but when it occurs it also involves eyelashes and eye brows.

The chief symptoms are severe pruritis involving infested region. Though adult lice are difficult to find, nits (egg-capsules) are easily seen firmly cemented to hair on which they can be slided but not flicked off. The lesions may show secondary infection, eczematization and occipital lymphadenopathy.

All family members should be treated. The chief pediculocides are:

- *Permethrin,* 1% lotion, single 10 min application to wet hair followed by rinsing. Repeat application after 7 days.
- *Gamma benzene hexacloride,* 1% single over night application to dry hair followed by rinsing. Second application used after 7 days.





Figs 25.55A and B: Infantile scabies. (A) Multiple papulovesicular lesions on soles; (B) nodular lesions of genitalia

- *Malathion,* 0.5% water based lotion, applied on dry hair for 6 hr. Has residual effect, so second application is not needed.

Petrolatum (twice daily for 7–10 days) is used, with good results, for eyelash infestation. The petrolatum covers the lice and their nits, preventing respiration. The dead lice are removed mechanically with a pair of tweezers.

Papular Urticaria

Papular urticaria is due to bites of arthropods such as mosquitoes and fleas. An initial itchy urticarial weal that develops at the site of bite evolves into a firm pruritic papule, which persists for several days. The lesion often has a central hemorrhagic punctum (Fig. 25.56) and may be surmounted by a tiny vesicle.

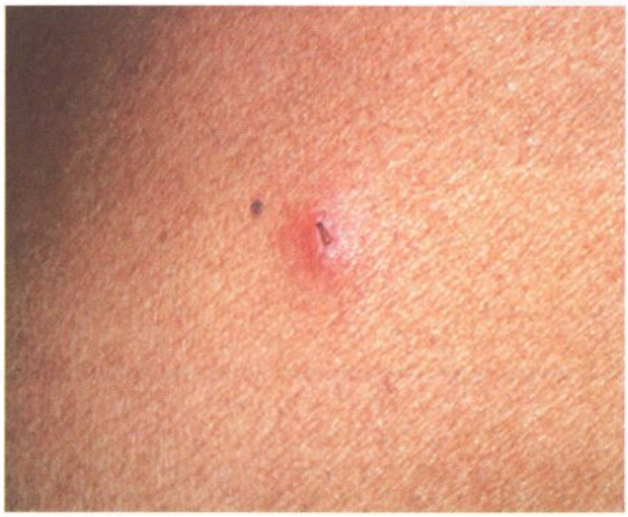


Fig. 25.56: Papular urticaria: Papule with a central hemorrhagic punctum

Complications. Secondary infection, eczematization, hyperpigmentation and hypopigmentation, particularly in darkly pigmented individuals are not uncommon. New bites by the same species often causes a recrudescence of activity in existing and even healed lesions.

Prevention of repeated insect bites through use of protective clothings, judicious use of insect repellents and treatment of pets with infestation is recommended. Topical steroids combined with topical antibiotics may help with individual lesions. Oral antihistaminics help in reducing pruritus and hypersensitivity reaction.

Pityriasis Alba

Ill-defined hypopigmented macules with fine scales are seen on face, in children 2–6-yr-old. The lesions are asymptomatic and clear up spontaneously after a few months or in some cases 2–3 yr. The family is reassured regarding the benign nature of the illness. Mild emollients may be useful in some cases.

Suggested Reading

Bhutani LK, Khanna N. Bhutani's Color Atlas of Dermatology, 5th edn. Mehta Publishers, New Delhi, 2006

Grichnik JM, Rhodes AR, Sober AJ. In: Fitzpatrick's Dermatology in General Medicine, Wolff K, eds. McGrawhill Medical, New York; 2008: 1099–109

Khanna N. Illustrated Synopsis of Dermatology and Sexually Transmitted Diseases. 4 edn. Elsevier, New Delhi, 2011

26 Poisonings, Injuries and Accidents

P Ramesh Menon

Accidents, poisoning, vehicular trauma and falls are an important cause of childhood mortality and morbidity. Toddlers are especially predisposed as they are mobile, inquisitive and cannot differentiate between harmful and harmless things. It is important to implement strategies involving careful supervision and interventions to reduce incidence of accidents and poisoning, especially in children less than 5-yr-old.

A *poison* is any agent of self-injury absorbed into the body through epithelial surfaces. *Toxins* are poisons produced by a natural biological process. *Venoms* are toxins that are injected by a bite or sting to cause their effect. An *accident* is a sudden unexpected event of an afflictive or unfortunate character by chance occurrence.

POISONING

Poisoning in children in developing countries is usually caused by ingestion of pesticides and plants while pharmaceuticals and chemicals form the major cause of poisoning in the developed world. Common causes of poisoning in children are household products including kerosene oil, drugs (particularly barbiturates), chemicals (corrosives) and pesticides (organophosphate compounds). Majority of poisons are ingested by children at home and include products that are familiar and visually appealing due to glossy packaging. Nontoxic household items (like nail polish, shampoo, ink) are also consumed by toddlers. Two distinct patterns of poisoning are observed. While children younger than 11 yr usually have accidental poisoning, toxic exposures in adolescents are primarily intentional (suicide, abuse) or occupational.

Databases on toxicology, hazardous chemicals, environmental health and toxic releases are available at *www.toxnet.nlm.nih.gov.*

Diagnosis

Identification of poisoning in children requires a high index of suspicion since history of ingestion of a chemical is uncommon. Clues to poisoning are shown in Table 26.1. Clinical features may simulate common conditions (Tables 26.2 and 26.3). Figure 26.1 depicts the approach to a child with suspected poisoning.

Table 26.1: Clues to poisoning in children

Acute onset of symptoms (e.g. encephalopathy) in a otherwise healthy child*
Unexplained multisystem involvement
Metabolic acidosis
Acute renal failure; acute liver failure
Arrhythmias in a child with no known cardiac illness

* High index of suspicion in children between 1 and 3 yr of age

Table 26.2: Clinical clues to nature of poisoning

Features	*Toxin*
Bradycardia	Digitalis, organophosphates, β-blockers, opioids
Tachycardia	Atropine, salicylate, amphetamine
Tachypnea	Salicylate, ethylene glycol
Apnea	Barbiturates, alcohol, opioids
Hypothermia	Barbiturates
Fever	Atropine, organophosphates, salicylates, theophylline, quinine
Flushed skin	Carbon monoxide, cyanide
Cyanosis	Methemoglobinemia, carbon monoxide
Diaphoresis	Organophosphates, salicylates
Hypertension	Phenylpropanolamine, anticholinergics
Miosis	Organophosphates, opioids, barbiturates
Mydriasis	Atropine, amphetamines, alcohol
Ataxia	Phenytoin, alcohol, barbiturates, anticholinergics
Paralysis	Botulism, heavy metals
Seizures	Ecstasy
Spasms	Strychnine
Diarrhea	Arsenic
Jaundice	Acetaminophen, carbon tetrachloride
Characteristic smell	Methanol (acetone), cyanide (bitter almonds), alcohol, kerosene, organophosphate or arsenic (garlic)

Table 26.3: Common toxidromes (constellation of signs and symptoms in a category for toxin identification)

Findings	*Adrenergic*	*Anticholinergic*	*Anticholinesterase (cholinergic)*	*Opioid*	*Sedative, hypnotic*
Heart rate	↑	↑	↓	↓	Arrhythmia, QT prolongation
Temperature	↑	↑	Normal	Normal	Normal
Pupil	Dilated	Dilated	Constricted	Constricted	Dilated
Mucosa	Wet	Dry	Wet	Normal	Normal
Skin	Diaphoresis	Dry	Diaphoresis	Normal	Normal
Respiratory	Tachypnea	Tachypnea	Wheeze, tachypnea increased secretions	Hypoventilation	Hypoventilation
Neurologic	Agitation, tremors, seizures, hallucinations	Agitation, hallucinations	Coma, fasciculations	Sedation	Convulsions, coma, myoclonus, hyperreflexia

↑ = Increased; ↓= Decreased

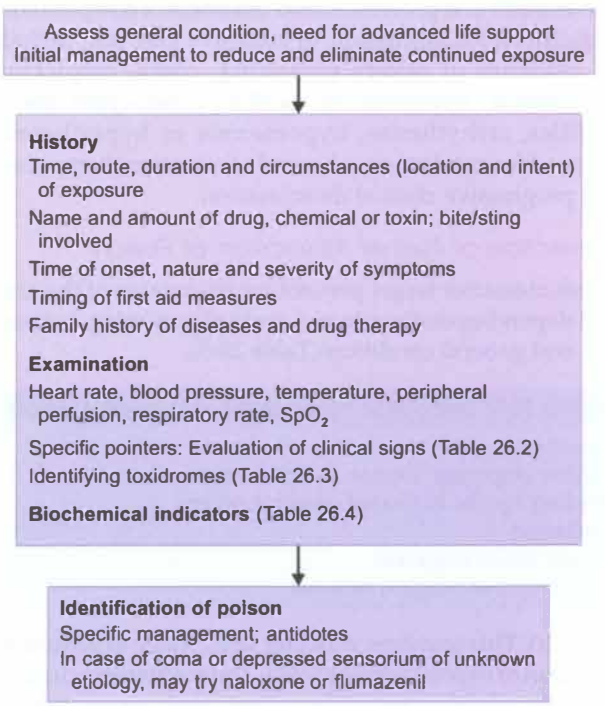


Fig. 26.1: Approach to a child with suspected poisoning

Bedside Screening Tests

Urine Tests

Urine should be examined for abnormal color. In phenol poisoning, urine turns smoky dark green on standing. Oxalate crystals suggest the possibility of ethylene glycol poisoning. Ketones in urine suggest exposure to acetone, salicylate or isopropyl alcohol. *Ferric chloride test* may help in identifying the incriminated toxin and requires the addition of 5–10 drops of freshly prepared 10% ferric chloride solution to 10 ml of boiled and acidified urine. Change of color to red suggests exposure to salicylates; purple green color indicates phenothiazine overdose and violet suggests phenol exposure.

Blood Tests

Measurement of anion gap and osmolal gap detects accumulation of unmeasured ions and osmotically active agents in blood. Blood appears chocolate color in patients with methemoglobinemia. This turns pink on addition of potassium cyanide.

Gastric Aspirate

Addition of two drops of 30% hydrogen peroxide and deferoxamine (0.5 ml, 125 mg/ml) to 1 ml of gastric fluid leads to color change in the gastric aspirate of a patient with iron poisoning.

Laboratory Evaluation

Poisoning is associated with accumulation of toxins in the body. The aim of laboratory evaluation is to identify the toxin, assess the amount of exposure and detect organ dysfunction and metabolic derangements produced by the toxin. Initial samples in any child with suspected poisoning should include vomitus or gastric aspirate for identification of the incriminated agent and urine and blood for qualitative and quantitative assessment, respectively.

Complete blood counts, ECG, chest X-ray, liver and renal function tests and blood gas analysis should be performed. Toxins may produce characteristic abnormalities that help in their identification (Table 26.4).

Management

Early suspicion and appropriate management are essential. General measures should be instituted immediately, since early treatment is associated with improved outcomes.

Principles

All patients are treated as medical emergencies. Based on the child's general condition, triage is done. If the child is brought in the *pre-toxic phase*, decontamination is the highest priority and treatment is based on history. The maximum potential toxicity based on greatest possible

Table 26.4: Laboratory pointers to identification of toxins

Observation	*Possible toxin*
Hypocalcemia	Ethylene glycol, oxalate
Hypokalemia	Beta agonists, diuretics, theophylline
Hyperkalemia	Beta blockers, digoxin, alpha agonist
Hyperglycemia	Acetone, theophylline, calcium channel blockers
Hypoglycemia	Oral hypoglycemic agents, ethanol, quinine, salicylates
Hyperglycemia with ketoacidosis	Salicylate, theophylline
Increased anion gap	Methanol, ethanol, ethylene glycol, salicylate, isoniazid, iron
Decreased anion gap	Lithium, bromide
Increased osmolal gap	Mannitol, ethylene glycol, isopropyl alcohol, glycerol, acetone, sorbitol
Pulmonary edema	Carbon monoxide, cyanide, irritant gas
Radiopaque density	Calcium, heavy metal
Bradycardia, atrioventricular block	Beta blockers, digoxin, calcium channel blockers
Prolonged QRS complex	Hyperkalemia, membrane active agents
Abnormal liver enzymes	Paracetamol

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exposure should be assumed. During *toxic phase*, the time between the onset of poisoning and peak effects, management is based primarily on clinical and laboratory findings. Resuscitation and stabilization are the first priority. During *resolution phase*, supportive care and monitoring should continue until clinical and laboratory abnormalities have resolved.

Components of management include: (i) provision of basic life support and supportive care; (ii) prevention of further poison absorption; (iii) enhancement of poison elimination; (iv) administration of antidotes; and (v) prevention of re-exposure.

Basic Life Support

Airway. This includes airway maintenance, establishment of breathing and restoration of circulation. Establishing airway may be difficult in children with poisoning due to caustic and thermal upper airway injuries, neck and facial injuries or angioedema. In a child with altered mental status, respiratory depression and pupillary constriction, a trial of naloxone should be given before intubation. Bag and mask ventilation is associated with a higher risk of aspiration. The risk of aspiration is minimized by aspirating gastric contents prior to intubation, use of the Sellick maneuver during intubation and synchronized mechanical ventilation.

Breathing. Adequacy of breathing should be assessed by respiratory effort, chest movement, air entry and oxygen saturation.

Circulation. Shock, particularly noted in poisoning due to cardiotoxic agents and in children with cardiopulmonary diseases, is managed initially with fluid boluses, repeated if needed, under monitoring for fluid overload. Dopamine is the vasopressor of choice if shock remains unresponsive, except in poisoning due to tricyclic antidepressant or monoamine oxidase inhibitors where its use is avoided. Hypotension may be refractory to these measures in patients with exposure to myocardial depressants or vasodilators, and in presence of concomitant visceral injury, pulmonary embolism, ruptured aortic aneurysm, sepsis or severe acidosis.

Supportive Therapy

The goals of supportive therapy include maintenance of homeostasis and prevention and treatment of complications. Indications for admission to intensive care unit include: (i) evidence of severe poisoning, coma, respiratory depression, hypotension, cardiac conduction abnormalities, arrhythmias, hypothermia or hyperthermia; (ii) need for antidote or enhanced elimination therapy; and (iii) progressive clinical deterioration.

Prevention of Further Absorption of Poison

These measures target preventing absorption of the toxin and depend upon the site and route of poisoning, patient's age and general condition (Table 26.5).

Table 26.5: Methods to decrease the absorption of toxins

Dilution
Gastric emptying: Emesis, gastric lavage
Binding agents: Activated charcoal, others
Cathartics
Whole bowel irrigation
Endoscopic or surgical removal

Dilution This involves washing with water to reduce the duration of exposure to the toxin. The mechanism depends upon the site of exposure. In patients with corrosive burns and poisoning with organophosphorus (readily absorbed from the skin), all clothes should be removed and the contaminated area washed with liberal amount of water and soap. *It is important to emphasize that neutralization of an agent using alkali for acid exposure or vice versa is harmful and contraindicated.* Skin cleaning is done irrespective of duration of exposure to the toxin. Lubricants like grease or cream may cause poison to stick on to the skin.

Oral and ocular mucosa is washed with plenty of water. Eyes should be irrigated with lids fully retracted for at least 20 min. In patients with corrosive ingestion, liberal amounts of water or clear fluid are given orally as soon as possible. This is contraindicated in poisoning due to tablets as it may increase their absorption.

Gastrointestinal decontamination In the past, a regimented approach to decontamination was used, which consisted of gastric emptying by emesis or orogastric

lavage, followed by adsorption of residual poison within the gut by nonabsorbable agents, preferably activated charcoal. A cathartic, such as sorbitol was used to hasten the excretion of charcoal. However, there is no evidence of actual benefit with this approach. Gastric emptying remains a cardinal principle in management of poisoning by toxin ingestion and the desired outcome is the prevention of continued absorption of poison from the gut into bloodstream. The procedure of choice for decontamination, if needed, is activated charcoal. Administration of *syrup of ipecac* may remove 30 to 40% of ingested toxin when administered within one hour of the ingestion. However, ipecac induced emesis and cathartics are no longer recommended as gastric emptying procedures.

Gastric lavage may be considered in situations where a potentially lethal toxin has been ingested within the last hour. Gastric lavage is preferred in patients below 6-month-old, impaired level of consciousness, seizures, absent gag reflex or mercury chloride poisoning. The procedure is contraindicated in children with corrosive poisoning. Gastric lavage is performed with a large tube with multiple lateral holes at the distal end and funnel at the proximal end. The size of the tube is selected according to age 28 Fr neonates, 36 Fr older children; narrow tubes are ineffective in removing solids. Before gastric lavage is performed, the gag reflex is ensured; if absent, the patient is first intubated. The child is kept in lateral decubitus position with head end lowered. Lavage is done with 15 ml/kg of normal saline until clear fluid is drained.

Activated charcoal should be instilled after the lavage is completed. Activated charcoal is produced by destructive distillation of organic materials like wood, coconut and petroleum and treatment of the distillate at high temperatures (about 900°C) using steam. The latter process increases the adsorptive capacity of charcoal by increasing its surface area, removing adsorbed material and reducing the particle size. Its total adsorptive surface is 1600 to 1800 m^2 per g of activated charcoal, making it an ideal binding agent.

Activated charcoal is an effective nonspecific adsorbent and should be considered in all cases of poisoning. It should be avoided in patients with corrosive ingestion, ileus, intestinal hemorrhage and patient with unprotected airway at risk of aspiration. Activated charcoal, available as 400 mg tablet, is used in a dose of 1–2 g/kg and should be crushed, made into slurry and administered. Under most circumstances, a single dose is effective, with the greatest benefit being within an hour of ingestion. Repeat administration is indicated in patients with massive ingestion of toxin or desorption of toxin from activated charcoal (Table 26.6). Causes of nonresponse include ingestion of toxin not adsorbed by activated charcoal, ingestion of additional substances, delayed toxic effects and secondary complications including surgical causes.

Table 26.6: Indications for repeat doses and nonresponse to charcoal

Mechanism	*Condition*
Reduced absorption, enhancement of elimination	Anticholinergics, sustained release agents
Gastrointestinal dialysis	Theophylline, phenobarbitone, phenytoin, salicylates
Interruption of entero-hepatic circulation	Cyclic antidepressants, diazepam, carbamazepine, phenothiazines, thyroid hormones

Superactive charcoal, with thrice the adsorptive area, has been tried in some situations. Carbonized resin and modified silica gel are as effective as activated charcoal in adsorbing methanol, ethylene glycol, kerosene and turpentine *in vitro*. Other binding agents including attapulgite, bentonite, fuller's earth and kaolin pectin are less effective. Burnt toast possesses little, if any, adsorption capacity and has been abandoned. Cholestyramine is effective in paracetamol and digitalis toxicities but is less well tolerated. Routine use of cathartics either alone or with activated charcoal is not recommended.

Whole bowel irrigation with polyethylene glycol has been used in patients with poisoning and drug overdosage. This is the only procedure which decontaminates beyond the pylorus without inducing emesis or causing fluid overload and dyselectrolytemia. It is, however, not a substitute for activated charcoal. It is particularly useful following ingestion of sustained release drugs, slowly dissolving agents, ingested crack vials and drug packs. The procedure is not helpful in the management of ingestion of rapidly absorbed drugs, liquids, parenteral drugs and caustics. Whole bowel irrigation can be achieved with administration of 500 ml per hour of polyethylene glycol over 4–6 hr.

Enhancing Elimination

Procedures directed towards enhancing elimination are indicated in patients with significant delay following poisoning or when methods to prevent absorption are ineffective or not applicable. Specific indications are provided in Table 26.7. Methods used commonly to enhance drug elimination include the following.

Table 26.7: Indications for enhancing elimination of toxins

Ingestion of drug or poison whose removal is enhanced by >30%, and:
- Intense exposure with severe or lethal toxicity
- Toxin with serious, delayed effects
- Impaired natural removal mechanism, or
- Deteriorating condition, as suggested by hypotension, coma, metabolic acidosis, respiratory depression, dysarrhythmia or congestive cardiac failure

Manipulation of pH and diuresis. The rate of elimination of ingested substances can be increased by increasing glomerular filtration or by altering urine pH for toxins excreted by kidneys. Alkalization of urine may be used in patients with poisoning due to weak acids like salicylate, phenobarbital and herbicides. This is achieved by administration of sodium bicarbonate at a dose of 1–2 mEq/kg given every 3–4 hr, targeting urine pH between 7 and 8. Sodium bicarbonate also reduces the toxicity of tricyclic antidepressants, quinine and some antiarrythmic drugs. Acidification of urine to enhance elimination of weak bases is not advised.

Dialysis. The indications of dialysis are given in Table 26.8. *Peritoneal dialysis* enhances elimination of compounds like alcohol, lithium and salicylates. It is more effective in children than adults due to presence of larger peritoneal surface in relation to body surface area. It has the disadvantages of gradual removal of toxins and decreased efficacy in hypotensive subjects. The procedure may be used as a temporizing measure before hemodialysis or hemoperfusion.

Hemodialysis is preferred for removal of compounds like bromide, chloral hydrate, ethanol, methanol, ethylene glycol, lithium and salicylates. In addition to removing toxins, it also rapidly corrects metabolic abnormalities and fluid overload. The procedure carries risk of possible elimination of agents like folinic acid and ethanol, administered therapeutically during acute poisoning.

Hemoperfusion is the procedure of circulating blood through a cartridge with a large surface area coated with activated charcoal or carbon. The procedure has the advantage of being not limited by protein binding and is the preferred method for elimination of carbamazepine, phenobarbital, phenytoin and theophylline. Substances which are not adsorbed by activated charcoal, like alcohol, lithium and many heavy metals, are not removed. The procedure may be associated with complications like thrombocytopenia, leukopenia and hypocalcemia.

Exchange transfusion removes poisons affecting the red blood cells, as in methemoglobinemia or arsenic induced hemolysis. The elimination of heavy metals is enhanced by *chelation* and removal of carbon monoxide can be increased by *hyperbaric oxygen*.

Table 26.8: Indications of dialysis in a patient with suspected poisoning

Prolonged coma
Hepatic and renal failure; serious underlying illness
Correlation between plasma concentration and toxicity
Plasma levels in fatal range
Removal of toxin or its toxic metabolite possible by dialysis (e.g. barbiturates, chloral hydrate, ethylene glycol, theophylline, salicylates, heavy metals)

Administration of Antidotes

Antidotes counteract the effects of poisons by neutralizing them (antibody-antigen reactions, chelation, chemical binding) or by antagonizing their physiologic effects (activation of opposing nervous system activity, provision of metabolic or receptor substrate). Antidotes may reduce morbidity and mortality significantly, but are potentially toxic. Their safe use requires correct identification of specific poisoning or toxidrome. Table 26.9 enlists antidotes used commonly for management of poisonings.

Prevention of Re-exposure

Poisoning is a preventable illness. The best approach to prevent poisoning in children is to limit the access of poison. Alcoholic beverages, medications, products used for automotives, household cleaning and petcare, fuels and toiletry products, nonedible plants, medications and vitamins should be kept out of reach or locked inside childproof cabinets. Poison prevention education should be an integral part of all well child visits. Counseling parents and other caregivers about potential poisoning risks, how to 'poison-proof' a child's environment and steps to be taken if a poisoning occurs diminishes the likelihood of serious morbidity or mortality from an exposure. Adolescents with suicidal poisoning or drug addiction need proper counseling before discharge.

COMMON POISONINGS

Acetaminophen (Paracetamol)

This is the most common and safest analgesic and antipyretic used in children. The toxic dose is usually >200 mg/kg in children below 12-yr-old. Hepatic damage after paracetamol overdose usually begins at >150 mg/kg and occurs due to formation of a highly reactive intermediate, N-acetyl-p-benzoquinoneimine. This is normally detoxified by endogenous glutathione. Overdose of paracetamol results in depletion of glutathione, allowing the intermediate metabolite to damage hepatocytes. The stages of paracetamol toxicity are as follows:

Stage I (12–24 hr): Nausea, vomiting and cold sweats

Stage II (24–48 hr): Clinical recovery with biochemical evidence of hepatorenal injury; elevation of hepatic transaminases to above 1000 IU/l is associated with serious hepatic damage

Stage III (48–96 hr): Peak hepatotoxicity

Stage IV (7–8 days): Recovery is heralded by return of consciousness and improvement in the hepatic function tests. Histological recovery may take up to 3 months.

Death may occur within 2–7 days of ingestion. Overdosage is treated with N-acetylcysteine used orally within 16 hr after ingestion at doses indicated in Table 26.9. Once hepatic failure occurs, the agent is contraindicated. Supportive treatment includes correction of hypoglycemia,

Table 26.9: Antidotes for common poisonings

Poison	*Antidote*	*Dose*
Acetaminophen	N-acetyl cysteine	Loading dose 140 mg/kg; maintenance dose 70 mg/kg q 4 hr for 17 doses as oral solution mixed with fruit juice
Anticholinergics	Physostigmine	0.02 mg/kg slow IV
Benzodiazepines	Flumazenil	0.01 mg/kg IV bolus; total dose 1–3 mg
Digoxin	Digoxin immune antibody fragment	10–20 vials IV bolus
Methemoglobinemia	Methylene blue	1–2 mg/kg slow IV
Opioids	Naloxone	0.1 mg/kg IV (up to 2 mg); repeat every 2 min till reversal (up to 10 mg)
Organophosphates	Atropine	0.05 mg/kg IV; repeat dose titrated to effect
Salicylates	Sodium bicarbonate	150 mEq/l + 40 mEq KCl/l of 5% dextrose
Ethylene glycol, methanol	Fomepizole	Loading dose of 15 mg/kg followed by 10 mg/kg q 12 hr for 4 doses, then 15 mg/kg q 2 hr until ethylene glycol levels are <20 mg/dl; dialysis is required in presence of renal failure or ethylene glycol level >50 mg/dl; fomepizole is given q 4 hr during dialysis to prevent washout
Organophosphate	Pralidoxime aldoxime methiodide (2–PAM) renal failure	25–50 mg/kg IM (maximum 2000 mg) every 12 hr (maximum 2500 mg in young children); adjust dose in

maintenance of hydration, electrolyte balance, treatment of coagulopathy, hemodialysis for acute renal failure and management of fulminant hepatic failure.

The following are poor prognostic factors in patients with hepatic failure due to paracetamol: blood pH <7.3, prothrombin time >100 sec, grade III or more hepatic encephalopathy, elevated serum bilirubin >4 mg/dl and SGOT >1000 IU/l. A ratio of factor VIII to factor V >30 is associated with poor outcome.

Organophosphorus Compounds

Pesticides and insecticides are the most common cause of poisoning throughout the tropics and are associated with a high mortality rate. Pesticides include insecticides herbicides, fungicides, nematocides, rodenticides and fumigants. Chronic exposure may be dietary or non-dietary. Aggregate exposure refers to total exposure to a single pesticide through food, water and nondietary exposure. Cumulative exposure is the summated exposure to multiple pesticides with a common mode of action. Children are at higher risk in view of higher body surface area and high body mass ratio, absorption of pesticide through intact skin and mucosa and higher minute ventilation rates in young children resulting in increased pulmonary exposure.

Clinical features appear when cholinesterase activity falls to 25–30% of normal. Symptoms of excessive parasympathetic activity including blurred vision, headache, giddiness, nausea, pain in the chest, profuse salivation and sweating occur within a few hours. Pupils are constricted and papilledema may occur. At low doses of organophosphates, muscarinic symptoms may be most prominent. In more severe intoxication, nicotinic and central muscarinic activity may predominate. Thus, tachycardia and hypertension are important signs of severe poisoning. Carbamates are less toxic than organophopsphorus pesticides. Death is usually due to respiratory failure.

Intermediate syndrome occurs due to prolonged cholinesterase inhibition and causes chronic effects, muscle necrosis and delayed sensory polyneuropathy. Definitive diagnosis of organophosphate poisoning can be made by estimation of red cell cholinesterase activity, before administration of cholinesterase reactivator. Red cell acetylcholinesterase is considered a satisfactory marker of synaptic function and atropine needs in patients with organophosphorus poisoning, and is therefore a marker of severity. Patients with red cell enzyme activity of at least 30% have normal muscle function and no need for atropine; in contrast, patients with less than 10% of normal activity have grossly deranged muscle function and need high doses of atropine.

Treatment includes reduction of dermal contact and gastric emptying. Gastric decontamination should be considered only after the patient has been fully resuscitated and stabilized. Atropine sulphate is the primary antidote and is given at 0.05 mg/kg IV; the dose is repeated after 15 min and then every hour until atropinization (maximum 1 mg/kg in 24 hr). Atropine is a competitive antagonist of muscarinic receptors, reverses the peripheral symptoms of excessive secretions and airway resistance and arrests the early phase of convulsions when given within 5 min of exposure. Infusions of atropine are reported to be better than repeated bolus doses. Glycopyrrolate is a reasonable alternative for mildly affected victims as an anti-sialogogue or as a peripheral parasympatholytic. This agent does not cross the blood

brain barrier and is ineffective for those with central nervous system involvement.

Pralidoxime aldoxime methiodide (2-PAM) hydrolytically cleaves the organophosphate from the enzyme acetylcholinesterase restoring enzymatic function. It is often highly effective in reversing nicotinic effects of pesticides including muscle fasciculations, weakness and respiratory depression. *It is not given in carbamate poisoning.* Common untoward effects include dizziness, transient diplopia and blurred vision. Dose adjustment is required in individuals with renal insufficiency since it is excreted almost entirely unchanged by the kidneys. Rapid IV administration can cause laryngospasm and rigidity. Hypertension is the most serious untoward effect at higher doses.

Patients must be carefully observed after stabilization for changes in atropine needs, worsening respiratory function because of intermediate syndrome and recurrent cholinergic features occurring with fat-soluble organophosphorus compounds.

Toxicity with *diethyltoluamide (DEET),* the component of most insect repellant creams, may occur through covered skin surfaces or ingestion. Seizures are the most severe manifestation but are usually self limited.

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Hydrocarbon Poisoning

Aliphatic hydrocarbons, including kerosene, turpentine, lubricating oils and tar, have the greatest risk of aspiration and pulmonary symptoms. Aromatic compounds include benzene compounds and have mainly neurological and hepatic toxicity. The type of toxicity with a hydrocarbon depends on its volatility, viscosity or surface tension. The lower the viscosity, higher is the risk of pulmonary aspiration. Substances with low viscosity and volatility (e.g. mineral oil, kerosene, furniture polish) have a higher risk of aspiration. Substances with high volatility and low viscosity (e.g. benzene derivatives like toluene, xylene used in solvents and degreasers, gasoline, naphtha in lacquer diluent) may also act as toxins through inhalation, manifesting with neurological depression.

Kerosene and paraffin oils are often kept in unsafe containers (e.g. soft drink and beer bottles) and are a major cause of accidental ingestion among young children. Kerosene toxicity has also been noted following application of kerosene on the skin of neonates, indicating that transdermal absorption can also result in toxic effects. Intravenous kerosene injections have been reported among IV drug abusers, causing major injury to the lungs.

Respiratory symptoms, as a result of chemical pneumonitis, restlessness, fever and abdominal distension are common. Convulsions and coma may occur. Radiological changes, which might occur within one hour include basilar infiltrates, emphysema, pleural effusion and pneumatoceles. Ingestion of 30 ml is lethal.

Management is symptomatic with preservation of the airway in unconscious patients. Gastric emptying is contraindicated and is done only when large quantities of turpentine have been ingested or the hydrocarbon product contains benzene, toluene, halogenated hydrocarbons, heavy metals, pesticides or aniline dyes. Mortality ranges from 2 to 10% and is higher in malnourished children. Death may ensue within 24 hours. Avoiding oil and milk at home as antidotes should be emphasized. Steroids have no role in treatment.

For DDT poisoning, phenobarbitone is given for convulsions. Cholestyramine, an anion exchange resin should be administered to all symptomatic patients of DDT poisoning.

Iron Intoxication

Ingestion of tablets of ferrous sulfate may cause acute poisoning, characterized by gastrointestinal toxicity, followed by a period of relative stability (up to 48 hr), and then circulatory shock with metabolic acidosis and myocardial dysfunction. Hepatic fibrosis and gastric scarring are longterm effects. Gastrointestinal symptoms can be seen at doses of 15 to 30 mg/kg. Significant toxicity is uncommon at amounts less than 50 mg/kg. The lethal oral dose is between 200 and 500 mg/kg of elemental iron. The toxic dose is not absolute and fatal reactions have been reported with small amounts. Peak serum iron levels of >500 µg/dl may result in severe toxicity. Vomiting, diarrhea, serum glucose greater than 150 mg/dl, leukocyte count greater than 15,000/mm^3 and the finding of radioopaque material on abdominal radiograph correlate with an elevated serum iron level greater than 300 µg/dl. The child may develop complications within a few hours or after a latent period of 1–2 days.

Treatment includes gastric emptying, followed by stomach wash with sodium bicarbonate. IV sodium bicarbonate (3 ml/kg diluted twice with 5% dextrose) is given for treatment of acidosis. Fluid resuscitation may be necessary. Iron is chelated with IV infusion of deferoxamine (dose 15 mg/kg/hr) until the serum iron is <300 µg/dl or until 24 hr after the child has stopped passing 'vine rose' colored urine. In case of renal failure, dialysis may be required to remove deferoxamine iron complexes.

Dhatura (Belladonna) Poisoning

Accidental ingestion of dhatura seeds causes delirium, confusion, visual disturbances, photophobia, dilated sluggishly reacting pupils, dryness of skin and mouth, fever, tachycardia and urinary retention. Treatment is by gastric lavage and physostigmine at a dose 0.1 mg/kg (max 2 mg) IV slowly.

Unconventional poisons and toxins include herbal or shrub products, inhalational agents, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, paraben in plastics and packaged food.

Information sources on poisoning are available at: *www.cehn.org* and *www.ace.orst.edu/info/nptm*

HELP CENTRE

National Poison Information Centre
All India Institute of Medical Sciences, New Delhi
Telephone +91 11 26589321, 26593677
Email: npicaiims@hotmail.com, npicaiims2010@gmail.com
Website: www.aiims.edu/aiims/departments/NPIC/NPIC intro.htm

ENVENOMATION

Snake Bites

Snake bites cause 125,000 deaths annually worldwide, chiefly in young adults in rural areas in tropical climates. About 400 of 3000 snake species worldwide are poisonous, chiefly belonging to the *Elapidae* (cobra, krait, coral snake, death adders, sea snake) and *Viperidae* (rattlesnake, saw scale, Russell viper) families. The venom of these snakes contains neurotoxins, cardiotoxins, hemotoxins or cytotoxins that cause: (i) neurotoxicity (sea snake, cobra, mamba, coral snake) with ptosis, diplopia and bulbar palsy progressing to dysarthria and generalized weakness; (ii) coagulopathy (viper, Australian elapids) with gum bleeding, epistaxis or intracranial bleeding; (iii) rhabdomyolysis (Russell viper, sea snake, some Australian elapids) with muscle pain, tenderness, dark urine with acute tubular necrosis; (iv) hypotension and/or shock due to vasodilation, myocardial toxicity and/or hypovolemia with bleeding; and (v) tissue necrosis (viper and cobra) with pain, tenderness, swelling, bleeding and blisters at the location of the bite. Initial symptoms are nonspecific, such as nausea, vomiting, abdominal pain and headache.

Management. Management of snake bite is directed at reducing the spread of venom and expediting transfer to the hospital, summarized by the mnemonic 'Do it RIGHT' (R for reassuring the patient, I to Immobilize the limb in a functional position below the level of heart, G and H to Get to the Hospital immediately and T to Tell the doctor of any symptoms during transit). The wound is cleansed thoroughly without using alcohol. Pressure immobilization to decrease venous outflow may delay systemic absorption of venom that contains primarily neurotoxins but is not recommended for venoms with cytotoxins since this may worsen local necrosis. Incision and suction by mouth or using mechanical devices are ineffective.

The evaluation of the patient in the hospital should take into account common syndromes caused by snake bites. Identification of the snake requires knowledge of local snake fauna, venom kit testing and clinical syndrome. Fang bites are often obvious for cobra and viper bites due to local tissue necrosis, but are easily missed in bites by Australian elapids. Since most snake bites do not cause envenomation, a large proportion of patients only require observation.

Clinical and laboratory assessment and management should focus on supportive care for specific syndromes. Continuous attention to vital signs and fluid status is important, with central pressure monitoring for patients with shock. Serial evaluation for serum creatine kinase and electrolytes, and urine dipstick for myoglobinuria helps detect rhabdomyolysis. Patients with this complication benefit from plasma volume expansion with isotonic saline, avoiding nephrotoxic medications, and ensuring diuresis targeting urine pH of 6.5. Patients with established renal failure may require short-term dialysis. Patients with poisoning by snakes with neurotoxic venom require close monitoring for signs of muscle weakness and development of hypoxia; severe cases require mechanical ventilation for airway protection or respiratory paralysis.

The whole blood clotting test is a useful bedside screening test for coagulopathy. The failure of blood to clot in a clean dry glass tube after 20 min suggests severe hypofibrinogenemia, caused usually by vipers (and not cobra or krait). Antivenom administration reverses this abnormality and improves other changes such as elevated international normalized ratio, prolonged activated partial thromboplastin time, severe thrombocytopenia and low fibrinogen. Patients with life-threatening hemorrhage despite antivenom use may require whole blood or fresh frozen plasma.

The administration of adequate amounts of antivenom is the only specific management for envenomation. Its use depends upon availability and an individualized assessment of risk-benefit ratio. Administration of antivenom is indicated in patients with neurological signs, spontaneous bleeding and/or incoagulable blood; it should also be considered for rhabdomyolysis, persistent hypotension, renal failure and/or severe local tissue destruction. Preparation, dosing and administration should follow product information guidelines and do not differ between adults and children. To prevent allergic reactions, antivenom is administered slowly (over 1 hr) with continuous monitoring; epinephrine (0.01 mg/kg intramuscularly) may be necessary if a reaction develops.

Suggested Reading

Simpson ID. The pediatric management of snakebite: National protocol. Indian Pediatrics 2007;44:173–6

Warrell, DA.Guidelines for the management of snake-bites. World Health Organization 2010

www.who.int/neglected-diseases/diseases/snakebites/en/index.html; www.toxinology.com

Scorpion Sting

Scorpion sting is an important hazard in tropical regions, particularly in dry rural areas in south and central India. Envenomation by 30 of 1500 known species of scorpions (*Buthidae* or *Scorpionidae* family) can result in neurotoxicity, cardiovascular toxicity or respiratory dysfunction. Severe excruciating pain radiating along corresponding dermatomes and life-threatening systemic effects may be noted. Scorpion venom is more potent than snake venom or

cyanide and mortality is high, deaths occurring chiefly in patients with delayed diagnosis or therapy.

Scorpion venom is a complex mixtures of mucopolysaccharides, hyaluronidase, phospholipase, acetylcholinesterase, serotonin, histamine, protease inhibitors, histamine releasers and neurotoxins. The neurotoxin causes incomplete inactivation of sodium channels during depolarization of neurons, resulting in membrane hyperexcitability, repetitive uncontrolled firing of axons, enhanced release of neurotransmitters at synapses and neuromuscular junction, excessive neuromuscular activity and autonomic dysfunction. The venom of the Asian black scorpion has high concentrations of noradrenaline and acetylcholine, which account for localized burning and algesia, respectively. Hemodynamic changes are secondary to transient cholinergic effects and secondary prolonged adrenergic effects and/or severe inflammatory response syndrome.

Neurotoxicity after envenomation is categorized into four clinical grades, including local pain and paresthesias at the sting site without inflammation (Grade I); local symptoms and remote pain and paresthesias (radiating proximally up the affected limb or generalized) with agitation (Grade II); cranial nerve dysfunction (blurred vision, involuntary conjugate, slow and roving eye movements; slurred speech, tongue fasciculations, hypersalivation) or somatic neuromuscular dysfunction (restlessness, fasciculations, alternating opisthotonos and emprosthotonos) in an alert individual (Grade III) and presence of both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction (Grade IV). An 'autonomic storm' is a common presentation, with transient parasympathetic activity (vomiting, profuse sweating, hypersalivation, bradycardia, ventricular premature contraction, priapism and hypotension) and prolonged sympathetic (cold extremities, hypertension, tachycardia, pulmonary edema and shock) stimulation. Many patients show hypertension and/or left ventricular dysfunction at presentation. The onset and progression of symptoms is rapid with maximum severity within 5 hr. Children show earlier onset of symptoms (15–30 min in infants) and are more likely to require intensive supportive care.

The management of scorpion stings involves relief of pain (paracetamol or ibuprofen), wound cleaning and tetanus prophylaxis. These patients may be discharged after observation for 4 hr to ensure lack of symptom progression.

Severe cases with restlessness, muscle fasciculations, hypersalivation, cranial nerve dysfunction and roving eye movements require monitoring for respiratory distress, hyperthermia, rhabdomyolysis or multiple organ failure. Fluid balance should be maintained to correct losses due to vomiting, sweating and salivation. Oral secretions should be suctioned frequently and the need for intubation and mechanical ventilation anticipated in patients who cannot maintain airway or develop pulmonary edema. Midazolam infusion helps provide sedation and relief from muscle spasticity. Intravenous fentanyl is preferred to morphine of pain relief, since it does not cause histamine release. Prazosin is useful in the management of vasoconstriction and hypertension associated with α-receptor stimulation, since it reduces preload without causing tachycardia and increase in myocardial oxygen demand. Patients with left ventricular dysfunction due to hypertension may benefit from sodium nitroprusside infusion or use of an angiotensin converting enzyme inhibitor.

Scorpion antivenom reverses the excitatory effects of the venom and neutralizes circulating unbound venom to minimize parasympathetic stimulation. Its use reduces the duration of symptoms and the need for benzodiazepines. Scorpion-specific F(ab') equine antivenom should be administered as early as possible to patients with Grade III or IV neurotoxicity. While specific antivenom is not available in India, nonspecific antivenom can be procured. Goat-derived antivenom carries risks of anaphylaxis and delayed serum sickness.

Suggested Reading

Bawaskar HS, Bawaskar PH. Scorpion sting: update. J Assoc Physicians India 2012;60:46–55
www.toxinology.com

INJURIES AND ACCIDENTS

Injuries and accidents are a leading causes of death in children who survive beyond their first birthday and represent a major epidemic of non-communicable disease throughout the world. WHO estimates suggest that over 10% of those killed due to any type of accident are children. Most accidents occur in the age group of 2–5 yr, mostly in boys. India has among the highest rates of road traffic accidents in the world. Burn injuries are second only to motor vehicle accidents as the cause of accidental death in children 1–4-yr-old.

Details of epidemiology are available at http//whqlibdoc.who.int/publications/924156220X.pdf.

Epidemiology of Injury

The agent-host-environment model used to describe the epidemiology of communicable diseases can be extended to childhood injuries (Fig. 26.2).

Injuries are of 2 types, unintentional and intentional. Unintentional injuries can be broadly divided into three categories: injuries at home, sports injuries and road injuries. Intentional injuries such as homicide and suicide are rare in children but not uncommon in adolescents.

Injury Control

Injury control operates in 3 phases: prevention, minimization of damage, and post injury care. In planning injury prevention strategies, 3 principles deserve emphasis.

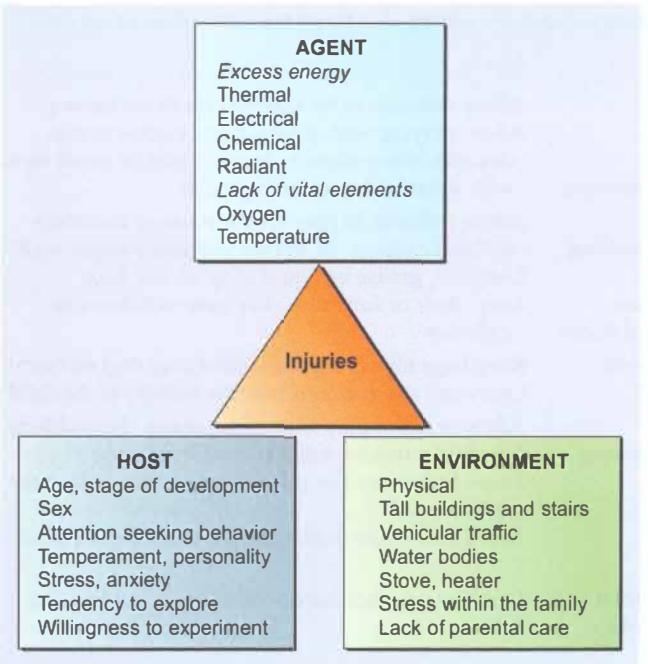

Fig. 26.2: The epidemiology of childhood injuries

i. *Passive injury prevention,* such as automatic locks for medicine cabinets, are preferred over active strategies, e.g. "yuck" stickers on bottles.
ii. *Specific instructions,* e.g. keep water heater temperature lower than 120°F, are more likely to be followed than general advice, e.g. reduce the temperature of hot water tap in your home.
iii. Reinforcement by *community wide education programs* are more effective than individual education sessions.

Targeted messages for prevention of injuries should be discussed with the parents (Table 26.10).

Fire and Burns

Injury following burns is an important cause of death in India. Scald burns secondary to household accidents constitute 70% of all thermal injuries in infants, toddlers and preschool children. Burns may also occur with chemicals (particularly corrosives), cigarettes (child abuse) and electrical current. Burns have higher mortality in children than adults since the former have (i) thinner and more sensitive skin, (ii) markedly increased ratio of body surface area to body mass; (iii) limited physiological reserves; (iv) significant metabolic and systemic disturbances; (v) immature immune system; and (vi) increased fluid requirements.

First Aid

While approaching a child with fire, a blanket or coat should be kept in between rescuer and the burning child. Flames may be extinguished with water, blanket or by rolling the victim on the ground. Running with clothes on fire is avoided. The victim is kept lying in flat position away from source of heat.

In case of minor burns or scalds, one should pour cold water, apply cold water soaks or submerge the burned portion immediately in cold water, continuing till pain disappears. Application of any ointment, grease, soda, oil, powder, butter or herbs is avoided. Blistered skin is not ruptured; it should instead be covered with a clean cloth. Charred cloth is removed only if it comes out easily. The wound is covered with clean sheets of sterile dressing and the patient is wrapped in blanket or foil.

Inhalation injury, frequently associated with large burns, is an important early predictor of mortality and is the most common cause of death during the first hour after burns. The singeing of the nasal vibrissae is common in facial burns but does not reliably indicate inhalation injury.

Electrical burn. The power supply should be switched off. Using nonconductor material like dry wooden stick or dry cotton clothes, the victim should be pulled away from the electric source.

Chemical burns. The burnt area should be flushed with plenty of running cold water. If an eye is burnt by chemical, especially an acid or an alkali, it should be flushed gently but thoroughly with tap water for prolonged time. Both eyes should be covered with clean cloth. The burn wound should be kept as clean as possible, protecting it from dust and flies.

Management

Estimation of burn size. The primary determinants of survival in patients with burn injury are patient age and the size and depth of the burn wound. Young children below 4 years of age do not tolerate thermal injury as well as adults. The Berkow body surface area chart and the rule of nines used to estimate surface area with burn injuries in adults are not applicable to children. The Lund and Browder modification, which divides the body into small portions and takes into account childhood differences in body proportions, is used. More simply, the child's palm together with fingers is considered as representing 1% of total body surface area (TBSA).

Hospitalization. Minor burns can be treated at home with topical ointments. Indications for inpatient care include: (i) third-degree burns involving 5% or more of TBSA; (ii) second-and third-degree burns involving more than 10% TBSA; and (iii) burn injuries involving the face, hands or genital areas.

Resuscitation. The goals of resuscitation and early management are: (i) adequate fluid replacement; (ii) correction of hypoxia and ventilatory disturbances; (iii) prevention of hypothermia; and (iv) adequate control of pain and anxiety. Children with inhalation injury should be intubated and supportive ventilation is initiated early; hyperventilation with 100% oxygen shortens the half-life of carbon monoxide elimination from 4 hr to 40 min.

Table 26.10: List of Do's and Don'ts for parents of toddlers and older children (age 12 mo–12 yr) for prevention of injuries

Type of injury	*Do's*	*Don'ts*
At play	Choose toys and games appropriate to age Regularly inspect the condition of toys Set mattresses at low levels as activity increases Visit healthy, safe playgrounds and playing conditions	Allow children to fly kites in rain or on terrace Allow playing with plastic bags, electric cords, dupatta, sharp objects, beads, coins or small toys with detachable or moving parts
Falls	Use beds with rails for children below 6 yr Set a good example by avoiding standing on a rocking chair Remove and replace torn or frayed carpet or linen Fix a nonskid device under rugs laid on polished floors	Allow children to play on the stairs or balconies without railings or terrace without parapet wall Leave oil, grease or liquid soap on the floor Keep chair or furniture near open windows or galleries
Cuts	Remove rusty nails and broken bottles immediately Teach child how to handle tools and mechanical instruments safely	Keep large toys in the crib (infant may step on them) Leave any sharp objects near the vicinity of the child Allow to run or play with sticks or any sharp objects
Burns	Keep children far away from the stove while cooking; be careful while using portable stoves Have an adequate fire guard hooked in place Allow the child to play with firecrackers under supervision by an adult	Let child enter the kitchen to recover a toy Leave hot utensils or pans in the kitchen within the child's reach Leave an electric iron switched on close to a child
Scalds	Keep children away from pots cooking on the stove Turn pan handles away from the front of the stove Check temperature of the milk before feeding	Drink or pass hot tea or coffee while holding the infant
Electrocution	Use safe electric points so that the child cannot insert a lead pencil or other object through the hole Keep all switch boards in good working condition	Keep electric equipments plugged on when not in use Keep electric cables within the reach of children
Poisoning	Keep medicines, cleaning agents, drugs, kerosene and pesticides out of reach of children in their original containers and not in fruit juice or colored bottles Instruct elder siblings not to give any medications to their brother or sister	Leave any medicines in the child's bedroom Store inedible products in food shelves Take medicines in front of the child
Drowning	If the child close to water, remove child before answering a call	Leave young children and those with history of seizure(s) unattended in bathtubs or near swimming pools, ponds, beaches or full buckets in the bathroom
Suffocation by inhaled or ingested objects	Remove broken rattle and other play items immediately Keep plastic bags, scarves, ropes and cords out of reach of children	Give (pea) nuts to children below 2 yr of age Give bolus of food to infants or toddlers Allow children to run about with food in the mouth or to play while eating
Fire injuries	Turn off the gas after use; store inflammables in child-proof containers	Light firecrackers in hand; bend over while lighting crackers; touch half-lit firecrackers
Road traffic injuries	Teach older children how to cross the road safely Teach older children traffic safety rules Ensure adequate lightning, construction of sidewalks and roadway barriers in areas of high pedestrian traffic Ensure that your child's bicycle is maintained in good condition; make him wear properly fitting approved cycle helmets and shoes while riding Ensure use of reflectors, mirrors and bright reflecting clothes	Allow younger children to cross the streets alone Allow doubling on the bicycle, especially with infants Carry more than one child on a 2-wheeler; allow child to stand in front of a rider Riding at night; play near/on roads Allow child to occupy front seat of car, lean out of vehicle windows or take any body part out of the window

Adequate fluid replacement. The goal of fluid resuscitation is to restore and maintain perfusion and tissue oxygen delivery at optimal levels in order to protect the zone of ischemia in burnt tissues without overloading the circulation. Monitoring urine output and a nasogastric tube for continuous suction to prevent emesis and aspiration are essential. Oliguria occurs due to dehydration and other factors, including excessive secretion of antidiuretic hormone. Urine output should be maintained between 0.7–1 ml/kg/hr. Isotonic solutions (normal saline or Ringer lactate) should be administered initially at a rate of 20 ml/kg/hr until calculation of appropriate replacement can be made. The Parkland formula estimates the amount of fluid to be replaced over 24 hr as follows:

Volume of Ringer lactate (mL) = 4 ml × weight (kg) × % TBSA burn

In addition, the child require maintenance fluid therapy. However, while this estimation is adequate for children over 10-yr-old, the formula underestimates the requirements for children weighing less than 20 kg. Potassium is not administered during the first 12–24 hr, or until normal kidney function is demonstrated.

Topical therapy. 65% of pediatric burns heal spontaneously, without the need of skin grafting, with topical therapy alone. The most commonly used topical agents are 0.5% silver sulphadiazine, 0.5% silver nitrate and mafenide acetate. Silver sulphadiazine offers advantages in small children; its application is painless, it has a soothing effect and restricts fluid and heat loss from the burn surface. It can cause skin rash, leukopenia and thrombocytopenia. Silver nitrate is not an effective antibacterial agent because of poor penetration of the burn eschar. Further, it can cause hyponatremia, hypokalemia, hypochloremia and hypocalcemia. Mafenide acetate penetrates the burn eschar effectively; its application can be painful and may be associated with skin reaction and metabolic acidosis since it is a carbonic anhydrase inhibitor. Daily dressing changes are required after thorough cleansing. Maintaining such dressings intact in a young child is difficult over the face and hands. Moist exposed burn ointment (MEBO) is promising in this regard. A judicious combination of topical therapy, eschar excision and skin grafting helps in quick healing. Decompressive escharotomy of circumferential burns of the chest, abdomen and extremities must be performed without delay.

Analgesia. Adequate control of pain and anxiety is essential to minimize the stress response in burn injury. Narcotics are the commonest form of analgesia in major burns.

Nutrition. Attention to the nutritional needs of a burned child is an essential component of management (Table 26.11). High caloric and nitrogen intake is crucial for survival.

Table 26.11: Caloric requirement in children with burns

Infants:	2100 Cal/m^2 + 1000 Cal/m^2 burn surface area
Children:	1800 Cal/m^2 + 1300 Cal/m^2 burn surface area
Adolescents:	1500 Cal/m^2 surface area and burn surface area

Adequate protein intake (2–3 g/kg body weight) and supplementation of trace vitamins and minerals are necessary. Whenever feasible, particularly in children with less than 15–20% burns, nutrients should be administered by the enteral route. Tube feeding is started on the first day of admission with rapid advancement towards intake goals. In children with more extensive burns, inhalation injury or prolonged paralytic ileus, parenteral nutrition may be considered.

Supportive measures. Assessment of physical abilities and enabling full range of joint movements by physical and occupational therapy and play therapy is encouraged. Family support and evaluation of the child's social environment should not be overlooked.

Drowning

Drowning is a form of asphyxial death in which the access of air to the lungs is prevented by the submersion of the body in water or other fluid medium. In India, drowning is an important cause of child mortality. Though drowning occurs most frequently in natural bodies of water like ponds, lakes and rivers, deaths due to drowning in swimming pool and bath tubs are increasing.

Aspiration and Suffocation

Many young children die every year due to suffocation caused by ingestion of foreign objects. More than 50% accidental deaths among infants are caused by aspiration of food during or after feeding. Peanuts are usually responsible for aspiration-related suffocation fatalities in 2–4-yr-old children. Eating rapidly, improper chewing, running with food in mouth or holding a potential foreign body in the mouth (such as a pin, nail or small toy) may cause such accidents. Less common reasons include accidental suffocation due to pacifier cords, cords of cradles, small chains, necklace and rarely, by being crushed by adults sleeping in the same bed as a young infant.

Most injuries can be prevented by ensuring discipline, which includes immediate stopping of all dangerous practices such as door banging, throwing objects around the room and playing on the stairs. Even a young child of 1 to 1½ yr can be trained to keep away from the kitchen stove or electrical connections. Parents should not allow any dangerous habits such as turning on the gas taps that are done for attention seeking. However, they should be aware that excessive discipline and overstrictness may force their children to rebel against restrictions making them vulnerable to injuries.

Suggested Reading

Child Health Dialogue 15. Dealing with accidents and injuries. www.healthlink.org.uk/PDFs/chd15.pdf

Children's Environmental Health Annual Report 2011. http://www.who.int/ceh/publications/ceh_annualreport_2011.pdf

Summary of principles for evaluating health risks in children associated with exposure to chemicals. http://www.who.int/ceh/publications/health_risks_exposure_chemicals/en/index.html

27 Pediatric Critical Care

Rakesh Lodha, Manjunatha Sarthi

The availability of facilities for pediatric intensive care has resulted in improved child survival. In tertiary care hospitals, 5–10% of total pediatric beds should be earmarked for ICU; greater if the hospital has surgical units. The common indications for admission to PICU are listed in Table 27.1.

Table 27.1: Indications for admission to PICU

Hemodynamic instability or shock requiring inotropic support and intensive monitoring; cardiac arrhythmias or cardiorespiratory arrest; severe anemia or hemorrhage
Respiratory distress requiring oxygen therapy; impending or established respiratory failure requiring mechanical ventilation
Altered sensorium due to any cause; encephalopathy; status epilepticus; raised intracranial pressure
Acute hepatic failure or its complication
Acute renal failure or its complications
Severe hyper- or hypokalemia; severe hyper- or hyponatremia; hypoglycemia; diabetic ketoacidosis
Severe malaria; severe pneumonia
Acute poisoning
Procedures: Peritoneal dialysis, exchange transfusion, central venous cannulation, postoperative monitoring

The optimal number of beds in an ICU is six to ten, with an area of about 200–250 square feet provided per bed. The unit should have an uninterrupted power supply. Preferably, the unit should be air-conditioned. The type and arrangement of beds should allow rapid access to the head end for airway management. A trolley having all the necessary drugs and resuscitation equipment should be available all the time. The ICU should have equipment for cardiorespiratory monitoring, ECG monitoring, pulse oximeters, devices for oxygen therapy, mechanical ventilators, nebulizers and devices for IV therapy including infusion pumps. The ICU should have access to laboratory facilities, preferably relying on micromethods. The ICU physicians, nurses and technical staff have a key role in care of critically ill children.

Suggested Reading

Consensus guidelines for pediatric intensive care units in India. Indian Pediatr 2002;39:43–50

ASSESSMENT AND MONITORING OF A SERIOUSLY ILL CHILD

Assessment

The primary assessment is done using the ABCDE approach. **A** stands for '**A**irway assessment' and is categorized as clear, maintainable and not maintainable. **B** stands for '**B**reathing assessment' and includes the respiratory rate, respiratory effort, tidal volume, abnormal sounds by auscultation and pulse oximetry. **C** stands for '**C**irculation assessment' by skin color and temperature, heart rate, heart rhythm, blood pressure, central and peripheral pulses, capillary refill time and assessment of end organ perfusion (mental status, skin perfusion and urine output). **D** stands for '**D**isability' which establishes the level of consciousness and is assessed by AVPU pediatric response scale (**A** for alert, **V** for response to vocal stimuli, **P** for response only to painful stimuli, or **U** if unresponsive) or the Glasgow Coma Scale and pupillary response to light. **E** stands for '**E**xposure' where the body parts are examined for temperature (hypo- or hyperthermia), skin rashes or wounds.

Features suggestive of serious illness are listed in Table 27.2. These features predict a serious condition particularly in young infants. In addition, history should focus on identifying any underlying chronic illness. Commonly performed investigations in a sick child include complete blood count, blood glucose and electrolytes, and if feasible, arterial blood gas estimation. Further investigations are tailored to the clinical profile.

Table 27.2: Common danger signs in children

Drowsiness, decreased activity
Excessive or inconsolable cry
Seizures
Increased work of breathing
Abnormal sounds on breathing
Apneic episodes or cyanosis
Cold extremities (particularly in warm environment)
Decreased urine output (e.g. less than 4 wet nappies in 24 hr)
Decreased feeding or decreased intake of fluids
Bilious vomiting

Monitoring

Monitoring of critically ill children is an essential component of management. The purposes of monitoring are: (i) to measure intermittently or continuously key indices that help in early diagnosis and management; (ii) to provide alarms that notify the health care team that changes have occurred in the child's condition; and (iii) to evaluate trends that help in the assessment of response to treatment and prognosis.

Respiratory Monitoring

Physical examination. The child should be observed for respiratory rate and pattern, nasal flaring, use of accessory muscles and color. Auscultation is done for symmetry of air entry, type of breath sounds and presence of stridor, rhonchi and crepitations.

Use of monitors. Respiratory rate (Table 27.3) can be monitored continuously by *impedance pneumography*, which requires the presence of three electrodes over the chest. *Pulse oximetry* has made it possible to noninvasively measure percent oxygen saturation of hemoglobin. Pulse oximetry is reliable in most settings. However, some conditions lead to inaccuracies, e.g. dyshemoglobinemias (methemoglobin, carbon monoxide), dyes and pigments (methylene blue), poor peripheral perfusion, increased venous pulsations and optical interference with external light sources like phototherapy unit or fluorescent light.

Table 27.3: Normal respiratory and heart rates according to age

Age, yr	*Respiratory rate, breaths/min*	*Heart rate, beats/min*
1	30 (22–38)	120 (80–160)
2	25 (17–33)	110 (80–130)
4	23 (17–27)	100 (80–120)
6	21 (15–26)	100 (75–115)
8	20 (15–26)	90 (70–110)
10	18 (15–25)	90 (70–110)
12	18 (14–26)	85 (65–105)
14	17 (15–23)	80 (60–100)
16	17 (12–22)	75 (55–95)

Numbers in parentheses indicate normal range

Transcutaneous blood gas monitoring is now feasible and makes continuous monitoring of PO_2 and PCO_2 possible. However, it has limitations of need for frequent calibration, high costs and occasional burns. *Capnography* is the graphic waveform produced by variations in CO_2 concentration throughout the respiratory cycle. A side stream or mainstream sampler samples the gases inspired and expired by the patient. CO_2 is estimated in these samples by infrared spectroscopy. *End-tidal* CO_2 can be used a substitute for $PaCO_2$. $EtCO_2$ also has a role in determining endotracheal tube placement, dead space, and mechanical ventilation failures. In mechanically ventilated children, respiratory mechanics help in understanding of respiratory pathophysiology. Apart from these continuous monitoring modalities, *chest radiography* and *arterial blood gas* analyses are performed periodically.

Hemodynamic Monitoring

Physical examination. Repeated examination of a critically ill child is the cornerstone of hemodynamic monitoring. The rate and character of pulse should be examined. Blood pressure can be monitored by noninvasive or invasive methods. The pressures may be determined manually (aneroid manometers) or by use of automated (oscillometry) systems. Invasive methods rely on placement of a catheter in an artery and pressure measurement by manometer.

The state of microcirculation can be assessed by the capillary refill time. Pressure is applied with the index finger or ball of thumb over sternum or forehead for 5 seconds to cause blanching. On removal of pressure, the color returns and the time taken for complete return of color is noted. The normal capillary refill time is 3 seconds or lower; prolongation signifies impairment of microcirculation. This helps in diagnosing hemodynamic compromise earlier than drop in arterial blood pressures. Another way of determining adequacy of the peripheral perfusion is noting the core peripheral temperature gradient; gradient of more than 5°C indicates hypoperfusion.

Continuous ECG monitoring. This is mandatory in critically ill children admitted in ICU.

Central venous pressures. These are monitored by placing a catheter through a large vein into the right atrium. The pressure gives information about the venous return and the preload. Normal right atrial pressure is less than 6 mm Hg. If the pressure is low in a child with hypotension, it signifies a low intravascular fluid volume. On the other hand, central venous pressure may be increased due to myocardial dysfunction, fluid overload or increased pulmonary artery pressures.

Monitoring vital organ perfusion. This is assessed by monitoring urine output, which is a surrogate marker of renal perfusion and function. Urine output less than 0.5 ml/kg/hr in a child with normal kidneys signifies poor

renal perfusion. Monitoring of the sensorium and neurologic status also gives information about vital organ perfusion.

Suggested Reading

Cheifetz IM, Venkataraman ST, Hamel DS. Respiratory monitoring. In: Nichols, David G, (Eds.). Roger's Textbook of Pediatric Intensive Care, 4th edn. Philadelphia (USA): Lippincott Williams & Wilkins, 2008; 662–85

Frankel LR. Monitoring techniques for the critically ill infants and children. In: Behrman RE, Kliegman RM, Jenson HB (Eds) Nelson Text book of Pediatrics,19th edition. Philadelphia: WB Saunders; 2010

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Tibby SM, Murdoch IA. Monitoring cardiac function in intensive care. Arch Dis Child 2003; 88:46–52

PEDIATRIC BASIC AND ADVANCED LIFE SUPPORT

Cardiopulmonary arrest in children is much less common than in adults and frequently represents the terminal event of progressive shock or respiratory failure. The major causes of death in infants and children are respiratory failure, sudden infant death syndrome, sepsis, neurologic diseases, submersion or drowning and injuries. Basic life support (BLS) refers to a protocol mandatory in cases of cardiopulmonary arrest providing cardiopulmonary resuscitation (CPR) with or without devices and bag-mask ventilation till advanced life support (ALS) can be provided. Two major objectives of cardiopulmonary resuscitation are to preserve organ viability during cardiac arrest and to help return of spontaneous circulation.

27

Basic Life Support

To maximize survival and intact neurological status in postresuscitation stage, early recognition of the cardiac arrest and strict adherence to the BLS sequence is necessary. BLS guidelines give a series of skills performed sequentially to assess and restore effective ventilation and circulation in the child with respiratory or cardiorespiratory arrest. Evaluation and interventions in pediatric BLS should be a simultaneous process. The sequence of BLS is (i) assessment; (ii) circulation; (iii) airway; and (iv) breathing.

Assessment

Initial assessment is done to look for the evidence of cardiac arrest so that life-saving measures such as CPR are initiated. The most accurate method of recognizing cardiac arrest is the combination of unresponsiveness and absent or abnormal breathing. Palpation of the pulse (for its absence) as the sole determinant of cardiac arrest is unreliable. If the victim is unresponsive, not breathing normally and there are no signs of life, rescuers should begin CPR. In infants and children with no signs of life, health care providers should begin CPR unless they can definitely palpate a pulse within 10 seconds.

Circulation

The CPR should begin with chest compression rather than opening the airway and delivering the rescue breathing. Chest compressions are serial rhythmic compressions of the chest that cause blood flow to the vital organs (heart, lungs and brain) in an attempt to keep them viable until ALS (advanced life support) is available. To provide optimum chest compression, victim should be lying supine on a hard and flat surface. High quality chest compressions should be given by pushing hard, to a depth of at least one-third the anterior-posterior dimension or approximately 1½ inches (4 cm) in infants, and at least one-third the anterior-posterior dimension or approximately 2 inches (5 cm) in children. The compression rate should be at least 100 per minute, allowing full chest recoil and minimizing the interruptions in chest compressions.

Chest compressions in infants (<1 yr)

i. *Two-thumb technique.* The infant's chest is encircled with both hands; fingers are spread around the thorax and the thumbs brought together over the lower half of the sternum avoiding the xiphisternum. The sternum is compressed with the thumbs and the thorax with the fingers for counter pressure. The 2 thumb–encircling hands technique is preferred because it produces higher coronary artery perfusion pressure, more consistently results in appropriate depth or force of compression and may generate higher systolic and diastolic pressures. While one provider performs chest compressions, the other maintains the airway and performs ventilations at a ratio of 15:2 with as short a pause in compressions as possible.

ii. *Two-finger technique.* If the rescuer is alone or unable to physically encircle the victim's chest, chest compression is done using 2 fingers. Two fingers of one hand are placed vertically over the sternum just below the intermammary line (between the two nipples) ensuring that the fingers are not over xiphoid process. One hand may be placed under the infant supporting the body and head and the other hand performs the compression.

Chest compressions in children (1–8 yr age) The heel of one hand should be placed over lower half of sternum avoiding pressure over xiphoid with fingers lifted above the chest wall to prevent compression of rib cage (Fig. 27.1). Rescuer should position himself vertically above the victim's chest.

Chest compression for large children and those above 8-yr-old The two-hand method for chest compression is used to achieve an adequate depth of compression. This is achieved by placing heel of one hand over the lower half of sternum and heel of the other hand over the first hand, interlocking the fingers of both hands with fingers lifted above the chest wall.

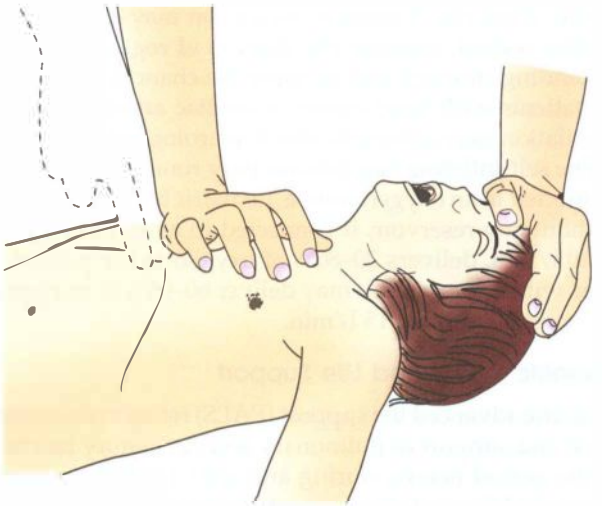

Fig. 27.1: Chest compression in a child

External chest compression in children and infants should always be accompanied by rescue breathing. Ventilations are relatively less important during the first minute of CPR for victims of sudden arrhythmia induced cardiac arrest than they are after asphyxia-induced arrest, but even in asphyxial arrest, a minute ventilation that is lower than normal is likely to maintain an adequate ventilation-perfusion ratio because cardiac output and therefore, pulmonary blood flow produced by chest compressions is quite low. The lay rescuers should use a 30:2 compression-ventilation ratio for all (infant, child and adult) victims. For one healthcare provider, the compression-ventilation ratio should be 30:2 for all age groups. For two rescuers, the compression-ventilation ratio should be 30:2 for all adult CPR and 15:2 compression ventilation ratio for infant and child up to the start of puberty. When advanced airway (tracheal tube) is *in situ*, the compression should not be interrupted for ventilation.

The victim should be reassessed after 2 min. If signs of spontaneous circulation have reappeared, chest compression should be stopped and only ventilation continued till return of adequate spontaneous breathing.

Airway

Infants and children are at higher risk of having respiratory obstruction and failure due to the following reasons: smaller size of upper airway in comparison to adults, large size of tongue in relation to the size of oropharynx, smaller and compliant subglottic area prone for collapse and/or obstruction, relatively compliant chest wall and rib cage, and limited oxygen reserve.

Positioning the victim If the child is unresponsive but breathing or signs of life present, the child should be placed on a hard surface with face up or in supine position. If head or neck trauma is suspected, head and torso should be moved as a unit and the neck immobilized.

Opening the airway The tongue is the most common cause of respiratory obstruction in unresponsive children and all the measures are targeted to lift the tongue away from the posterior pharynx to keep the airway patent.

i. *Head tilt chin lift maneuver.* If the victim is unresponsive, the airway is opened by tilting the head back and lifting the chin (Fig. 27.2). One hand is placed over the child's forehead and the head is gently tilted back. At the same time the fingers of the other hand are placed on the lower jaw to lift the chin to open the airway. This maneuver should not be used if there is suspicion of trauma to head and/or neck.

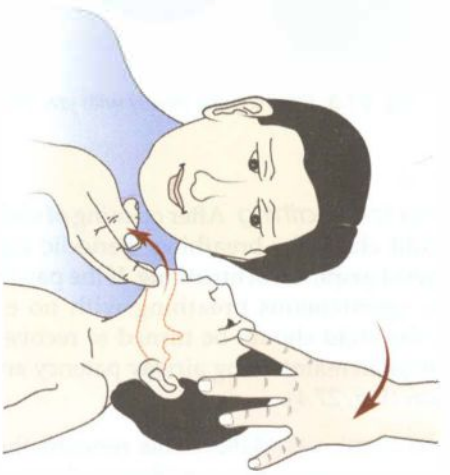

Fig. 27.2: Head tilt chin lift maneuver

ii. *Jaw thrust.* Two or three fingers are placed under each side of lower jaw at its angle to lift the jaw upwards and outwards (Fig. 27.3). If this method is unsuccessful, the head may be extended slightly and another attempt is made. This method should be used in all victims with blunt trauma, craniofacial injury, and those having Glasgow Coma Scale score of less than 8. This method is no longer recommended for the lay rescuer because it is difficult to learn and perform, is often not effective and may cause spinal movement.

Foreign body airway obstruction. If this is suspected, one should open the mouth and look for the foreign body. If seen, it should be carefully removed under vision. If the victim is an infant who is responsive and has had features of airway obstruction, back slaps and chest thrusts should be performed till the foreign body comes out or till the infant becomes unresponsive (*see* Chapter 28). Similarly, if the victim is an older child or adolescent, abdominal thrusts can be given by standing behind the victim till the foreign body is expelled out or till the patient becomes unresponsive. If such a victim becomes unresponsive, CPR should be initiated with an additional maneuver of checking the airway for the foreign body after giving the chest compressions and before breaths are given.

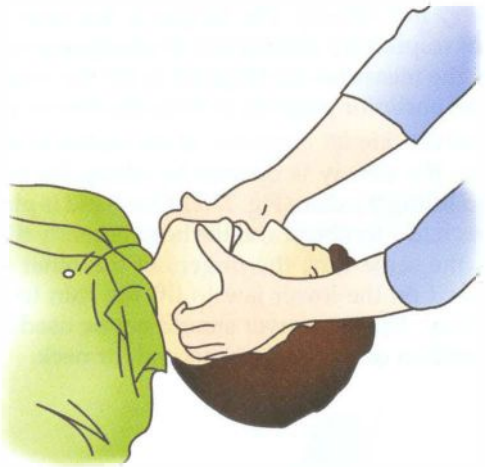

Fig. 27.3: Opening the airway with jaw thrust

Breathing

Checking for breathing After opening of child's airway, one should check for breathing. Periodic gasping, also called *agonal gasps*, is not breathing. If the patient is having effective spontaneous breathing with no evidence of trauma, the child should be turned to recovery position which helps in maintaining airway patency and prevents aspiration (Fig. 27.4).

Bag and mask ventilation This remains the preferred technique for emergency ventilation during the initial steps of resuscitation. *Self-inflating* bags are available in pediatric and adult sizes. *Flow-inflating* bags need oxygen flow for inflation and can be used in the hospital setup. For term neonates, infants and children <8 yr of age, ventilation bags of minimum volume 450–500 ml should be used to deliver adequate amount of tidal volume. Neonatal size bags (250 ml) may be useful for preterm neonates. Regardless of the size of ventilation bag, adequate amount of tidal volume should be used to cause visible chest rise. Excessive expansion may compromise cardiac output, increase the chances of regurgitation by distending stomach and increase the chances of air leak. In patients with head injury or cardiac arrest, excessive ventilation may adversely affect neurological outcome.

The self-inflating bag delivers only room air unless it is connected to an oxygen source. Pediatric bag-valve device without any reservoir, if connected to an oxygen inflow of 10 l/min, delivers 30–80% of oxygen to the patient. If used with a reservoir, it may deliver 60–95% of oxygen at an oxygen inflow of 15 l/min.

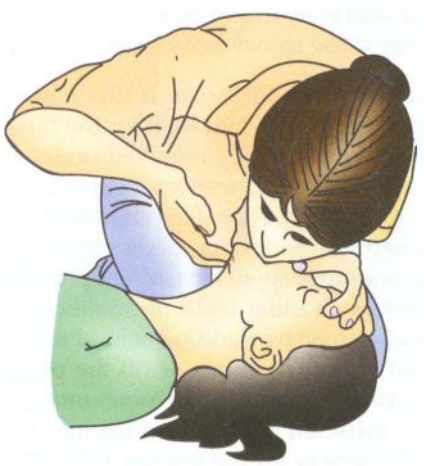

Fig. 27.4: Rescue breathing in a child

Pediatric Advanced Life Support

Pediatric advanced life support (PALS) refers to the assessment and support of pulmonary and circulatory function in the period before, during and after cardiorespiratory arrest. PALS targets the prevention of causes of arrest and early detection and treatment of cardiopulmonary compromise and arrest in critically ill or injured child.

Components of PALS

- Basic life support (BLS), as discussed above
- Use of equipments and techniques to establish and maintain effective oxygenation, ventilation and perfusion
- Clinical and ECG monitoring along with arrhythmia detection and management
- Establishing and maintaining vascular access
- Identification and treatment of reversible causes of cardiopulmonary arrest
- Emergency treatment of patients with cardiac and respiratory arrest
- Treating patients with trauma, shock, respiratory failure or other pre-arrest conditions.

Adjuncts for Airway and Ventilation

Oxygen should be given to all seriously ill or injured children with respiratory insufficiency, shock and trauma. During mouth-to-mouth rescue breathings, 16–17% oxygen is delivered with alveolar oxygen pressure of 80 mm Hg, and optimal external chest compressions provide only a fraction of cardiac output, resulting in reduced tissue perfusion and oxygen delivery. Ventilation-perfusion mismatch during CPR and underlying respiratory conditions causes right to left shunting resulting in reduced oxygenation.

Oxygen can be administered by facemask, nasal cannula, pharyngeal mask, laryngeal mask and endotracheal tube with ventilation. All fluids from patients should be treated as potentially infectious and standard universal precautions should be followed.

Endotracheal Intubation

If used properly, this is the most effective and reliable method of ventilation. The advantages of endotracheal intubation are that it (i) ensures adequate ventilation;

(ii) reduces risk of aspiration of gastric contents; (iii) inspiratory time and peak inspiratory pressure can be controlled; (iv) suction can be done to keep airway patent; and (v) positive end-expiratory pressure can be provided. The disadvantages of endotracheal intubation over bag and mask ventilation are that (i) a skilled person is required for the intubation and (ii) it is associated with complications like hypoxia, cardiac arrest or injury to airway during the procedure. Hence, it is recommended that bag and mask ventilation be continued in infants and children who require ventilatory support in the out of hospital setting, when transport time is short or when an expert is not available for intubation. The indications for endotracheal intubation are listed in Table 27.4.

Table 27.4: Indications for endotracheal intubation

Excessive work of breathing leading to fatigue
Apnea or poor respiratory effort
Functional or anatomical airway obstruction
Need for high peak inspiratory and/or positive end-expiratory pressure for effective gas exchange
Lack of airway protective reflexes
Prolonged cardiopulmonary resuscitation

The airway in a child is more compliant with a relatively large tongue and anteriorly placed glottis. As the subglottic area is the narrowest part of the airway, uncuffed endotracheal tubes are used in children below 8 yr of age. In certain circumstances (e.g. poor lung compliance, high airway resistance, or a large glottic air leak) a cuffed tube may be preferred. If cuffed tracheal tubes are used, the cuff pressure should not exceed 20 cm water. An appropriate sized endotracheal tube should be used (Table 27.5). Beyond 1 yr of age, the size of the tracheal tube is estimated as follows:

Tracheal tube size (in mm) = (Age in yr/4) + 4.

In general, tubes 0.5 mm smaller and 0.5 mm larger than the estimated size should be available for use. The size of suction catheter is usually twice the internal diameter of the tracheal tube in mm, i.e. 8 Fr suction catheter for tracheal tube of size 4 mm.

Procedure Endotracheal intubation should always be preceded by supplemental oxygen and the attempt at intubation should not exceed approximately 20 seconds, as hypoxia created during prolonged intubation attempts increases morbidity. The procedure should be aborted if bradycardia (rate below 60 per minute), deterioration in hemodynamic status, change in color (sudden pallor or cyanosis) or fall in oxygen saturation are noted. Assisted ventilation should be continued by bag-mask ventilation with supplemental oxygen until the patient's condition improves. In special circumstances, like acute respiratory distress syndrome (ARDS) requiring high peak inspiratory pressure that cannot be maintained by bag-mask ventilation alone, intubation should be considered despite presence of bradycardia or cyanosis.

Table 27.5: Sizes of endotracheal tube and suction catheters in infants

Age	*Tube size (mm)*	*Suction catheter size (Fr)*
Premature newborn <1 kg	2.5	5
Premature newborn 1–2 kg	3.0	5–6
Newborn 2–3 kg	3.0–3.5	6–8
Newborn >3 kg	3.5– 4.0	8
Infant (1–12 mo)	3.5–4.0	8

A straight blade laryngoscope is used for infants and curved ones for children beyond 1–2 yr of age. The blade tip is passed over the epiglottis followed by blade traction to lift the base of tongue and epiglottis anteriorly, exposing the glottis. Endotracheal intubation should be attempted after visualizing the glottic opening. Confirmation of intubation is done by detection of exhaled CO_2 using colorimetric detection or capnography. While intubating, the black mark on the tracheal tube (vocal guide) should be kept at the level of vocal cords to place the tube in proper position. It is recommended that the tube placement should be confirmed by looking for the symmetrical chest rise bilaterally and checking for equal air entry on both sides by auscultation at the axillae. Auscultation over upper abdomen is required to rule out esophageal intubation. Other markers of proper endotracheal tube placement are improving heart rate, color, perfusion and improving oxygen saturation. The position of the endotracheal tube should be confirmed by chest radiograph.

The depth of insertion of the endotracheal tube is approximately three times the inner diameter of the tube used. In newborns the depth of insertion depends on the birth weight, and is calculated as:

Depth of insertion (cm) = birthweight + 6

In children above 2 yr of age, the depth of insertion of endotracheal tube can be calculated as:

Depth of insertion (in cm) = (age in yr/2) + 12

Establishing and Maintaining Vascular Access

Intravenous access. During CPR, the preferred access is the largest, most easily accessible vein, cannulating which does not require interruption of the resuscitation. Central venous lines provide secure access to the circulation, rapid action and high peak drug levels and permit administration of drugs that might injure the peripheral sites if extravasated, such as vasopressors, hypertonic solutions like sodium bicarbonate or calcium gluconate. Femoral vein is the safest and easiest to access. Subclavian veins may be considered. Agents with short half-life such as vasopressors, adrenaline and adenosine act better if given through central venous access. Catheter lengths of 5 cm in infants, 8 cm in young children and 12 cm in older children are usually suitable.

Intraosseous access. Intraosseous access should be tried in all patients irrespective of age if the central or peripheral

venous access is not achieved. The usual site for intraosseous access is the upper end of the tibial, medial to tibial tuberosity (*see* Chapter 28). Other sites where the intraosseous lines can be secured in children are the distal end of femur, lower end of the tibia above the medial malleous and anterior superior iliac spine. Drugs like adrenaline, adenosine or vasopressors can be transfused by this route. It can be used to take samples for chemical analysis, blood grouping and cross matching.

Tracheal administration. Tracheal route is not the preferred route of administration of drugs even in emergency situation. If intravenous or intraosseus assess is not established in time, the tracheal route may be used for administration of lipid soluble drugs like lidocaine, epinephrine, atropine, naloxone. Nonlipid soluble drugs (e.g. sodium bicarbonate and calcium) may injure the airway and should not be administered *via* the endotracheal route.

Fluid Therapy

Early restoration of the circulating blood volume is important to prevent progression to refractory shock or cardiac arrest. Volume expansion is best achieved with isotonic crystalloid fluids, such as Ringer's lactate or normal saline. Blood replacement is indicated in patients with severe hemorrhagic shock who remain hypotensive even after the infusion of 40–60 ml/kg of crystalloid. Dextrose solutions should not be used for initial resuscitation as they do not expand the intravascular volume effectively and may cause hyperglycemia leading to osmotic diuresis, setting a vicious cycle of polyuria and hypovolemia. Recommendations cannot be made about the use of colloid solutions in fluid resuscitation of infants and children due to lack of studies. Hypoglycemia, if suspected or documented, should be managed readily with intravenous glucose with measures to prevent recurrence.

Drugs used for Cardiac Arrest and Resuscitation

Table 27.6 shows the drugs used commonly during resuscitation.

Arrhythmias

Most arrhythmias are the consequences of hypoxemia, acidosis and hypotension. However, children with myocarditis, cardiomyopathy and after cardiac surgery are at increased risk of primary arrhythmias. Drugs in therapeutic or toxic doses can also cause arrhythmia. About 10% of pediatric patients with cardiac arrest have ventricular fibrillation or pulseless ventricular tachycardia.

Bradyarrhythmias. Hypoxemia, hypothermia, acidosis, hypotension and hypoglycemia depress sinus node func-

Table 27.6: Drugs used during cardiopulmonary resuscitation

Drug	*Indications*	*Dosage*	*Adverse effects; caution*
Epinephrine	Symptomatic bradycardia, pulseless arrest	0.01 mg/kg (1:10,000, 0.1 ml/kg) IV or IO 0.1 mg/kg (of 1:1000) into ET; flush with 1–2 ml of saline Repeat every 3–5 min, if required	Tachyarrhythmia, hypertension
Atropine	Bradyarrhythmias	0.02 mg/kg (minimum dose: 0.1 mg)	Tachycardia, pupil dilatation
Calcium gluconate	Hypocalcemia, hypermagnesemia, hyperkalemia	1 ml/kg (1 ml of 10% solution contains 9 mg of elemental calcium) IV or IO, as slow push	Bradycardia; flush the line with saline before and after infusing; avoid extravasation
Glucose	Suspected or documented hypoglycemia	0.5–1 g/kg	Avoid hyperglycemia
Sodium bicarbonate	Severe metabolic acidosis, hyperkalemia	1 mEq/kg IV or IO slowly	Use only if ventilation is adequate; flush the line with saline before and after infusing
Adenosine	Supraventricular tachycardia	0.1 mg/kg IV or IO as rapid bolus; Repeat dose 0.2 mg/kg if required	Monitor ECG during dose; administer preferably through a vein close to the heart
Amiodarone	Pulseless ventricular fibrillation or ventricular tachycardia	5 mg/kg IV or IO	Monitor ECG during dose
Lidocaine	Ventricular fibrillation or ventricular tachycardia	1 mg/kg IV or IO followed by infusion at 20–50 µg/kg/min	Monitor ECG during dose
Naloxone	Opioid intoxication	0.1 mg/kg IV, IO or ET	Repeat doses may be required; watch for respiratory depression and hypotension
Magnesium sulfate	Torsades, suspected hypomagnesemia, acute severe asthma	25–50 mg/kg rapid push for first two indications; infusion over 30 min for asthma	

ET endotracheal tube; IO intraosseous; IV intravenous

tion and slow conduction through the myocardium. Excessive vagal stimulation, raised intracranial pressure or brainstem compression may cause bradycardia. Sinus bradycardia, sinus node arrest with junctional or idioventricular rhythm and AV blocks are the usual preterminal rhythms observed in infants and children. All slow rhythms resulting in hemodynamic instability require immediate treatment. Epinephrine is a useful drug in treating symptomatic bradycardia unless due to heart block or vagal overtone. For bradycardia due to vagal overtone, atropine is the drug of choice. If no effect is observed after ventilation and oxygenation, continuous infusion of epinephrine or dopamine should be considered.

Pulseless electrical activity. This is a state of electrical activity observed on a monitor or ECG in absence of detectable cardiac activity. This is often the preterminal state preceding asystole representing the electrical activity of a hypoxic and acidotic myocardium. Occasionally, the state may be due to sudden impairment of cardiac output, with normal ECG rhythm and increased or rapidly decreasing heart rate. Pulses or other evidence of cardiac output are absent and child appears lifeless, as in electromechanical dissociation. The reversible causes of electromechanical dissociation are severe hypovolemia, hypoxia, hypothermia, hyperkalemia, tension pneumothorax, toxins and drugs, pericardial tamponade and pulmonary thromboembolism.

Defibrillation. Defibrillation is the asynchronous depolarization of a critical mass of myocardium that successfully terminates ventricular fibrillation or pulseless ventricular tachycardia. It is successful in cases of sudden onset fibrillation along with oxygenated normothermic myocardium without significant acidosis. Small paddles are used in infants and children weighing less than 10 kg. Larger size defibrillator paddles, i.e. 8 to 10 cm in diameter, are recommended in children weighing more than 10 kg to maximize the current flow. One paddle is placed over the right side of the upper chest and the other one over the apex of the heart (to the left of the nipple over the left lower ribs).

The optimal electrical energy dose for defibrillation is not conclusively established in children, but varies from 2 to 4 J/kg. If this is unsuccessful, higher energy dose should be used. Single shock strategy followed by immediate CPR (beginning with chest compressions) is recommended for children with out-of-hospital or in-hospital ventricular fibrillation or pulseless ventricular tachycardia. After 5 cycles of CPR, the rhythm is checked to look for reversion to sinus rhythm. Simultaneous correction of hypoxia, acidosis and hypothermia is necessary. After failure of 3 attempts, a trial of defibrillation is repeated after administering epinephrine and CPR for 30 to 60 seconds. After the fourth failed defibrillation, the use of amiodarone (5 mg/kg bolus) or lidocaine (1 mg/kg) followed by defibrillation with 4 J/kg is recommended.

Suggested Reading

2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations; part 10: Pediatric Basic and Advanced Life Support. *Circulation* 2010;122:S466–515

SHOCK

Shock is an acute syndrome that occurs because of cardiovascular dysfunction and inability of circulatory system to provide adequate oxygen and nutrients to meet the metabolic demands of vital organs. Shock can be classified as: (i) hypovolemic; (ii) distributive (septic, anaphylactic, drug toxicity, neurogenic); (iii) cardiogenic (congenital heart disease, ischemic heart disease, cardiomyopathy, tamponade or arrhythmias); (iv) obstructive (pulmonary embolism); and (v) due to miscellaneous causes (pancreatitis, heat stroke or adrenal insufficiency).

Pathophysiology

The body has several regulatory systems that maintain adequate perfusion to vital vascular beds.

Baroreceptors. Reduction in mean arterial pressure or pulse pressure results in decreased stimulation of carotid sinus and aortic arch baroreceptors which leads to vasoconstriction by inhibition of vasomotor center. Vasoconstriction is severe in skeletal muscles, splanchnic and cutaneous vascular beds whereas flow is preserved in cerebral, coronary and renal circulation due to autoregulation.

Chemoreceptors. Hypotension causes reduced perfusion, local tissue hypoxia and acidosis leading to firing of signals from chemoreceptors. Increased signals from these receptors cause respiratory stimulation, increased vasoconstriction and cardiac function.

Humoral receptors. Release of epinephrine and norepinephrine from adrenal medulla and systemic adrenergic nerve endings causes vasoconstriction and inotropic and chronotropic effects. Release of vasopressin from the posterior pituitary leads to vasoconstriction and water reabsorption.

Renin-angiotensin-aldosterone system. Reduced renal perfusion stimulates release of renin from the juxtaglomerular cells of kidney. Renin enhances conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin converting enzyme. Angiotensin II is a potent vasoconstrictor and also stimulates release of aldosterone, enhancing renal sodium reabsorption.

Diagnosis

Diagnosis of shock at an early stage and appropriate management may improve the outcome. The management of a child with classic features of shock, including lethargy, ashen gray color, tachypnea, cold extremities with diminished peripheral pulses and hypotension, is difficult. Early diagnosis of shock requires a high degree of suspicion and

knowledge of conditions that predispose to shock. Children who have fever, an identifiable source of infection or hypovolemia due to any cause are at increased risk of developing shock. Signs of early shock include tachycardia, mild tachypnea, prolonged capillary refill (>2–3 sec), orthostatic change in blood pressure or pulse and mild irritability. Table 27.7 summarizes the features of various stages of shock. Unexplained tachycardia may be the earliest indicator of shock. Decreased tissue perfusion can be identified by changes in body temperature (i.e. cold extremities) and decreased capillary refill (rate of refill after firm pressure over soft tissues or nail bed for 5 seconds). Narrowing of pulse pressure is an early finding of shock due to reduction in systolic blood pressure and mild increase in diastolic blood pressure. Early septic shock reveals increased peripheral pulses, warm and overperfused extremities, widened pulse pressure and hyperdynamic precordium.

If the state of shock continues, the compensatory mechanisms are not enough to maintain the metabolic needs of the tissues. The cellular ischemia and inflammatory mediators released affect the microcirculation to compromise the functioning of brain, kidney and heart. Increase in tachypnea due to metabolic acidosis leads to reduction in $PaCO_2$ and respiratory alkalosis. Skin shows features of reduced capillary refill and mottling. Hypotension and oliguria sets in with hypothermia. Mental changes in the form of agitation, confusion, stupor and finally coma may occur.

Clues in the history that suggest hypovolemic shock include (i) fluid losses due to diarrhea, vomiting, blood loss, profuse and prolonged sweating, or polyuria or a combination of these; and (ii) decreased intake due to vomiting, poor appetite or fluid deprivation. Physical examination shows dry mucous membranes, absence of tears and decreased urine output. Others features are poor perfusion, delayed capillary refill, diminished peripheral pulses and poor color. The central venous pressure is usually low. Laboratory investigations show elevated blood urea and to a lesser extent creatinine, elevated uric acid levels and small cardiac silhouette on chest X-ray.

Patients with cardiogenic shock show presence of a murmur, extra heart sounds (S3, gallop), elevated JVP, hepatomegaly or friction rub. Central venous pressure is usually elevated. Chest X-ray film may show a large silhouette and pulmonary edema.

The triad of fever, tachypnea and tachycardia is common in benign infections in children. Septic shock is suspected if, in addition to these, there are features such as altered mentation, prolonged capillary refill of >2 seconds (cold shock) or flush capillary refill (warm shock), diminished or bounding peripheral pulses, or decreased urine output of <1 ml/kg/hr. Hypotension is a relatively late finding in septic shock.

Monitoring

Monitoring of patients who are in shock or impending shock is done to detect the alteration in physiologic status and intervene at the earliest. Clinical parameters to be monitored are pulse rate and volume, respiratory rate and pattern, temperature, skin color, blood pressure, sensorium, urine output, ECG and pulse oximetry. Metabolic parameters to be monitored are blood glucose, electrolytes and arterial blood gases. Invasive pressure monitoring should be done wherever possible by measurement of central venous pressure and by pulmonary arterial catheterization using a Swan-Ganz catheter.

Treatment

Therapy essentially depends on the type of shock. In hypovolemic shock, replacement of intravascular volume by isotonic intravenous fluid is the mainstay of therapy. Cardiogenic shock usually requires inotropic support. In some cases of cardiogenic shock, reduction of afterload by use of vasodilators may be beneficial.

Fluid Therapy

Vascular access. A large bore intravenous cannula on catheter should be placed in a large vein like femoral vein. In older children and adolescents, cannulation of internal jugular, external jugular, subclavian veins can be considered.

If there is undue delay in establishing central or peripheral venous access, intraosseous access should be considered in an emergency setting (*see* Chapter 28).

Choice of fluids and blood products. The first choice of fluid for acute resuscitation is normal saline or Ringer lactate. Large volumes of fluid for acute stabilization have not been shown to increase the rate of acute respiratory distress syndrome or cerebral edema in children. Crystalloids are the fluid of choice in the acute phase but if the fluid

Table 27.7: Stages of shock

Clinical parameter	*Compensated*	*Uncompensated*	*Irreversible*
Mental status	Agitation or confusion	Drowsiness	Unresponsive
Heart rate	Tachycardia	Marked tachycardia	Bradycardia
Respiration	Normal or mild tachypnea	Tachypnea and acidosis	Acidosis and/or apnea
Skin and capillary refill time	Increased capillary refill time with cold peripheral skin	Very slow capillary return and mottling	Cold and cyanotic skin
Urinary output	Adequate	Oliguria or anuria	Anuria
Blood pressure	Normal	Hypotension	Unrecordable

requirement is high, colloids (dextran, gelatin, 5% albumin) may be used. Experience with starch, hypertonic saline or hyperoncotic albumin is limited in pediatric practice. Packed RBC should be given at 10 ml/kg to maintain hematocrit at 33%.

Volume of fluids. Fluid infusion is best started with boluses of 20 ml/kg titrated with clinical parameters of cardiac output like heart rate, capillary refill, sensorium. The ideal first fluid should be normal saline or Ringer lactate and infused rapidly over 5–10 min. If no significant improvement is noticed, repeat boluses of 20 ml/kg should be given. Large volume fluid deficits may require 40 to 60 ml/kg and maximum up to 200 ml/kg for replenishing the deficit. The patients who do not respond to rapid boluses of 40–60 ml/kg in first hour of therapy are labeled as fluid refractory shock and should be given inotropic support. Such patients require invasive monitoring and need intubation and mechanical ventilation.

Vasoactive Drugs

Vasopressor therapy. Dopamine is accepted as the inotrope of choice for shock with high output and low systemic vascular resistance in both newborns and children (Table 27.8). Dopamine increases cardiac output at doses of 5–10 µg/kg/min. The vasoconstrictor effect of dopamine is evident at doses above 15 µg/kg/min due to release of norepinephrine from sympathetic vesicles which may not be well developed in infants below 6 months. Administering dopamine in 'renal' doses (2–5 µg/kg/min) does not have a role in preventing or treating acute kidney injury. Patients with shock refractory to dopamine may respond to norepinephrine or high doses of epinephrine. Some intensivists use low dose norepinephrine as the first line agent for warm hyperdynamic shock. The dose of vasopressors used can be titrated to perfusion pressure or systemic vascular resistance that ensures optimum urine output and creatinine clearance.

Inotropic therapy. After initial fluid resuscitation, myocardial contractility should be augmented to improve the cardiac output to meet the metabolic demand and catecholamines are the most useful drugs for this effect (Table 27.9). Dobutamine and mid-dose dopamine are first line inotropic agents in adults, but children may be less responsive. Epinephrine infusion is useful in cases of dopamine or dobutamine refractory shock. Low dose epinephrine may be used as first line choice for cold hypodynamic shock, i.e. low cardiac output states.

In children remaining normotensive with low output state and high vascular resistance despite epinephrine and vasodilator, use of type III phosphodiesterase inhibitors should be considered. These agents increase cyclic AMP and potentiate the α receptor stimulating effect on cardiac vascular tissue. These drugs should be discontinued at the first sign of tachyarrhythmia, hypotension or diminished systemic vascular resistance. Hypotension can be overcome by stopping epinephrine and starting norepinephrine which acts by stimulating α receptor activity.

Vasodilator therapy. Vasodilators are of use in pediatric patients remaining in hypodynamic with high systemic vascular resistance shock despite fluid and inotropic support (Table 27.8). Figure 27.5 outlines the plan of management of a child with septic shock.

Acid-base and Metabolic Parameters

Therapy with sodium bicarbonate rarely maintains the arterial pH if the perfusion and ventilation are not optimized. So, it should be considered as a temporary and immediate therapy to improve the myocardial function, only when the pH is less than 7.2. Improved circulation and oxygenation improves the acid-base homeostasis. Hypoglycemia and hypocalcemia should be rapidly diagnosed and corrected along with attempt to prevent recurrence.

Table 27.8: Vasoactive agents

Drug	*Dose range, µg/kg/min*	*Receptor activity*	*Use*	*Risk*
Vasopressor drugs				
Dopamine	5–20	$D_1/D_2 > \beta > \alpha$	Early inotropic need, septic shock	Peripheral vasoconstriction
Epinephrine	0.01 – 2*	$\beta_1 = \beta_2 > \alpha$	Anaphylaxis, cardiogenic shock	Ischemia, hypertension
Norepinephrine	0.05 – 1	$\beta_1 > \alpha > \beta_2$	Severe vasodilatation, hypotension	Acidosis from poor perfusion, ischemic injury
Phenylephrine	0.1– 0.5	α selective	Severe hypotension, hypercyanotic spells	Acidosis, ischemic injury
Vasodilator drugs				
Nitroprusside	0.3–7	Arteries > veins	Afterload reduction	Cyanide toxicity, hypotension
Nitroglycerin	0.5–5	Veins > arteries	Preload and afterload reduction	Hypotension, methemoglobinemia

*Vasoconstrictive dose is >0.2 µg/kg/min

Table 27.9: Inotropic drugs

Drug	*Dose range, µg/kg/min*	*Site of action*	*Use*	*Risk*
Inotropic drugs				
Dopamine	5–20	$D_1/D_2 > \beta > \alpha$ receptor	Early inotropic need, septic shock	Peripheral vasoconstriction
Dobutamine	3–20	$\beta_1 > \beta_2 > \alpha$ receptor	Contractility	Tachycardia, vasodilation
Epinephrine	0.01–2	$\beta_1 = \beta_2 > \alpha$ receptor but both actions noted	Contractility, vasoconstriction (at higher doses)	Tachycardia, vasoconstriction
Milrinone	0.3–0.7	Phosphodiesterase inhibitor	Inotropy, vasodilation	Tachycardia, vasodilation
Amrinone	5–10	Phosphodiesterase inhibitor	Inotropy, vasodilation	Tachycardia, vasodilation

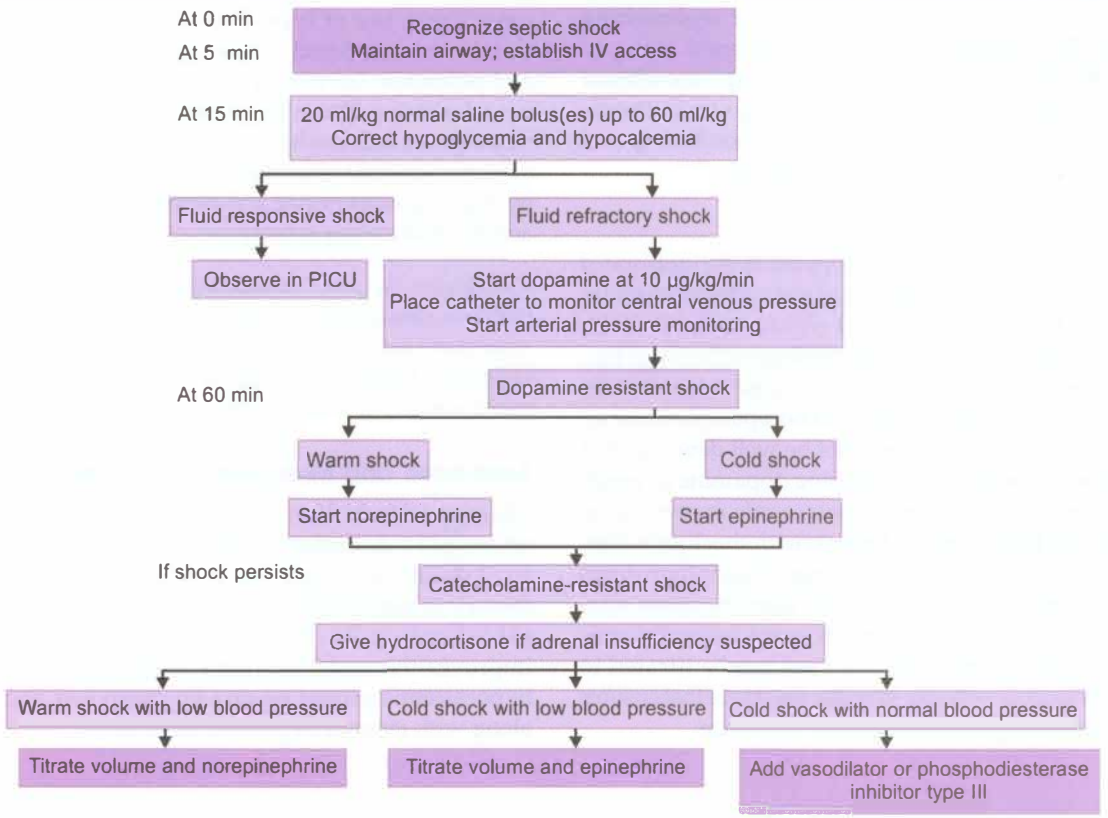

Fig. 27.5: Guidelines for management of septic shock. The first 60 minutes form the "golden hour" for management of shock

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Antibiotic Administration

Appropriate antibiotics should be administered to patients in septic shock. The choice of antibiotics depends on the focus of infection and the most likely pathogen. If no focus is obvious, the patient is given antibiotics that cover both gram negative and gram positive bacterial infections (e.g. third generation cephalosporin and vancomycin). Pus collections should be drained.

Steroids

Therapy with corticosteroids is recommended in patients with catecholamine-resistant shock and suspected or proven adrenal insufficiency. Other therapies that have been used anecdotally include naloxone hydrochloride (blocks endorphin effect), methylene blue (inhibits nitric oxide release), activated protein C and extracorporeal membrane oxygenation.

Suggested Reading

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MECHANICAL VENTILATION

Principles

The maintenance of normal gas exchange depends on adequate oxygenation and ventilation. Oxygenation depends on the fraction of O_2 (FiO_2) and the extent of ventilation-perfusion mismatch. Increasing the FiO_2 increases the alveolar PO_2 (PaO_2) and thereby the arterial PO_2 (PaO_2). Ventilation-perfusion mismatch is usually due to atelectasis or poorly ventilated alveolar units, which act as right to left shunts. These units can be recruited by increasing the mean airway pressure (MAP), which reduces mismatch and increases the end expiratory volume, thereby improving lung compliance. MAP depends on the peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), inspiratory time (Ti), expiratory time (Te) and the characteristics of the waveform (k).

$$MAP = \frac{k(Ti \times PIP) + (Te \times PEEP)}{(Ti + Te)}$$

$PaCO_2$ depends on CO_2 production and the alveolar ventilation.

Alveolar ventilation = [Tidal volume (V_T) – dead space volume (V_D)] × respiratory frequency (f)

The $PaCO_2$ can be altered by regulating V_T and frequency. Efforts should be made to minimize the dead space during mechanical ventilation. Tidal volume (V_T) depends on the difference between PIP and PEEP, airway resistance, compliance, and inspiratory time (Ti).

Indications

The indications for mechanical ventilation are listed in Table 27.10.

Modes

Mechanical ventilators can deliver four different types of breaths: mandatory, assisted, supported, or spontaneous, or a combination of these.

Mandatory or Controlled Ventilation

In controlled ventilation, all breaths are triggered, limited and cycled by the ventilator. This mode is used when the patient's ventilatory drive is limited or absent and during neuromuscular blockade by drugs.

Table 27.10: Indications for mechanical ventilation

Established or imminent respiratory failure due to (i) pulmonary disease and (ii) hypoventilation or apnea caused by central nervous system pathology
Impaired ventilation due to neuromuscular diseases or chest wall trauma
Postresuscitation for circulatory arrest
To reduce the work of breathing in circulatory shock
For hyperventilation to reduce raised intracranial pressure
Prophylactic indication: During and after surgery

Pressure control ventilation. The ventilator delivers positive pressure up to a predetermined pressure above PEEP at a set frequency during preset inspiratory time. The tidal volume delivered depends on the lung compliance. This mode is preferred in newborns and young infants.

Volume control ventilation. In this mode, a preset tidal volume is delivered during the set inspiratory time and a set frequency. In contrast to pressure control ventilation, a fixed tidal volume and minute ventilation are maintained. However, in newborns and young infants, the tidal volume required is small. In this scenario, the losses in the ventilator circuit significantly reduce the effective volume delivered to the lungs leading to ineffective ventilation, hence the pressure controlled mode is preferred.

Pressure regulated volume control ventilation. This mode combines the features of volume and pressure control modes. It uses decelerating inspiratory flow waveform to deliver a set tidal volume during the selected Ti and at set frequency. The advantage of this mode over volume control is that ventilation occurs at lower pressures, thereby reducing barotrauma.

Assisted Ventilation

Assisted ventilation is identical to the controlled modes except that the patient's inspiratory effort triggers the ventilator to deliver the breath using preselected limit and cycle variables, i.e. the ventilator completes patient triggered breathing efforts. Assisted ventilation thus reduces patient efforts and optimizes comfort. These modes are often used during weaning.

Assist control ventilation (ACV). In this mode of mechanical ventilation, the ventilator provides a preset V_T or pressure in response to every patient-initiated breath. If the patient fails to initiate a breath within a preselected time period, the ventilator delivers the V_T or pressure at the predetermined frequency. Since every inspiratory effort detected by the machine results in a mechanical breath, hyperventilation and respiratory alkalosis may occur.

Synchronized intermittent mandatory ventilation (SIMV). In this mode, mechanical breaths are delivered at a preset frequency, but the machine tries to deliver these breaths in response to the patient's spontaneous inspiratory efforts. For example, if a SIMV frequency of 20/minute is chosen, a breath is due every 3 seconds. If the machine detects patient's inspiratory effort during a small time window when the breath is due, it synchronizes the breath. If no such effort is detected during the time window, the machine delivers the breath on its own. In between the mandatory breaths, the patient can breathe spontaneously. There is no risk of hyperventilation even if patient is

breathing rapidly because only the set SIMV frequency will be delivered. While this mode has conventionally been used as a weaning mode, this mode can be used as a starting mode.

Supported Ventilation

Supported ventilation is defined as breaths that are triggered by the patient, limited by the ventilator and cycled by the patient. In *pressure support ventilation*, the patient triggers the ventilator to deliver a flow of gas sufficient to meet the patient's demands while the pressure in the circuit increases because of closure of the expiratory valve. Inspiration is terminated when the inspiratory flow decreases to a percentage of its initial peak value. This mode decreases inspiratory work and abolishes diaphragmatic muscle fatigue and enables weaning.

Adjusting Settings on Mechanical Ventilation

Patient age and weight, the specific disease and the underlying pathophysiology are important parameters considered when ventilator settings are adjusted. The choice of initial settings is summarized in Table 27.11. Higher PEEP may be required in ARDS.

While a patient is receiving mechanical ventilation, clinical assessment includes evaluation of chest movements/expansion, air entry, breath sounds and the color of the skin. Pulse oximetry is a useful adjunct. The patient ventilator interaction should be evaluated carefully and efforts are made to improve synchronization. After a short time of stabilization, blood gases are measured and necessary adjustments made.

Table 27.11: Guidelines for initiating positive pressure ventilation

Maintenance of adequate oxygenation
Set FiO_2 at 1.0
Keep peak end expiratory pressure (PEEP) at 3 cm H_2O or higher as required by underlying lung disease
Assess for signs of adequate oxygenation (e.g. color, pulse oximetry) and circulatory status
Measure PaO_2; decrease FiO_2 while maintaining PaO_2 70–80 mm Hg. In restrictive disease (low compliance, low functional residual capacity), increase PEEP to achieve PaO_2 >70 mm Hg at FiO_2 <0.6
Providing adequate alveolar ventilation
Set respiratory rate at physiologic norm for age
Select tidal volume (V_T) of 5–6 ml/kg
Keep peak inspiratory pressure (PIP) at about 15–20 cm H_2O for normal lungs, 20–25 cm H_2O for moderate pulmonary disease and at 25–30 cm H_2O for severe disease
Begin ventilation with the ratio of inspiratory to expiratory time (I:E) at 1:2, keeping the inspiratory time initially at 0.4–0.5 seconds in young infants and higher for older children
In obstructive disease, use longer expiratory time and avoid prolonged inspiratory time
Assess chest expansion and breath sounds to determine adequacy of ventilation
Measure $PaCO_2$; adjust V_T, PIP or rate to maintain $PaCO_2$ between 35 and 45 mm Hg

Weaning from Ventilation

Weaning is the process of discontinuation of mechanical ventilation. As the child's condition improves, the need for ventilatory support decreases. Decreasing support earlier than indicated imposes greater work of breathing which would delay extubation. Discontinuation of mechanical ventilation can be considered when: (i) the child is hemodynamically stable and neurologically improved; (ii) underlying disease and its complications have improved; (iii) ventilator support is minimal compared with the patient's spontaneous breathing; and (iv) the FiO_2 is low (≤0.4).

During weaning, the ventilator's contribution to total ventilation is gradually reduced, as the patients' share is increased. Usually during SIMV (preferable) mode or by reducing the frequency of pressure controlled breaths. This goes on until no or minimal ventilator breaths are used.

NUTRITION IN CRITICALLY ILL CHILDREN

A critically ill child is prone to develop malnutrition. Decreased intake and accelerated demands of severe illness due to stress results in increase in resting energy expenditure, proteolysis, gluconeogenesis, urinary nitrogen loss, glucose intolerance and resistance to insulin. In sick children, reduced nutrition intake is an important factor determining outcome. It is essential to provide adequate nutrition early in course of severe illness in order to improve the outcomes.

Two routes are available for administration of nutrients, enteral and parenteral. If the intestines are functioning, the enteral route is preferred, since it is safer and more cost effective than parenteral nutrition. Enteral nutrition helps in maintaining the gut barrier, preserves the indigenous flora and prevents overgrowth of the pathogens, reducing the risk of bacteremia and pneumonia. Enteral feeding prevents gut mucosal atrophy, so that resumption of oral feeds is easier during recovery.

While a milk based feed is simple, various commercial formulae are available to supplement nutrition. The elemental formulae contain carbohydrates as oligosaccharides, maltodextrins or hydrolyzed corn starch; nitrogen as peptides or free amino acid and lipids as various oils or medium-chain triglycerides. Special formulae are also available, e.g. low lactose or lactose free diets. It is important to start with 10–15 ml/kg/day of feeds and increase by 10–15 ml/kg/day till target calories are achieved. Enteral feeds may be delivered directly into the stomach by nasal/oral routes. Small-bowel feedings are useful in cases of gastroparesis. Supplementation of vitamins and minerals is best done by enteral route.

Common conditions where enteral feeding is contraindicated are severe gastrointestinal hemorrhage, recent gastrointestinal surgery and intestinal obstruction. Complications of enteral feeding are intolerance, misplacement of the feeding tube, esophagitis and esophageal ulceration. Gastroesophageal reflux may lead to pulmonary aspiration. Diarrhea may occur because of hyperosmolar formulae, infection or malabsorption.

Parenteral nutrition refers to the delivery of all the nutrients directly into the bloodstream, through amino acid mixtures, lipids, glucose and trace mineral and vitamins. These may be infused into a peripheral or central vein. The use of peripheral veins is limited by the osmolality of infusate (should be <700 mOsm/kg). Thus, for delivery of adequate calories, central venous access is essential.

For infants, the goal for calories is about 100 cal/kg/day. Glucose infusions are started at a rate of about 5–6 mg/kg/minute and increased gradually; insulin may be used if there is hyperglycemia. Amino acids are begun at 1 g/kg/day; then increased over 2–3 days to 2.5 g/kg/day. Lipids are infused at 0.5 g/kg on day 1 and increased to 2–2.5 g/kg/day over 4–5 days. Appropriate combination can be achieved by considering fluid requirements. Trace elements and vitamin preparations are added. Use of TPN requires regular monitoring blood glucose thrice a day; serum electrolytes and urea twice a week; and serum chemistry, triglycerides and complete blood counts once a week. Weight is recorded daily; other anthropometric measurements recorded once a week. Complications include catheter related infections, liver dysfunction, hyperglycemia, hyperlipidemia, acidosis and electrolyte imbalances.

The use of enteral formulae supplemented with immunonutrients has been demonstrated to modulate gut function, inflammatory and immune responses. Agents used for immunonutrition include glutamine, arginine, ω-3 fatty acids, nucleotides, taurine, cysteine, certain complex carbohydrates and probiotic bacteria. Use of immunonutrition might reduce morbidity and the risk of infectious complications in critically ill patients.

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SEDATION, ANALGESIA AND PARALYSIS

The management of acute pain and anxiety in children undergoing therapeutic and diagnostic procedures has improved substantially. The goal of sedation is safe and effective control of pain and anxiety so as to allow necessary procedures to be performed and to provide appropriate amnesia or decreased awareness.

The state of sedation varies from conscious sedation to deep sedation to general anesthesia. In conscious sedation, the consciousness is depressed but the protective airway reflexes are maintained and the child can respond appropriately to verbal command or physical stimulation. Deep sedation refers to a medically controlled state of depressed consciousness from which the child is not easily aroused. This is accompanied by partial or complete loss of protective reflexes and the child cannot respond purposefully to physical stimulation or verbal commands.

Monitoring is very important during sedation. The child's face, mouth and movement of chest wall must be continuously observed. Vital signs should be measured before and after administration of the drugs, on completion of the procedure, during recovery and at completion of recovery. ECG monitoring and pulse oximetry are useful adjuncts. The sedation and procedure room should have all the equipment for airway management and essential drugs for resuscitation.

Table 27.12 summarizes the details of commonly used drugs for sedation and analgesia. Table 27.13 lists various clinical scenarios requiring sedation or analgesia. For children undergoing mechanical ventilation, continuous infusion of midazolam or diazepam may be used for better control of ventilation. In addition, intermittent doses or continuous infusion of fentanyl or morphine may be used for pain control.

Neuromuscular Blocking Drugs

The use of neuromuscular blocking drugs is common in intensive care units. Succinylcholine is the only depolarizing muscle relaxant available. Nondepolarizing drugs include pancuronium, atracurium, vecuronium and rocuronium. Short-term indications for use of these drugs are to: (i) facilitate airway instrumentation; and (ii) facilitate invasive procedures; while longterm use is required (i) to facilitate mechanical ventilation, overcome patient-ventilation asynchrony and allow ventilation at high settings; (ii) for reduction of work of breathing and metabolic demands; (iii) for treatment of agitation unresponsive to maximum sedation and analgesia; (iv) to treat tetanus; and (v) to facilitate treatment of status epilepticus, under continuous EEG monitoring.

Children receiving neuromuscular blocking drugs should be monitored very carefully, particularly for position of artificial airway and adequate ventilation. Any child who requires paralysis should be sedated.

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NOSOCOMIAL INFECTIONS IN PICU

Nosocomial or hospital acquired infections are infections that occur during hospitalization and are not present or

Table 27.12: Drugs used commonly for sedation and analgesia

Drug	*Clinical effects*	*Dose*	*Onset of action, min*	*Duration of action, min*
Chloral hydrate	Sedation, motion control, anxiolysis; no analgesia	25–100 mg/kg PO	15–30	60–120
Triclofos	Sedation, motion control; no analgesia	20–100 mg/kg PO	30–45	4–6 hr
Midazolam	Sedation, motion control, anxiolysis; no analgesia	IV 0.05–0.1 mg/kg; maximum 0.4–0.6 mg/kg Infusion: 0.5–3.0 µg/kg/min	2–3	45–60
Diazepam	Sedation, motion control, anxiolysis; no analgesia	IV 0.2–0.3 mg/kg Infusion: 0.1–0.5 mg/kg/ hr	2–5	60–120
Propofol	Sedation, motion control; no analgesia	IV 0.5–1 mg/kg; then 0.1–0.5 mg/kg every 3–10 min Infusion: 5–10 µg/kg/min	1	10
Analgesic agents				
Morphine	Analgesia, sedation	IV 0.1 mg/kg		
Fentanyl	Analgesia	1 µg/kg/dose; may be repeated every 3 min. Infusion: 1–5 µg/kg/hr	2–3	30-60
Ketamine	Analgesia, dissociation, amnesia, motion control	IV 1–1.5 mg/kg over 1–2 min IM 3–5 mg/kg	1 3–5	15–60 15–150

IM intramuscular; IV intravenous; PO per orally

Table 27.13: Common indications and strategy for sedation and analgesia

Clinical scenarios	*Examples*	*Sedation strategy*
Noninvasive procedures	Computerized tomography Echocardiography Electroencephalography Magnetic resonance imaging Ultrasonography	Comforting in older children Chloral hydrate PO Triclofos PO Midazolam IV
Procedures associated with low level of pain and high anxiety	Intravenous cannulation Phlebotomy Lumbar puncture Flexible bronchoscopy	Comforting; local anesthesia
Procedures associated with high levels of pain and anxiety	Central catheter placement Bone marrow aspiration Endoscopy Incision and drainage of abscess Interventional radiology procedures Intercostal drainage Paracentesis	Midazolam and fentanyl or morphine IV; ketamine IV or IM

IM intramuscular; IV intravenous; PO per orally

incubating at admission. These also include infections that appear to have been acquired in hospital but do not manifest until after discharge. Hence, all infections diagnosed 48 hr after admission until 72 hr after discharge are considered nosocomial.

Nosocomial infections are a significant problem in PICUs. The increased risk of infection results from the severity of underlying disease, frequent invasive interventions and the use of devices that bypass natural barriers to infection. The estimated rates vary between 10 and 20 per 1000 patient days or 6–10% of all admissions. Primary bloodstream infections account for 25–30% of nosocomial infections; other common infections include, pneumonia (20–25%) and urinary tract infection (15–20%). Usual pathogens include *S. aureus*, coagulase negative staphylococci, *E. coli*, *P. aeruginosa*, *Klebseilla* spp., enterococci and *Candida*. The overall mortality attributed to nosocomial infections is about 10%.

The risk of nosocomial infections is increased in proportion to the severity of illness, the level of invasive monitoring, the indiscriminate use of antimicrobial agents and the nature of diagnostic procedures. The duration of stay in an ICU is an important determinant of nosocomial infection. The use of invasive devices (endotracheal tubes, intravascular catheters, urinary catheters) has an important role in causation of bloodstream infections, pneumonia and urinary tract infections. Occasionally, the environment may be the source of organisms causing life-threatening nosocomial infections, e.g. aspergillosis in immunocompromised individuals.

Strategies to Prevent Nosocomial Infections

Well-directed infection control activities can reduce the nosocomial infection rates by up to 50%. Each PICU should have an infection control program aimed at reducing the incidence of nosocomial infections. A team of health professionals should ensure implementation of the policies and compliance on part of the PICU team.

The importance of hand washing and hand disinfection is well proven. Appropriate hand washing should be followed by drying with disposable paper or cloth towel. Hygienic hand rubs are increasingly used. Rubbing of 3–5 ml of a fast acting preparation (n-propanol, isopropanol, ethanol and chlorhexidine diacetate) is an effective substitute to hand washing.

In addition to the specific measures mentioned earlier for prevention of specific nosocomial infections, proper sterilization or disinfection of various medical items is mandatory. Aseptic precautions should be followed whenever an invasive procedure is being carried out. Nutrition should be maintained; enteral nutrition is preferred to parenteral nutrition. Appropriate and rational prescription of antibiotics is essential to prevent emergence of resistant strains. There should be constant surveillance and periodic review of the antibiotic policies and prescriptions. Education of staff about various infection control practices and procedure-specific guidelines has an important role in reducing the incidence of infections.

Surveillance for nosocomial infections is an essential element of any infection control program. This provides data for identifying infected patients, determining the sites of infection and identifying risk factors that contribute to nosocomial infections. Control measures can be evaluated objectively if the surveillance is good.

Specific Measures to Prevent Infections

Nosocomial pneumonias. The colonization of upper airway by pathogenic microbes and thereby, the risk of nosocomial pneumonias, can be reduced by compliance to hospital infection control policies and effective hand washing by health care personnel. The use of antacids and H_2 blockers raises gastric pH and facilitates gastric microbial colonization. When indicated, sucralfate may be preferred for prophylaxis against gastric bleeding. Selective decontamination of the gut using tobramycin, gentamycin, polymyxin and nystatin is not recommended.

Contaminated respiratory therapy equipment has been implicated in nosocomial pneumonias. Resuscitation bags, ventilator tubings and nebulizers should be disinfected. Only sterile fluids should be nebulized or used in humidifiers. Care should be taken to prevent contamination during suctioning. Ventilator circuit tubings should be changed every 48 hr. Positioning with head end elevation reduces the risk of aspiration and nosocomial pneumonias.

Bloodstream infections. The chief factors associated with development of catheter-related bloodstream infections are: (i) breach in sterility of technique of insertion and maintenance of the catheter; (ii) administration of parenteral lipid solutions through the intravenous catheter; (iii) increased number of 'break-ins' into the catheter and/or intravenous tubings; and (iv) the presence of infection elsewhere in the body.

The following measures help in reducing catheter-related infections: (i) preferring catheter insertion into the subclavian, basilic or cephalic vein instead of femoral or internal jugular vein; (ii) using maximal aseptic precautions during catheter insertion; (iii) use of mupirocin ointment (reduces the risk of bacterial colonization but increases colonization rate of fungi); (iv) use of cotton gauze rather than transparent dressing; (v) insertion of catheter by an experienced physician; (vi) avoiding the use of TPN catheters for infusions other than TPN; and (vii) provision of adequate staff for management of patients with central venous catheters.

Urinary tract infections. The need for catheterization must be strictly evaluated. Strict asepsis should be maintained during insertion of the catheter using sterile gloves, drapes and local antiseptics. Closed drainage should be maintained with the collection tubing and bag kept below the level of the patient's bladder. The system must be handled and manipulated as infrequently as possible. The urinary catheter should be replaced by closed condom drainage, whenever possible. While antibiotic prophylaxis does reduce the frequency of infections, it is not universally recommended as it selects multidrug resistant strains.

Suggested Reading

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TRANSFUSIONS

Blood

The common indications for red cell transfusion in children are listed in Table 27.14.

Table 27.14: Common indications for red cell transfusion

Infants
Hematocrit ≤20% and asymptomatic with reticulocytes <100,000/mm^3
Hematocrit ≤30% and any of the following:
Oxygen requirement >35%
Requiring mechanical ventilation or continuous positive airway pressure
Significant apnea or bradycardia
Heart rate >180/min or respiratory rate >80/min persisting for >24 hr
Weight gain <10 g/day over 4 days while on ≥100 Cal/kg/day
Children
Hemoglobin ≤4g/dl (hematocrit ≤12%), irrespective of the clinical condition
Hemoglobin 4–6 g/dl (hematocrit 13–18%) with hypoxia, acidosis or impaired consciousness
Anemia with features of cardiac decompensation
Hyperparasitemia (>20%) during malaria

Transfusion for acute blood loss. If the patient with acute blood loss is not stabilized after 2 boluses of 20 ml/kg of isotonic crystalloids, it is likely that the loss exceeds 30% of blood volume; hence such patients should receive transfusion with fresh blood.

Transfusion for chronic anemia. Children with chronic anemia usually tolerate hemoglobin levels as low as 4 g/dl. It is important to identify the underlying cause of anemia and treat it appropriately. Standard rules regarding choice of blood group should be followed. For red cell transfusion, the choices are based on the principle that the recipient plasma must not contain antibodies corresponding to donor A and/or B antigens. For plasma and platelet transfusion, donor plasma must not contain A/B antibodies corresponding to recipient A or B antigens. Patients who are RhD antigen positive may receive RhD positive or negative RBCs but patients who are RhD negative should receive only RhD negative RBCs.

Quantity of transfusion. The quantity of blood administered depends on the donor hematocrit, pretransfusion hemoglobin level and patient's weight. If the hemoglobin level is above 5 g/dl and packed red cells (hematocrit 0.7–0.75) are used, a transfusion of 10 ml/kg usually raises hemoglobin level by 2.5 g/dl. If anemia has developed slowly and hemoglobin level is below 5 g/dl, red cells transfusion should be given slowly or in small quantities to avoid precipitating cardiac failure from circulatory overload.

Massive transfusion. The replacement of blood loss equivalent to or greater than the patients total blood volume with stored blood in less than 24 hr (70 ml/kg) in adults and 80–90 ml/kg children/infants constitutes massive transfusion.

Platelets

The need for platelet transfusion depends on the platelet count, bleeding tendency, underlying etiology and interventions like invasive procedures or surgery (Table 27.15). Platelet concentrates are usually prepared from whole blood donation and less commonly by apheresis. Usually, each unit (bag) of platelets contain about 5.5×10^{10} platelets, 50 ml plasma, trace to 0.5 ml of red cells and varying number of leukocytes (up to 10^8). Units of platelet collected by apheresis contain 3×10^{11} platelets, approximately 250–300 ml plasma, trace to 5 ml of RBCs and $10^6 - 10^9$ leukocytes. These units can be stored for up to 5 days at 20–24°C.

Plasma

Plasma is prepared from a whole blood donation by centrifugation or can be collected using automated apheresis techniques. When prepared from whole blood donations, each unit contains 150–250 ml of plasma and, immediately following collection, approximately 1 unit/ml of each of the coagulation factors. Coagulation factors V and VIII are heat-labile and not stable in plasma stored at 1–6°C. After 24 hr of donation, the plasma contains <15% of factor V and VIII. Plasma frozen within 8 hr of donation contains at least 0.7 U/ml of factor VIII and is called fresh frozen plasma (FFP). FFP may be stored for 12 months at temperature at or below –18°C. The use of FFP is limited to the treatment or prevention of clinically significant bleeding due to deficiency of one or more plasma coagulation factors. The indications for FFP transfusion are listed in the Table 27.16.

Dosage and administration. Compatibility tests are not necessary before plasma transfusion and it is only essential that the plasma is ABO compatible with the recipient's red cells. The Rh group need not be considered unless where large volumes of FFP are required. FFP is thawed in a water bath at 30–70°C or in a microwave designed for this purpose. The dose of FFP depends on the clinical situation and the underlying disease. If used at a dose

Table 27.15: Indications for transfusion of platelets

Platelet count <10 × 10^9/l due to any cause
Platelet count <20 × 10^9/l and bone marrow infiltration, severe mucositis, disseminated intravascular coagulation or anticoagulant therapy
Platelet count <30–40 × 10^9/l and disseminated intravascular coagulation
Platelet count <50–60 × 10^9/l and major surgical intervention

Table 27.16: Indications for transfusion of fresh frozen plasma

Anticoagulant overdose
Severe liver disease with prolonged prothrombin time or bleeding tendency
Disseminated intravascular coagulation
Massive or large volume transfusion
Isolated congenital coagulation factor deficiency, e.g. hemophilia A or B

10–20 ml/kg, it increases the level at coagulation factors by 20% immediately after infusion.

Cryoprecipitate

Cryoprecipitate is the precipitate formed when FFP is thawed at 4°C. It is then refrozen within 1 hr in 10–15 ml of the donor plasma and stored at –18°C or less for a period up to one year. This unit contains 80–100 units of factor VIII, 100–250 mg of fibrinogen, 40–60 mg of fibronectin, 40–70% of vWF and 30% of factor XIII.

Indications. These include hemophilia, von Willebrand disease and congenital deficiencies of fibrinogen or factor XIII.

Dose. ABO compatible units should be used and compatibility testing or consideration of Rh group is not necessary. One unit is administered for every 5–10 kg of recipient weight, rapidly over 1–2 hr.

Risks from Transfusion

Before prescribing blood or blood products, it is essential to weigh the benefits against the risks of transfusion. Tables 27.17 and 27.18 summarize adverse effects of transfusion of blood or blood products. Specific risks include: (i) risk of serious hemolytic transfusion reaction; (ii) transmission of infectious agents including HIV, HBV, HCV, syphilis, malaria, CMV; and (iii) contamination of blood products with bacteria due to inappropriate collection or storage.

Table 27.17: Acute adverse effects with use of blood and blood products

Category	*Signs*	*Symptoms*	*Cause*	*Treatment*
Mild	Urticaria, rash	Pruritus	Hypersensitivity reaction	Slow infusion; administer antihistamine (chlorpheniramine maleate 0.1 mg/kg). If no improvement in 30 min, treat as next category
Moderately severe	Flushing, urticaria, rigors, fever, restlessness, tachycardia	Anxiety, itching, palpitations, mild dyspnea, headache	Hypersensitivity reaction	Stop infusion, replace IV set; notify blood bank; send sample from bag and patient for repeat cross-matching; administer antihistamine and antipyretic; given IV hydrocortisone and bronchodilator, send urine sample for hemolysis. If improvement noted, restart infusion slowly; if no improvement in 15 min; treat as next category
Life-threatening	Rigors, fever, restlessness, hypotension, tachycardia, hemoglobinuria, disseminated intravascular coagulation	Anxiety, chest pain, pain at IV site, respiratory distress, backache, headache, dyspnea	Hemolysis; bacterial contamination; fluid overload; anaphylaxis; transfusion associated lung injury; septic shock	Stop infusion; change IV set; administer 20 ml/kg of normal saline, repeat if needed; initiate inotropes if needed; elevate the legs; administer oxygen; maintain airway; give adrenaline (1:1000) 0.01 mg/kg IV or subcutaneous; IV hydrocortisone and bronchodilator; notify blood bank; send sample from bag and patient for repeat cross-matching; send urine sample for hemolysis. If bleeding, give platelets, cryoprecipitate, fresh frozen plasma or factor concentrates; institute supportive management for acute kidney injury

Table 27.18: Delayed complications of transfusion

Type of reaction	*Clinical features; timing after transfusion*	*Treatment*
Delayed hemolytic reaction	Fever, anemia, jaundice; 5–10 days	No treatment; if hypotensive, treat as acute intravascular hemolysis
Post transfusion purpura	Increased tendency to bleed, thrombocytopenia; 5–10 days	High dose corticosteroids; intravenous immunoglobulin; plasma exchange
Graft versus host disease	Fever, rash, desquamation, diarrhea, hepatitis, pancytopenia; 10–12 days	Supportive care
Iron overload	Cardiac and liver failure in transfusion dependent patients; several weeks to months	Iron chelating agents such as desferioxamine subcutaneously or deferiprone orally

Time Limit for Infusion

There is a risk of bacterial proliferation or loss of function in blood products once they have been removed from the storage conditions.

Whole blood, packed red cells. Transfusion should be started within 30 min of removing the pack from storage temperature (+2 to +6°C). The transfusion should be completed within 4 hr of start if the hospital temperature is between 22°C and 25°C. In case of high ambient temperature, faster infusion is preferred.

Platelets. These should be infused as soon as they have been received and infusion should be completed in 30 min.

FFP. In adults, one unit of FFP (200–300 ml) is administered over 30–60 min, starting within 30 min of receiving. In children, the rate of infusion depends on the clinical condition.

The blood products should be infused through a new, sterile blood administration set containing an integral 170–200 µm filter which is changed every 12 hr if multiple transfusions are needed. For platelet transfusions, a fresh set primed with saline should be used.

Suggested Reading

Lacroix J, Luban NLC, Wong ECC. Blood products in the PICU. In: Nichols DG, ed. Roger's Textbook of Pediatric Intensive Care. 4th edn. Lippincott Williams & Wilkins, Philadelphia; 2008:584–99

Common Medical Procedures

28

Sidharth Kumar Sethi, Arvind Bagga

Medical procedures involved in care of children include diagnostic procedures and therapeutic interventions, some of which may be critical or life-saving. It is important to observe universal sterile precautions during any medical procedure and dispose waste articles appropriately. This chapter shall cover indications, key steps of the performance and potential complications for these procedures.

Obtaining Blood Specimens

Sampling of biological specimens is the most common procedure in clinical practice.

Indication Blood sampling may be required for tests to diagnose a variety of conditions: Blood culture is essential to detect bacteremia in a newborn with suspected sepsis or an older febrile child with toxic appearance. Two or three sets of samples should be drawn from separate venipuncture sites in patients with suspected endocarditis or fever of unknown origin. Simultaneous sampling of peripheral blood and from catheter lumen is useful in patients with suspected catheter related bloodstream infections.

Procedure Disinfectants used for preventing culture contamination with skin flora include povidone-iodine, 70% isopropyl ethyl alcohol or chlorhexidine, and are often used in combination. The vein is palpated and a tourniquet applied if the vein is not palpated. The site for venipuncture is cleaned with an alcohol wipe and left to dry for a minute. Povidone-iodine is applied in concentric circles outwards, allowed to dry for at least 60 seconds. The two steps are repeated to minimize contamination. The vein is punctured at an acute angle to the skin with the bleb of the needle pointing upwards and directed cephalad. The appropriate volume for blood culture depends on the broth system used; most require drawing of 3–10 ml of blood. The likelihood and degree of bacteremia is more in children than adults, and therefore, a smaller volume may be sufficient. Some tube-based pediatric Bactec broths require only 0.5 ml of blood.

Complications Common complications with phlebotomy include local pain, swelling and extravasation of blood. Poor skin preparation is a common cause of blood culture contamination. Bacteria from the phlebotomist's hands or respiratory droplets may also contaminate blood culture.

Removal of an Aspirated Foreign Body

Foreign body airway obstruction is a common medical emergency, especially in children younger than 5-yr-old. Most events are witnessed and may be caused by choking on toy parts, seeds, nuts, grapes, pebbles or buttons. The usual presentation is with sudden onset of cough, gagging or stridor with or without respiratory distress. A foreign body obstructing the upper airway completely can cause hypoxemia, cyanosis and secondary cardiac arrest. If the child can speak, breathe or cough, partial obstruction is likely. While this indicates that there is no immediate threat to life, the foreign body may get dislodged and obstruct the airway totally.

Indication Patients with either complete airway obstruction or partial airway obstruction with poor air exchange require immediate relief.

Procedure A choking infant younger than 1 yr is placed face down over the rescuer's arm, with the head positioned below the trunk. Five measured back blows are delivered rapidly between the infant's scapulae using the heel of the hand (Fig. 28.1). If obstruction persists, the infant is rolled over and five rapid chest compressions are performed, similar to cardiopulmonary resuscitation. The sequence of back blows and chest compressions is repeated until the obstruction is relieved. Abdominal thrusts (Heimlich maneuver) may be performed in children older than 1 yr (Fig. 28.2). However, special care should be taken to avoid injury to abdominal organs, particularly in young children. When initial interventions fail, a jaw thrust is performed, since this may partially relieve the obstruction. If the

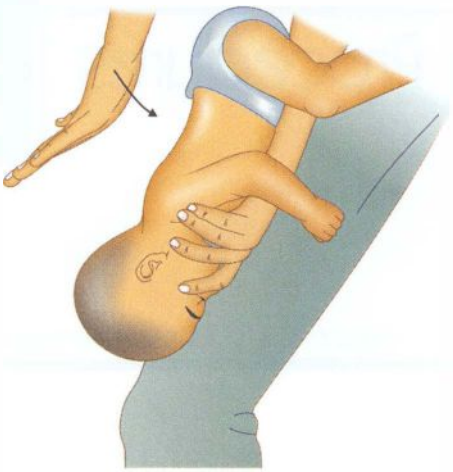


Fig. 28.1: Back blows in a choking infant

Fig. 28.2: Heimlich maneuver in a child

foreign body can be visualized, it should be removed manually using Magill or other large forceps.

In the unconscious apneic child, a tongue-jaw lift can be performed by grasping both tongue and lower jaw between the thumb and finger and lifting. Blind finger-sweeps are avoided in infants and young children because they may push the foreign body further back into the airway, worsening the obstruction. Children presenting with signs and symptoms of foreign body aspiration beyond the oropharynx into the trachea or bronchus require bronchoscopy by experienced personnel.

Complications Chest compressions may cause rib and cardiac damage in infants, but are rare if performed by experienced personnel. Uncommon complications of the Heimlich maneuver, if performed incorrectly, include pneumomediastinum, rupture of spleen or stomach and injury to the aorta.

Nasogastric Tube Insertion

Indications Nasogastric intubation is usually performed for: (i) administration of medications or nutrients in unconscious or anorexic children; (ii) gastrointestinal decompression in case of intestinal obstruction or trauma; and (iii) gastric lavage in a patient with upper gastrointestinal bleeding or toxin ingestion.

Procedure The largest size tube that does not cause undue discomfort to the child is chosen. Typically, an 8 Fr tube is used in neonates, 10 Fr for a 1-yr-old and increasing sizes in childhood up to 14–16 Fr tubes in teenagers. The length of tubing to be passed is estimated by adding 8–10 cm to the distance between the nostrils to the xiphoid process. The child is prepared by explaining the procedure as fully as possible; sedation is rarely needed.

Infants and obtunded children are placed supine with the head turned to one side. The curved tube is straightened and its patency checked with a syringe. Application of a lubricant facilitates atraumatic nasal passage. The tube is grasped 5–6 cm from the distal end and advanced posteriorly along the floor of the nose. It is inserted with its natural curve pointing downward in order to go past the bend of the posterior pharynx easily. The procedure is discontinued temporarily if the child coughs or gags or if the tube emerges from the mouth. When the tube is passed successfully to the measured length, its position is checked. Using a 5 ml syringe filled with air attached to the proximal end, the plunger is depressed rapidly while one auscultates for gurgling over the stomach. The tube is taped securely to the nose.

Complications The procedure may be associated with tracheal intubation, nasal or pharyngeal trauma, or vomiting.

Venous Catheterization

Peripheral Percutaneous Venous Catheterization

Small caliber plastic catheters and small over-the-needle catheters (22–24 gauge) are available to cannulate even the small veins of the hand, foot or scalp of neonates. Selection of catheter size and peripheral venous site are important issues. In older children, veins in the back of the hands and forearms are commonly used. For a patient in shock, the widest and shortest catheter is optimal, because longer, narrower catheters result in more resistance to flow. The greater saphenous vein, median cubital vein and external jugular vein are three sites that are often used because they are relatively large and consistent in location.

Before the vein is cannulated, the operator should wash his or her hands well and use universal precautions. The extremity should be adequately immobilized and the site cleansed with alcohol and povidone-iodine and allowed to dry. A tourniquet is applied proximally in order to engorge and distend the vein. The skin can be stretched taut with the operator's nondominant hand in order to immobilize

the vein. The operator should puncture the skin at a 15–30° angle, 5–10 mm distal to the expected entrance site into the vein. The subsequent puncture of the vein by the needle is suggested by blood return into the catheter hub. When this is noted, the catheter is advanced a few millimeters to ensure that the catheter tip, as well as the needle, is in the lumen of the vein. The catheter is then advanced over the needle into the vein, and the needle is removed. The tourniquet is released and saline is flushed intravenously to ensure patency of the catheter and vein. It is important to adequately secure and protect the catheter after successful cannulation.

The most common complication of peripheral venous cannulation is catheter displacement and infiltration of tissues with the infusing fluid.

Scalp Vein Catheterization

Indication To achieve intravenous access for delivering fluids and/or medications in infants, when peripheral extremity veins are unavailable.

Technique The infant below 1-yr-old has several easily accessible scalp veins. These include the frontal, supraorbital, posterior facial, superficial temporal and posterior auricular veins and their tributaries. The patient is restrained in a supine position while an assistant stabilizes the infant's head. The scalp is shaved in an area large enough to expose the desired veins and to allow adequate taping of the infusion needle. In this area, a vein is selected that has a straight segment at least as long as the part of the needle that is to be inserted.

The skin is prepared by cleansing with povidone-iodine solution followed by alcohol. A butterfly scalp vein needle is grasped by the plastic tabs or 'wings' and inserted in the direction of blood flow, piercing the skin approximately 0.5 cm proximal to the actual site where entry into the vein is anticipated. While applying mild traction on the skin of the scalp, the needle is slowly advanced through the skin toward the vein. Blood will enter the clear plastic tubing when successful venipuncture has occurred. Using a syringe filled with normal saline flush solution, 0.5 ml of saline is injected slowly. If the needle is satisfactorily inserted into the lumen of the vein, the solution will flow easily. Appearance of a skin wheal indicates that the vein has not been satisfactorily cannulated and another attempt must be made. After successful catheterization, the scalp vein needle is taped carefully.

Complications Inadvertent arterial puncture; ecchymoses and hematoma of the scalp may occur.

Central Venous Cannulation

Indications Usual indications include: (i) inability to establish venous access in the peripheral circulation; (ii) access for drugs and fluids that require central administration (e.g. vasopressors, hyperalimentation fluids, contrast medications); (iii) to monitor central venous pressure; and (iv) as an access for performing hemodialysis, plasmapheresis or continuous renal replacement therapies.

Procedure Principles common to all central venous catheter procedures, regardless of site, include: (i) strict attention to asepsis; (ii) use of the Seldinger technique (placement over a guidewire minimizes trauma and hematoma formation and enhances successful cannulation); (iii) adequate sedation to minimize movements; (iv) attention to appropriate location of catheter tip, avoiding high-risk sites such as ventricles and left atrium, verifying tip position with a radiograph; (v) avoiding placement in presence of a bleeding diathesis; and (vi) continuous monitoring of vital signs and oxygen saturation.

Sites The site of access depends on the indication (Table 28.1).

i. *External jugular vein.* The external jugular vein can be identified easily. There is less risk of pneumothorax. Complications are minimal because of the superficial position of the vein and the ability to compress the vein to prevent hemorrhage.

ii. *Internal jugular vein.* Internal jugular vein cannulation provides an excellent approach to the central circulation with a high success rate and minimal complications. Carotid artery puncture and pneumothorax are the most common complications. With left-sided cannulation there is potential for injury to the thoracic duct and there is a higher risk for pneumothorax because the apex of the left lung is higher than on the right.

iii. *Subclavian vein cannulation.* This vein is the preferred site in patients with longterm catheter requirements because of its relatively high level of patient comfort and ease of catheter maintenance. In patients with hypovolemia, the subclavian vein does not collapse as readily as other

Table 28.1: Preferred choices for placement of central line

Indication	*First choice*	*Second choice*
Emergency airway management or cardiopulmonary resuscitation	Femoral vein	Subclavian vein
Longterm parenteral nutrition	Subclavian vein	Internal jugular vein
Acute hemodialysis or plasmapheresis	Internal jugular vein	Femoral vein
Coagulopathy	Femoral vein	External jugular vein
Other purposes, e.g. access for surgery or medications	Internal jugular vein	Femoral or subclavian vein

major vessels because of fibrous attachments to directly below the clavicle. Major complication of subclavian vein cannulation are pneumothorax, subclavian artery puncture, or occasionally, hemothorax.

iv. *Femoral vein cannulation.* Femoral vein cannulation is the most common site for central vein cannulation as it is easily accessible, avoids possible pleura and lung puncture, does not require Trendelenburg position and serious complications are rare. All of these reasons make it popular in the pediatric patient, especially in one needing airway management or cardiopulmonary resuscitation. At the inguinal ligament the vein lies in the femoral sheath just below the skin line, just medial to the femoral artery, which is medial to the femoral branch of the genitofemoral nerve. The main complications are an arterial puncture, infection, and rarely, deep vein thrombosis (more common with long-dwelling catheters in adolescents).

Capillary Blood (Heel prick)

Indications Heel prick is a useful technique to obtain arterialized capillary blood for blood gas analysis, bilirubin, glucose, hematocrit and other parameters in newborns.

Technique Figure 28.3 indicates the appropriate areas to use for heel punctures for blood collection. Prewarming the infant's heel (using a cotton wad soaked in sterile warm water at 40°C or a hot towel) is important to obtain capillary blood gas samples as it increases the flow of blood, allowing collection of blood specimen. However, it is not recommended to use hot water, because baby's skin is thin and susceptible to thermal injury. After ensuring asepsis, a sterile blood lancet or a needle is punctured at the side of the heel in the appropriate regions as shown in Fig. 28.3. The central portion of the heel should be avoided as it might injure the underlying bone, which is close to the skin surface. Blood sample is obtained by alternate squeezing and releasing of calf muscles.

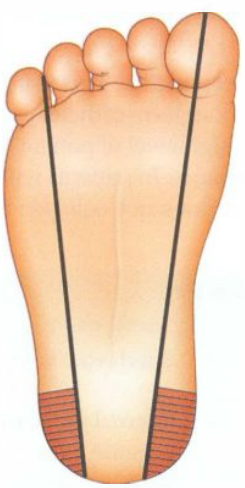


Fig. 28.3: Recommended sites for neonatal capillary blood sampling. Hatched areas indicate safe areas for puncture sites

Complications

The following complications may occur: (i) infection due to puncture of the calcaneus, resulting in necrotizing chondritis or osteomyelitis; (ii) calcified nodules of the heel; (iii) hemolysis, resulting in falsely elevated bilirubin and potassium levels from mechanical trauma; (iv) erroneously high glucose values due to alcohol in the swab; and (v) inaccurate pCO_2 and pO_2 values from poor blood flow.

Umbilical vessel catheterization

Indications The umbilical vein is a convenient route for obtaining vascular access in newborns during the first 7–10 days of life. The route is commonly used for administration of intravenous fluids or drugs during neonatal resuscitation, when establishing peripheral venous access is technically difficult. It is also employed as a route for central venous pressure monitoring and for performing exchange blood transfusion. Cannulation of the umbilical artery provides a route for arterial pressure monitoring or arterial blood sampling and alternative access for exchange blood transfusion.

Contraindications Omphalitis is a contraindication; the procedure should also be avoided in presence of peritonitis or necrotizing enterocolitis.

Equipment These include a 5 or 8 French catheter or feeding tube, 10 ml syringe, tape or silk suture to tie the base of the cord, normal saline for flushing, intravenous tubing and three-way connectors, a set of sterile drapes, sterile instruments (small iris forceps, needle holder and scalpel blade) and antiseptic for skin preparation.

Procedure The neonate is placed beneath a radiant warmer. Anesthesia is not required; the limbs are restrained gently. The abdomen and umbilicus are cleaned with chlorhexidine gluconate or povidone-iodine and sterile drapes placed, leaving the umbilical area exposed. Vital signs are monitored continuously. A suture is looped at the base of the cord with gentle constriction to anchor the cord and limit bleeding. The cord may need to be immobilized by two artery forceps grasping cord edges at 3 and 9 o'clock position. Using a scalpel blade, the cord is trimmed to 1–2 cm above the skin. The umbilical vessels are easily identified. The umbilical vein is a single, thin-walled, large diameter lumen, usually located at 12 o'clock position, while the two arteries have thicker walls with a small-diameter lumen (Fig. 28.4). The catheter or feeding tube is flushed with heparinized saline (1000 U/l) and attached to a three-way connector. A mark is placed at the length of insertion expected to place the catheter tip above the diaphragm but below the right atrium; this is calculated as 0.6 times the shoulder-to-umbilicus distance from the tip of the catheter. The closed ends of a pair of

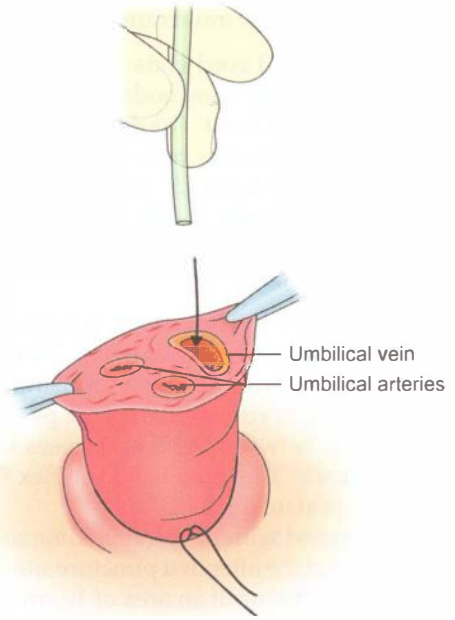


Fig. 28.4: Umbilical vein cannulation in a newborn. The umbilical vein is located at 12 o' clock position and is identified by its large lumen and thin walls

iris forceps are inserted into the lumen of the umbilical vein, and the lumen dilated by separating the ends of the forceps by opening it gently. Grasping the catheter with iris forceps 1 cm from its distal end, the catheter is inserted into the lumen of the umbilical vein and advanced gently inward until blood returns freely (Fig. 28.4). Resistance to advancement of the catheter indicates that the tip is in the portal vein or the ductus venosus; the catheter should be withdrawn until free flow of blood is noted. The catheter is flushed with saline and secured with a purse string suture. An X-ray is ordered to ensure that the tip of the catheter is in the inferior vena cava and not the hepatic vein or right atrium.

A similar procedure is followed for insertion of catheter into the umbilical artery. Since the lumen is smaller, the vessel is dilated carefully 2–3 times using a curved iris forceps and the catheter inserted gently, taking care to avoid vascular spasm. The catheter is advanced to either the high position (above the diaphragm between thoracic vertebrae T6 and T9) or the low position (above the aortic bifurcation between lumbar vertebral bodies L3 and L4).

Complications During insertion, vascular spasm, arterial injury or air embolism may occur and a false tract may get created. Other complications include bleeding due to accidental disconnection of IV tubing; catheter related infection, thrombosis and embolism; and incorrect position of the catheter tip causing cardiac arrhythmias, hepatic necrosis or portal hypertension. Vascular complications are common with the umbilical artery catheter, particularly if placed in the low position.

Suggested Reading

Anderson JD, Leonard D, Braner DAV, Lai S, Tegtmeyer K. Umbilical Vascular Catheterization N Engl J Med 2008;359:e18

Arterial Catheterization

Indications Arterial catheterization may be needed (i) to monitor blood pressure continuously, especially in hemodynamically unstable patients; and (ii) to monitor frequently the arterial blood gas.

Sites and procedure Radial artery cannulation is a primary site of arterial cannulation in infants and children. Right radial artery cannulation is performed when preductal arterial oxygen tension is required for evaluating and treating infants with congenital heart disease. It is often helpful to stabilize the hand and wrist on an arm board, placing the wrist in approximately 30–45 degrees extension over several gauze pads. Importantly, if the radial artery is selected for puncture or catheterization, adequacy of the palmar arterial arch should be assessed by the Allen test. The Allen test should be documented in the medical record before radial arterial puncture or catheterization is attempted.

Complications These include:

i. Disconnection of the catheter from the IV infusion
ii. Ischemia: The radial artery cannula should be withdrawn if ischemic changes develop
iii. Emboli: Blood clot or air may embolize to the digits or centrally, resulting in arteriolar spasm or ischemic necrosis
iv. Infection at the site of the catheter insertion can cause septicemia.

Intraosseous Infusion

Indications The bone marrow cavity is effectively a vascular space that does not collapse even in the setting of shock or cardiac arrest. Therefore, intraosseous access is the initial vascular access of choice in patients with severe hypotension such as cardiopulmonary arrest or decompensated shock. Almost any medication that can be administered into a central or peripheral vein can be safely infused into the bone marrow. Crystalloid solutions, colloids and blood products can be safely infused, as can hypertonic solutions.

Procedure The technique of intraosseous infusion is rapid and simple. The most commonly used sites are the proximal tibia, distal tibia and distal femur (Fig. 28.5). Due to differences in cortical thickness, the proximal tibia along the flat anteromedial surface of the shaft, 1–2 cm below the tibial tuberosity, is the preferred site in infants and young children. The distal tibia at the junction of the medial malleolus and the shaft of the tibia is the preferred site in older children. The distal one-third of the femur along the midline and approximately 3 cm above the sternal condyle can also be used.

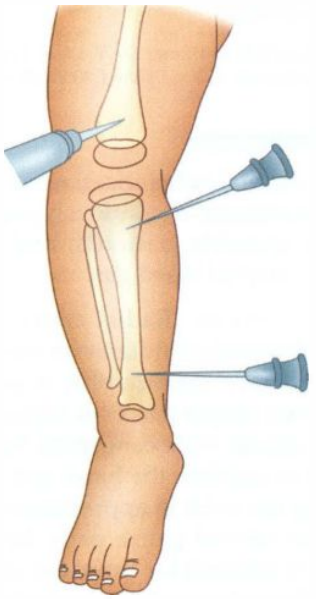


Fig. 28.5: Insertion sites for intraosseous infusion in the proximal tibia, 1–2 cm anteromedial from the tibial tuberosity, the distal tibia at the junction of medial malleolus and the shaft of the tibia, and the distal one-third of the femur

Technique Using aseptic technique, the site is prepared with an iodine solution. The skin is injected with 1% lidocaine for anesthesia in the awake patient. The needle is inserted at a 10° to 15° angle to the vertical, away from the joint space (caudal for the proximal tibia, cephalad for the distal tibia and femur). Pressure is applied in a 'to and fro' rotary motion. As the needle passes into the marrow, a 'give away' will be felt. The needle should stand without support. Evidence for successful entrance into the marrow include (i) the lack of resistance (or a 'give away') after the needle passes through the cortex, (ii) the ability of the needle to remain upright without support, (iii) aspiration of bone marrow into a syringe, and (iv) free flow of the infusion without significant subcutaneous infiltration. Aspiration of bone marrow into the intraosseous needle is not always possible, especially in very dehydrated patients. The stylet is removed. Proper placement is confirmed by aspiration of bone marrow into a 5 ml syringe and free flowing of a heparinized saline flush. The needle is connected to the desired intravenous tubing and solution. The site is observed for extravasation of fluids into the surrounding soft tissue. Presence of swelling indicates superficial needle placement or that the bone has been pierced posteriorly.

Complications Potential complications include osteomyelitis, subcutaneous abscess, extravasation of fluid into subcutaneous tissue, epiphyseal trauma and fat embolism.

Lumbar Puncture

Indications The procedure is performed to obtain cerebrospinal fluid (CSF) for the diagnosis of meningitis, meningoencephalitis, subarachnoid hemorrhage, metastatic leukemia or benign intracranial hypertension.

Procedure The spinal cord ends at approximately the level of the L1 and L2 vertebral bodies. Caudal to L2, only the filum terminale is present. The desired sites for lumbar puncture are the interspaces between the posterior elements of L3 and L4 or L4 and L5. These spaces are located by palpating the iliac crest. If one follows an imaginary 'plumb line' from the iliac crest to the spine, the interspace encountered is L4 to L5.

Lateral decubitus position. The patient is restrained in the lateral decubitus position as shown in Fig. 28.6A. The spine is maximally flexed without compromising the upper airway. Frequently, in young infants, the patient's hands can be held down between the flexed knees with one of the assistant's hands. The other hand can flex the infant's neck at the appropriate time.

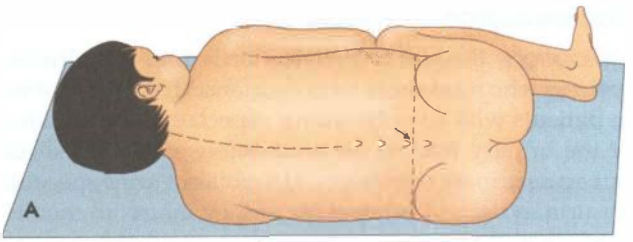
The skin is cleaned with povidone-iodine solution and alcohol beginning at the intended puncture site and sponging in widening circles until an area of 10 cm in diameter has been cleaned. This is allowed to dry. Local anesthesia is used in children older than 1 yr of age. The site is anesthetized by injecting 1% lidocaine intradermally to raise a wheal, then advancing the needle into the desired interspace and injecting the anesthetic, being careful not to inject it into a blood vessel or spinal canal.

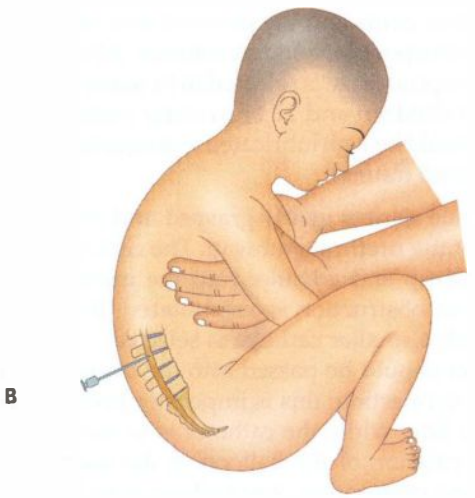
The spinal needle is grasped firmly with the bevel facing 'up' toward the ceiling, making the bevel parallel to the direction of the fibers of the ligamentum flavum. The needle is inserted into the skin over the selected interspace in the midline sagittal plane slowly, aiming slightly cephalad toward the umbilicus. When the ligamentum flavum and then the dura are punctured, a 'pop' and decreased resistance are felt. The stylet is removed to check for flow of spinal fluid.

About 1 ml of CSF is collected in sterile tubes for routine culture, glucose and protein determination and cell count. Additional samples are collected as indicated. The stylet is reinserted to remove the spinal needle with one quick motion. The back is cleaned and the puncture site covered.

Sitting position. The infant is restrained in the seated position with maximal spinal flexion (Fig. 28.6B). The assistant holds the infant's hands between his or her flexed legs with one hand and flexes the infant's head with the other hand. Drapes are placed underneath the child's buttocks and on the shoulders with an opening near the intended spinal puncture site. The interspace is chosen as noted earlier and the procedure follows steps as outlined for the lateral position. The needle is inserted so it runs parallel to the spinal cord.

Complications Lumbar puncture may be associated with headache, local back pain or infection. Brainstem herniation may occur in the presence of symptomatic intracranial hypertension.





Figs 28.6A and B: Lumbar puncture with the child in (A) decubitus position; (B) sitting position

Thoracocentesis or Pleural Tap

Indications Thoracocentesis is performed to evacuate fluid from the patient's pleural space for: (i) diagnostic purpose, e.g. pleural effusion or empyema; or (ii) therapeutic purpose, e.g. when large collections of pleural fluid compromise ventilatory function.

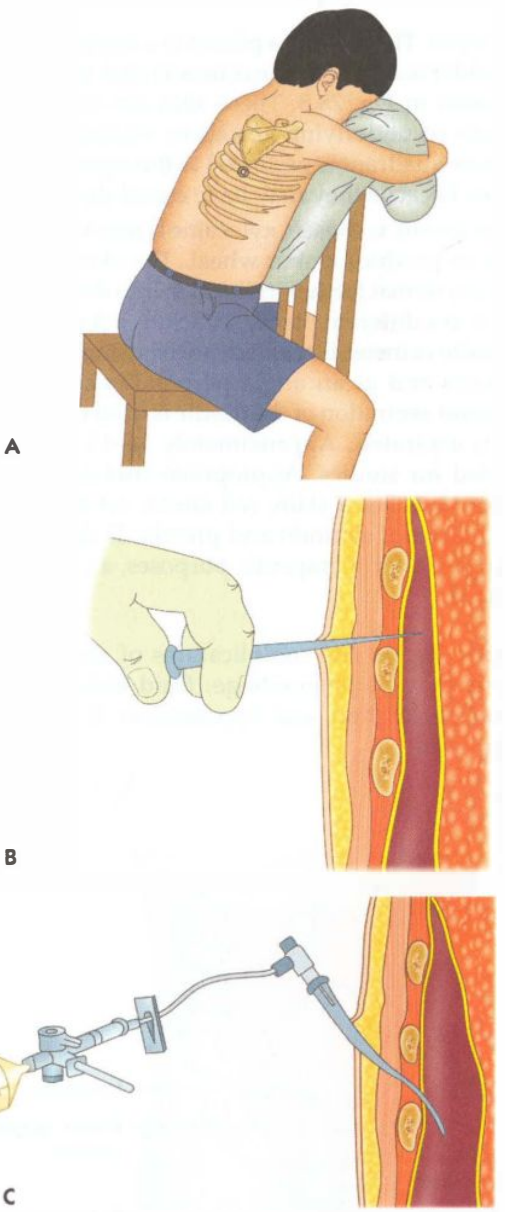
Contraindications These include: (i) uncooperative child; (ii) uncorrected coagulopathy; and (iii) persistent inability to draw fluid (which suggests a loculated effusion). The operator should consider withholding further attempts until the procedure can be performed under radiographic guidance (CT scan, ultrasound).

Technique The first step in thoracocentesis is to ensure by clinical and radiological methods that fluid is present in the area tapped. Decubitus films are helpful in demonstrating free fluid that shifts with movement.

The procedure (Figs 28.7A to C) is carried out with the patient appropriately positioned upright and leaning forward. The site of entry is anesthetized with local anesthetic. The landmark for evacuation of the fluid is the angle of the scapula that corresponds approximately to the eighth rib interspace. An appropriate catheter is used over a needle. The needle is introduced immediately above the superior edge of the rib to avoid puncturing the intercostal artery and vein. Once the pleural space is entered and fluid is aspirated, the catheter is advanced as the needle is withdrawn. The catheter is connected to a three-way stopcock and syringe (10–20 ml). It is important to control the aspiration of fluid such that air is not allowed to enter the pleural space from the outside.

Complications These include:

i. Intercostal artery puncture with severe hemorrhage
ii. Development of pneumo- or hemothorax



Figs 28.7A to C: Thoracocentesis: (A) The landmark for thoracocentesis is the angle of the scapula that corresponds approximately to the eighth rib interspace; (B) the needle is introduced immediately above the superior edge of the rib to avoid puncturing the intercostals vessels; (C) after inserting the catheter in the pleural space, the catheter is connected to a three-way stopcock and a syringe

iii. Malposition of the thoracocentesis needle, leading to injury of abdominal viscera or lung parenchymal puncture.

Abdominal Paracentesis or Ascitic Tap

Indications Ascitic tap is performed for diagnostic purpose, e.g. to determine the etiology of the peritoneal fluid and to determine whether infiltration is present, or for therapeutic reason, i.e. to remove large volumes of abdominal fluid which impair respiratory function.

Technique The patient is placed in a supine position and the bladder is emptied. The common sites for paracentesis are shown in Fig. 28.8. These sites are chosen to avoid puncture of underlying vessels or viscera. Usually, the left lower quadrant is preferred to the right in critically ill children because they may have caecal distension.

After the site is chosen, xylocaine is injected with a small needle to produce a skin wheal. The skin is then tilted anteriorly so that further infiltration into the subcutaneous tissue is in a different plane (Z tracking). A needle or over-the-needle catheter is then advanced using the Z tracking technique and at an angle perpendicular to the skin. Continued aspiration of the needle is used until peritoneal fluid is aspirated. Approximately 10–15 ml of fluid is aspirated for studies. Appropriate studies may include cultures and Gram stain, cell count, cytology, amylase, LDH, bilirubin, albumin and protein. If the paracentesis is performed for therapeutic purposes, a catheter should be placed.

Complications The complications of abdominal paracentesis may be hemorrhage, fluid leak, intestinal or bladder perforation, and hypotension, if large volumes are removed.

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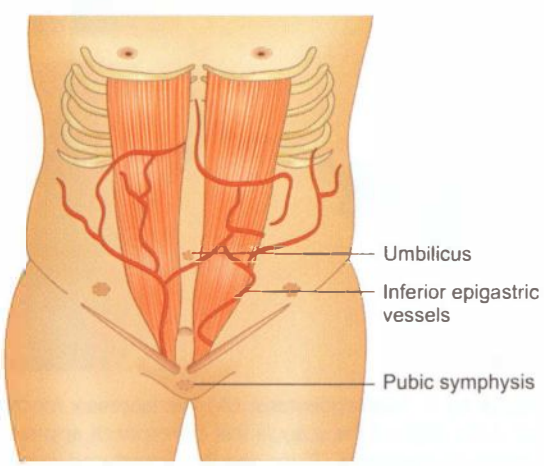


Fig. 28.8: Sites for abdominal paracentesis. The preferred sites are the linea alba (midway between the umbilicus and the pubic symphysis) and lateral to the rectus abdominis muscle

Catheterization of Bladder

Indications Bladder catheterization is done in bedridden patients who need short-term assistance. It is also required in patients with (i) polytrauma, especially for evaluation of the urinary tract in an unconscious child; (ii) shock; (iii) acute urinary retention; (iv) to obtain a urine specimen for urinalysis; and (v) in acute kidney injury, to monitor urine output.

Procedure The patient is restrained as necessary. The urethral meatus, penis and the perineal area are cleaned thoroughly with a povidone-iodine solution. A Foley catheter of the appropriate size is selected (8 Fr in the newborn, 10 Fr in most children and 12 Fr in older children). The catheter tip should be well lubricated with sterile lubricant to minimize local trauma.

Boys. The penile shaft is gently grasped and extended to straighten out the urethral pathway. The catheter is held near the distal tip and advanced up the urethra unless resistance or an obstruction is encountered. If resistance is encountered, a smaller catheter is selected.

The catheter should be passed into the bladder all the way to the Y-connection; this is important because urine may begin to flow while the catheter is in the proximal urethra and inflation of the balloon in the urethra may lead to urethral perforation. The balloon is inflated after advancing the catheter its entire length. The catheter is taped to the child's leg.

Girls. In the girls, the principles of catheterization are similar to those in the male. An assistant carefully spreads the labia. A well-lubricated Foley catheter is introduced into the bladder. The catheter is advanced its entire length before inflating the balloon. A catheter that is passed in its entirety is unlikely to be inadvertently located in the small vagina of a young girl. After withdrawing the catheter until a dunking sensation is appreciated, it is secured with tape.

Complications Injury to urethra or urinary bladder and inadvertent catheterization of the vagina may occur. Absence of aseptic precautions might result in urinary tract infection.

Peritoneal Dialysis

This modality of dialytic support is used for renal replacement therapy both in acute kidney injury (AKI) and end-stage renal disease. Catheters placed surgically for chronic ambulatory peritoneal dialysis are not discussed here

Indications The modality is used in patients with AKI in whom dialysis is indicated (*see* Chapter 16) and hemodialysis and continuous renal replacement therapies are not available, or if hemodialysis is contraindicated due to hemodynamic compromise or severe coagulation abnormalities. The technique is widely available, inexpensive and technically easy to perform even in newborns, allowing gradual correction of acid-base and electrolyte imbalance without need for anticoagulation.

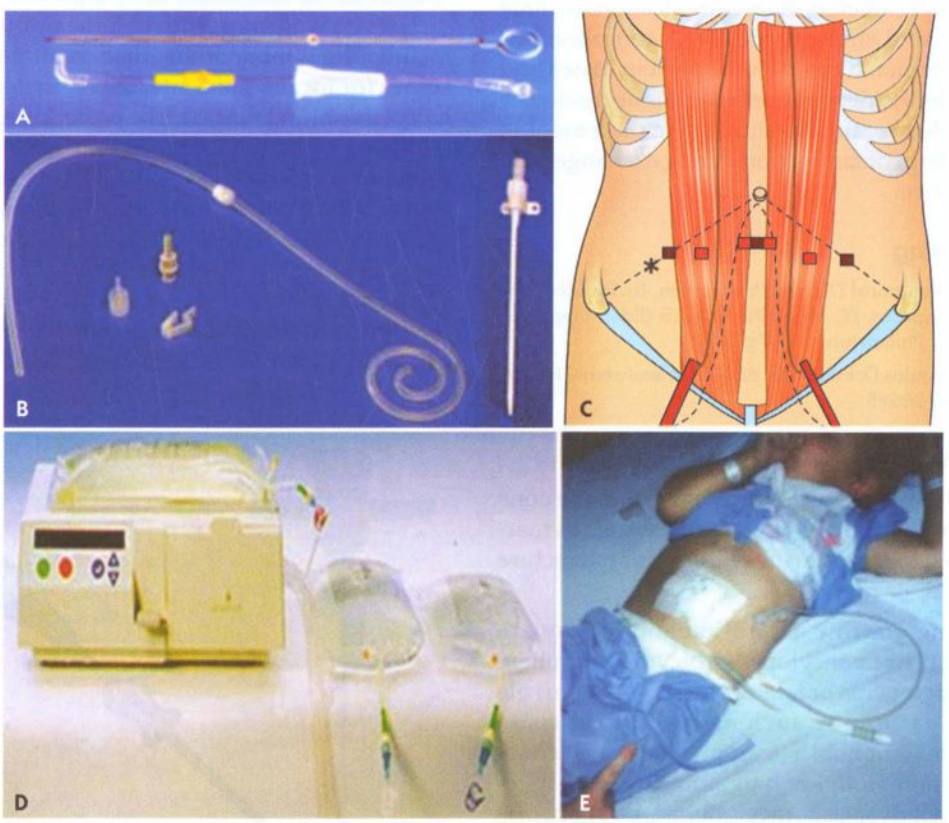
Contraindications Relative contraindications to peritoneal dialysis include recent abdominal and/or cardiothoracic surgery, diaphragmatic peritoneal-pleural fistula, fecal or fungal peritonitis and abdominal wall cellulitis.

Procedure Access for peritoneal dialysis can be achieved by inserting a rigid catheter (Fig. 28.9A) or a single cuff soft Tenckhoff catheter at the bedside (Fig. 28.9B). The double cuff Tenckhoff catheter, used for chronic peritoneal dialysis is placed in the operating room by a surgeon. A rigid acute PD catheter is easily available, inexpensive and relatively simple to insert. However, the risks of peritonitis are high, particularly if used for more than 48 hr.

The abdomen is cleansed with chlorhexidine and betadine and draped. Following administration of sedation and local anesthesia, an 18–22 gauge cannula is inserted below the umbilicus in the midline or lateral to the rectus abdominus muscle at two-thirds the distance between the umbilicus and the anterior superior iliac spine (Fig. 28.9C). About 20–30 ml/kg of peritoneal dialysis fluid is infused till the flanks appear full. The cannula is removed and the stiff catheter is inserted using the trocar. Once a 'give away' sensation is felt, dialysis fluid flows freely back into the catheter lumen. The catheter is inserted carefully avoiding injury to viscus by the trocar and guiding the tip of the catheter into the left iliac fossa. The trocar is removed and the catheter attached to a three-way connection to the peritoneal dialysis fluid and the drain bag. Once easy inflow and outflow are confirmed, the catheter is secured with a purse-string suture and manual cycles of dialysis are initiated.

The soft single cuff catheter is inserted using an introducer kit using the modified Seldinger technique. A tunnel is created in the soft tissue so that the exit site is away from the entry point into the peritoneum and the cuff protects from bacterial migration. This catheter is associated with lower risk of peritonitis particularly if used with an automated cycler device (Fig. 28.9D). It can be capped when not in use, allows ease of nursing, and can be used for several weeks (Fig. 28.9E).

Prescription Acute PD can be performed intermittently or continuously depending upon the desired amount of fluid and solute removal, and either manually by nurses or via an automated device. About 20–30 ml/kg is infused over 5 min, kept in the abdomen for 20–40 min, and then drained out. Ultrafiltration occurs due to the osmotic gradient created by the glucose in the fluid. The standard acute PD prescription includes the following components: length of



Figs 28.9A to E: Peritoneal dialysis. (A) Stiff uncuffed catheter used for acute peritoneal dialysis; (B) soft single cuff Tenckhoff catheter inserted bedside for acute dialysis; (C) the usual site of catheter insertion is in midline below the umbilicus or two-thirds of the distance between umbilicus and anterior superior iliac spine; (D) a device allowed automated control of dialysis and aseptic handling; (E) an infant undergoing dialysis with soft Tenckhoff catheter

the session, dialysate composition, exchange volume, inflow and outflow (drain) periods, dwell time, number of exchanges and additives such as heparin (for blood clots) or additional dextrose (to create more ultrafiltration). Ultrafiltration should not exceed 5–10% of body weight over 24–48 hr. The prescription is modified every 6–12 hr based on clinical evaluation and laboratory parameters. Acute manual PD requires constant supervision to ensure accurate inflow, dwell and drain times and the maintenance of a record of exchange and drain volumes and net ultrafiltration. By comparison, the use of the automated cycler reduces need for constant supervision and record maintenance and decreases the number of manual interruptions and risk of peritonitis.

Complications Acute PD may be associated with complications, some of which are serious. Abdominal pain or discomfort may occur due to abdominal distension, improper position of the catheter or peritonitis. Mild hemorrhage is frequent during catheter placement, particularly with rigid acute catheters. Leakage around the PD catheter site is common is managed by reducing the exchange volume or placing a suture at the exit site. Inadequate drainage is due to improper placement of the catheter tip or decreased bowel motility. Bowel perforations is rare but may be observed with the placement of stiff catheters. Rare complications include atelectasis and pleural effusion. Metabolic complications include hyperglycemia, hypokalemia, protein losses and hypernatremia. The incidence of peritonitis is decreased by maintaining sterile precautions during the placement of catheters, preventing contamination during exchanges and use of a cycler device.

Suggested Reading

Korbet, SM. Acute Peritoneal Dialysis Prescription. In: Handbook of Dialysis, 4th edn, Daugirdas, JT, Blake, PG, Ing, TS (Eds), Lippincott Williams and Wilkins, Philadelphia; 2007:p.382

Passadakis P, Oreopoulos D. Peritoneal dialysis in acute renal failure. Int J Artif Organs 2003;26:265

28

Bone Marrow Aspiration and Biopsy

A special bone marrow needle is introduced into the bone marrow space, and a sample aspirated for analysis. A marrow biopsy is taken to ascertain the cellularity, architecture of the marrow.

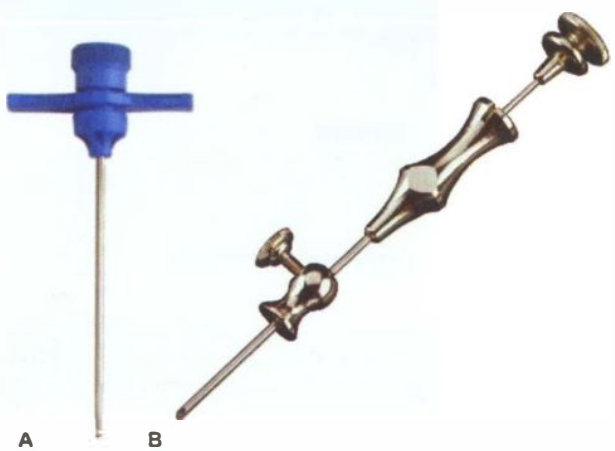
Indications Bone marrow aspiration and biopsy are indicated in presence of pancytopenia, bicytopenia, unexplained thrombocytopenia or leukocytosis in order to rule out significant pathology such as lymphoreticular malignancy (acute lymphoblastic or myelogenous leukemia, Hodgkin or non-Hodgkin lymphoma, chronic myeloid leukemia, myelodysplasia, myelofibrosis); hypoplastic or aplastic anemia; megaloblastic anemia; sideroblastic anemia; Langerhans cell histiocytosis; hemophagocytosis syndrome; suspected metastasis (retinoblastoma, neuroblastoma); infiltrative storage diseases (Gaucher disease) or infections involving the bone marrow (kala-azar, tuberculosis).

Sites The iliac crest is the most commonly used site. The sternum is not preferred in children because of associated pain and the risk of injuring underlying vital structures. Marrow may be aspirated from the proximal tibia medial to the tibial tuberosity in infants (<1-yr-old). This site is preferred in infants since biopsy from the iliac site in young children is difficult as the iliac crest is small and carries risk of injuring pelvic viscera.

Equipment Various types of bone marrow biopsy needles are available (Figs 28.10A and B). The Jamshidi needle and its modifications are used widely because of their light weight, sharp bevelled end that allows easy coring of bone, a tapering end that facilitates recovery of marrow specimen and suitability for both aspiration and biopsy.

Procedure The child should be fasting for 3–4 hr before the procedure. The child is positioned prone with face turned to a side and the pelvis stabilized by folding a sheet below it. If tibia is to be aspirated, the leg is slightly flexed at the knee joint. Sedation with intravenous midazolam and ketamine is administered during continuous monitoring of vital signs and oxygen saturation. Atropine is used to counteract the secretions associated with use of ketamine.

The site is cleaned with chlorhexidine and betadine to include the lumbar spine, iliac crests and posterior iliac spines (or for the tibial site, the entire leg up to the distal half of thigh) and draped. The posterior superior iliac spine is located by tracing the iliac crest backwards to its most prominent and elevated point. About 2 ml of 1% lidocaine is injected subcutaneously into the periosteum. The bone marrow needle is held firmly in the dominant hand with the index finger placed over the needle to act as a guard. The needle is advanced perpendicularly into the identified area with twisting motion till bone is felt. On advancing further, a 'give way' is felt that indicates that the needle is



Figs 28.10A and B: Needles for bone marrow aspiration and biopsy. (A) Jamshidi needles; (B) Vim Silverman needle

in the bone marrow. The stylet is removed and a 20 ml syringe attached. The piston is pulled to create negative pressure and aspirate slowly around 0.5 ml of marrow. The syringe is disconnected and the marrow placed on slides. To make a touch preparation, the marrow is spread on the slide by placing another glass slide so as to smear the marrow gently. Additional slides are prepared similar to a peripheral smear, using another glass slide at 30° angle to spread the marrow in a tongue shaped projection on the slide.

To perform marrow biopsy, the stylet is replaced and the needle withdrawn slightly. The needle is advanced through another site in the bone. Once the needle is lodged in the bone, the stylet is removed and the needle advanced in rotatory motion through the marrow space. The needle is withdrawn and biopsy specimen placed in a vial containing formalin. Once the needle is removed local pressure is applied to allow bleeding to stop. Drapes are removed, the skin is cleaned and pressure bandage applied.

Aspiration from the tibia is performed in a similar manner. The preferred site is medial to the tibial tubercle, one inch below the joint line to avoid the growth plate. The needle is introduced gently with a twisting motion similar to that described above. The bone cortex is thinner and the marrow space is reached more quickly than with the pelvic site. Obtaining a biopsy is often difficult as the marrow is more spongy.

Complications Bleeding and pain at the aspiration site are common. Bone injury with fractures of iliac bone and subcutaneous infections or osteomyelitis are rare.

Liver Biopsy

Indications Liver biopsy is used to evaluate hepatic histology in order to: (i) diagnose parenchymal liver disease (e.g. neonatal hepatitis, suspected metabolic liver disease); (ii) understand the cause of persistently abnormal liver tests; (iii) determine the etiology of focal or diffuse abnormalities on imaging studies; (iv) assess the prognosis of known liver disease (e.g. extrahepatic biliary atresia, autoimmune hepatitis, chronic viral hepatitis); (v) determine response to therapeutic interventions; (vi) develop a treatment plan based on histology; and (vii) monitor effects of hepatotoxic drugs. Analysis of the biopsy specimen may include evaluation of histology, metal content, enzymatic assays and cultures for viral, bacterial, or fungal pathogen.

Contraindications Absolute contraindications include coagulopathy, as suggested by low platelet count (<60.000/µl) or prolonged prothrombin time (international normalized ratio >1.5), and an inability to remain still (with or without sedation). Relative contraindications include anemia, peritonitis, marked ascites, high-grade biliary obstruction, and a subphrenic or right pleural infection or effusion.

Procedure The biopsy may be performed percutaneously at bedside with or without ultrasound guidance. An ultrasound guided biopsy carries lower risk of complications and allows visualization of the liver and any target lesions. Uncommonly, the biopsy is performed using the transjugular route, laparoscopically or by wedge resection during laparotomy. Transjugular venous biopsy is preferred in patients with severe coagulopathy.

The child should be fasting for 4–6 hr. An intravenous line is secured and the child made to lie supine. The abdominal girth is measured at the umbilicus to allow subsequent comparisons. The lower border of liver is localized by palpation or percussion, and its position on the midclavicular line marked.

During continuous monitoring of vital signs sedation is administered with (ketamine and midazolam). The site is cleaned and draped as described previously. The site of biopsy is chosen based on the liver span. If the liver is palpable, a subcostal approach may be used. However, a right lateral transthoracic approach is most common, in which the needle is inserted in the tenth intercostal space in the midaxillary line, after confirming liver dullness. Local anesthesia is administered. The biopsy is usually performed using a spring-loaded semiautomatic biopsy gun (Fig. 28.11) of size 18 (infants) or 16 (children) gauge. The gun is loaded and its needle inserted through the marked intercostal site just above the border of the lower rib, so as to avoid injuring the neurovascular bundle running along the lower border of ribs. The needle is inserted carefully along a horizontal plane to a depth at which a 'give way' sensation is felt upon rupture of the liver capsule. The tip of the needle should rest just beyond the capsule and should move well with respiration. The gun is fired and the needle withdrawn quickly. The sample is transferred to vials, e.g. formalin for histopathology.

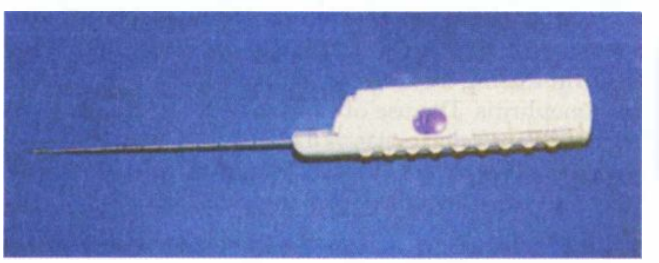


Fig. 28.11: Semiautomated gun for biopsy of liver and kidney

The biopsy site is sealed with tincture iodine and pressure dressing applied to prevent bleeding. The child is monitored over the next 6–8 hr for tachycardia, tachypnea, hypotension and increase in abdominal girth and excessive pain, which may suggest internal bleeding.

Complications Major complications such as intra-abdominal hemorrhage, biliary peritonitis, hepatic laceration, hemothorax, hemobilia, pneumothorax, gallbladder or intestinal perforation and iatrogenic arteriovenous fistula are none.

Renal Biopsy

Indications Examination of the renal histology is useful in a significant proportion of patients with acute or chronic renal diseases. Usual indications include: (i) acute glomerulonephritis where course is atypical for poststreptococcal glomerulonephritis (presence of fever, rash or joint pain; lack of serologic evidence of streptococcal infection; normal complement C3; delayed resolution of features) and/or rapidly progressive glomerulonephritis is present (suggested by elevated creatinine, anuria, need for dialysis); (ii) nephrotic syndrome with onset below 1 yr or in late adolescence; documented steroid resistance; presence of persistent hematuria, stage II hypertension, elevated levels of serum creatinine or low complement C3; likely secondary cause (infection with hepatitis B, C or HIV, collagen vascular diseases, amyloidosis, tuberculosis) and for evaluation for calcineurin inhibitor associated nephrotoxicity; (iii) suspected glomerular gross or microscopic hematuria persisting beyond 12–18 months (2+ or more proteinuria, red cell casts, dysmorphic red cells, and/or azotemia); (iv) unexplained proteinuria in nephrotic range (> 1000 mg/m^2/day) without low serum albumin or edema or in non-nephrotic range (100–1000 mg/m^2 per day) along with hematuria; (v) acute renal failure of unidentified etiology, particularly if lasting over 2–3 weeks to identify significant treatable etiology (e.g. crescentic glomerulonephritis, acute interstitial nephritis) or to assess the prognosis (extent of tubular or cortical necrosis); (vi) unexplained chronic kidney disease stage III or more; (vii) following renal transplantation for detecting allograft rejection, acute tubular necrosis or drug toxicity; and (viii) suspected renal involvement in Henoch-Schönlein purpura, systemic lupus erythematosus or microscopic polyarteritis.

Relative contraindications These include uncontrolled high blood pressure, coagulopathy (e.g. thrombocytopenia <75,000 U/µl, prolonged prothrombin time with INR >1.5, uremia, use of NSAIDs or warfarin in previous 5–7 days, heparin during last 6–8 hr), solitary kidney and active pyelonephritis. The use of IV desmopressin (DDAVP 0.3 mg/kg 30 min prior) or nasal DDAVP (2-4 mg/kg 2 hr before the procedure) reduces the risk of hematuria postbiopsy in patients with azotemia or prolonged bleeding time.

Procedure The patient should be fasting 4–6 hr prior; clear liquids are allowed until 2 hr before the biopsy. An IV access is established to administer anesthesia with ketamine and midazolam. The patient lies prone, with support under the lower chest and epigastrium. The patient's vital signs are closely monitored during the procedure.

The biopsy is performed using a semiautomatic biopsy gun of 16 or 18 gauge, usually under real-time ultrasonographic guidance. The site is cleaned and draped. The lower pole of the kidney is located at the midaxillary line either by ultrasound guidance or using a probing needle (1½ inch, 23 gauge; or 9 cm 20 gauge spinal needle) inserted at the renal angle (below the twelfth rib, lateral to the sacrospinalis muscle) to a depth where the needle moves well with respiration, indicating entry into the renal pole. During nonguided biopsy, the depth of the needle is marked while removing it and the site of entry is marked. Lidocaine is injected locally. A small nick is given at the biopsy site with a surgical blade. The needle of the biopsy gun is inserted to a depth such that the needle tip is visible just under the renal capsule on ultrasound; alternatively the needle is inserted to the depth indicated by the probing needle used for localizing the kidney. One to three cores of renal tissue are obtained for processing for light microscopy (in 10% formalin or paraformaldehyde), immunofluorescence (Michel's medium) and electron microscopy (glutaraldehyde).

Vital signs are monitored for at least 6–8 hr. At least three urine voids should be inspected for gross hematuria. The child is discharged after overnight observation. Contact sports, cycling or lifting of heavy objects should be avoided for 1 week.

Complications These may include adverse effects related to sedation (hypoxia, respiratory depression, vomiting), gross hematuria, perinephric hematoma and intra-abdominal bleeding with hypotension.

Suggested Reading

Uppot RU, Harisinghani MG, Gervais DA. Imaging-guided percutaneous renal biopsy: Rationale and approach. AM J Roentgenol 2010;194:1443–9

Rational Drug Therapy

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Anu Thukral, Ashok K. Deorari

INTRODUCTION

Medications play an important role in protecting, maintaining and restoring health. Irrational and indiscriminate use may lead to toxicity and adverse reactions. It is better to use medications with which the physician is familiar. The expected benefits and side effects should always be kept in mind when prescribing. The principles of rational drug therapy can be summarized as:

i. There should be a genuine indication for use of the medication.
ii. A minimum number of appropriate, familiar and inexpensive agents of good quality should be used.
iii. The drugs should preferably be prescribed by their generic name.
iv. The dosage should be optimum to achieve the desired benefits.
v. It is desirable to administer medication, as far as possible, through oral route.
vi. Adverse drug reactions should be anticipated, monitored and appropriately managed.

True synergism is rare; an exception is cotrimoxazole (trimethoprim and sulfamethoxazole). Combination of antibiotics may be necessary when the causative agent is not known. Multidrug therapy is indicated to prevent resistance to individual drugs, during longterm management of tuberculosis and leprosy and to reduce toxicity of individual drugs. Bactericidal drugs act best when the organism is actively multiplying and should ideally not be combined with bacteriostatic drugs.

Developmental and genetic factors affect the metabolism of drugs and thereby the response. Doses of drugs need to be modulated according to the individual responses. The dosages may vary in specific disease, e.g. pneumonia, meningitis, bacterial endocarditis and pyogenic arthritis.

The doses given below are approximate doses used in common practice. The reader is advised to consult the prescribing information for each medication.

Abbreviations. d day; g gram; GI gastrointestinal; hr hour; IM intramuscular; IV intravenous; kg kilogram; m^2 square meter body surface; mg milligram; µg microgram, PO per oral; PR per rectal; SC subcutaneous; T topical; wt weight; yr age in years

ANALGESICS, ANTIPYRETICS, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Non-narcotic Analgesics

Aspirin. Acute rheumatic fever: 90–120 mg/kg/day PO q 4 hr. Rheumatoid arthritis: 65–130 mg/kg/day PO q 4–6 hr; antipyretic dose: 30–60 mg/kg/day PO q 4–6 hr; Kawasaki disease 80–100 mg/kg/day PO q 4–6 hr till afebrile or for 2 weeks followed by 3–5 mg/kg/day PO OD for 6–8 weeks. *Side effects:* Hypersensitivity, hypoprothrombinemia. Due to an epidemiologic association of salicylate use with Reye encephalopathy, the use of aspirin for fever of undetermined origin in children is not advisable. Salicylates should be avoided empty stomach.

Paracetamol. 40–60 mg/kg/day PO q 4–6 hr or 15 mg/kg/dose PO 4–6 hr; 5 mg/kg IM. *Side effects:* Skin rashes, hepatotoxicity, and occasionally, renal damage.

Ibuprofen. Antipyretic/analgesic dose 20–30 mg/kg/day q 6–8 hr PO or 10 mg/kg/dose q 4–6 hr; maximum dose 40–60 mg/kg/day; juvenile rheumatoid arthritis: 30–70 mg/kg/day q 4–6 hr; closure of ductus arteriosus in neonates: 10 mg/kg followed by 5 mg/kg every 24 hr for 2 days. *Side effects:* Nausea, vomiting, rashes.

Naproxen. Juvenile rheumatoid arthritis: 10–20 mg/kg/day q 12 hr; analgesia 5–7 mg/kg/dose q 8–12 hr. *Side effects:* Nausea, vomiting, rashes.

Diclofenac sodium. 1–3 mg/kg/day PO q 8 hr. *Side effects:* Gastric bleeding, ulcer.

Mefenamic acid. 25 mg/kg/day PO q 6–8 hr. Antipyretic dose: 5–8 mg/kg/dose. *Side effects:* Gastric bleeding, rash, seizures.

Indomethacin. 3 mg/kg/day PO q 8 hr. Dose for ductal closure depends on the age of the neonate (Table 29.1). *Side effects:* Oliguria, hypoglycemia, platelet dysfunction.

Tramadol. 1–2 mg/kg q 4–6 hr up to maximum of 400 mg/day; avoid below 14 yr of age. *Side effect:* Seizures, renal and hepatic dysfunction.

Table 29.1: Dose of indomethacin dose (mg/kg) in neonates

Age at first dose	*1st*	*2nd*	*3rd*
<48 hr	0.2	0.1	0.1
2–7 days	0.2	0.2	0.2
>7 days	0.2	0.25	0.25

Narcotic Analgesics (Opioids)

Fentanyl. 0.5–5 µg/kg/dose q 1–4 hr IV, may be administered as a continuous infusion 1–5 µg/kg/hr. Potent narcotic analgesic; 0.1 mg dose possesses analgesic activity; equivalent to 10 mg of morphine. *Side effects*: Rapid infusion may cause chest wall rigidity; respiratory distress and respiratory arrest.

Codeine. For pain: 3 mg/kg/day PO q 4 hr; antitussive: 0.2 mg/kg/dose q 4 hr (1–1.5 mg/kg/day). *Side effects*: Respiratory distress, increased intracranial pressure. Contraindicated in patients with ventilator failure, obstructive airway disease.

Pethidine. 1–2 mg/kg/dose IM or IV. *Side effects*: Seizures.

Morphine. 0.1–0.2 mg/kg/dose q 4 hr (max. 15 mg) IV, IM, SC. For continuous infusion in neonates 0.01–0.02 mg/kg/hr; infants and children 0.01–0.04 mg/kg/hr. *Caution:* Keep naloxone (0.01 mg/kg IV) ready as antidote in case of respiratory depression. *Side effects*: Respiratory distress, increased intracranial pressure, seizures. Contraindicated in patients with ventilatory failure and obstructive airway disease.

ANTIARRHYTHMICS

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Adenosine. 0.1 mg/kg/dose rapid IV (over 1–3 sec); if no response in 1–2 min, give 0.2 mg/kg bolus through a three way. To ensure that the drug reaches the circulation, administer directly into a vein with a three way stop cock with 5–10 ml of saline flush ready to push immediately. Maximum single dose 0.25 mg/kg or 12 mg. *Side effects:* Transient chest pain, dyspnea, flushing, bronchospasm.

Atropine sulfate. 0.01 mg/kg/dose SC or IV. Minimum dose 0.1 mg, maximum single dose 0.5 mg; adolescent 1 mg. The dose can be repeated after 2 hr (max 4–6 times a day). Organophosphorus poisoning: 0.02–0.05 mg/kg every 10–20 min until atropine effect, then every 1–4 hr for at least 24 hr. *Side effects:* Dry mouth, blurred vision, tachycardia, urinary retention, constipation, dizziness, hallucinations and ventilatory restlessness.

Bretylium. 5–20 mg/kg/day q 8 hr PO or 5–10 mg/kg IM or IV. Repeated 1–2 hr if arrhythmia persists and subsequently given every 6–8 hr for 3 to 5 days.

Lidocaine hydrochloride. 1 mg/kg/dose IV (maximum 100 mg). May repeat after 5–10 min. Continuous IV infusion 0.02–0.05 mg/kg/min. Maximum dose 5 mg/kg/day. *Side effects:* Hypotension, seizures and asystole, respiratory arrest.

Phenytoin sodium. For arrhythmia: Loading 1.25 mg/kg IV over 3 min and repeat every 5–10 min to a maximum total dose of 15 mg/kg or until arrhythmia reverts or hypotension develops; maintenance 5–10 mg/kg/day q 12 hr PO. *For status epilepticus:* Loading 15–20 mg/kg IV, do not exceed 1–3 mg/kg/min. Maintain with 5–8 mg/kg/day PO or IV q 12–24 hr. *Side effects:* Gum hypertrophy, hirsutism, hypersensitivity, megaloblastic anemia, osteomalacia and vestibulocerebellar syndrome.

Procainamide. 2 mg/kg/dose IV followed by 0.5 mg/kg/hr by constant IV infusion. PO dose 50 mg/kg/day q 3–4 hr. *Side effects:* Thrombocytopenia, Coombs' positive hemolytic anemia, lupus like syndrome. *Contraindication:* Heart block and myasthenia gravis.

Propranolol. 0.01–0.25 mg/kg/dose; given as IV bolus over 10 min. Maximum dose 1 mg in infants; 3 mg in children. May repeat in 15 min and then every 4–8 hr. PO dose 0.5–1 mg/kg/day q 6 hr. *Side effects:* Life-threatening increase in pulmonary resistance, fatigue and bradycardia.

Quinidine sulfate. Test dose 2 mg/kg PO followed by 30 mg/kg/day PO q 6 hr. *Side effects:* Thrombocytopenia, anemia, tinnitus, hypotension, blood dyscrasias. Contraindicated in heart block and congestive heart failure.

Verapamil. 2–4 mg/kg/day q 8 hr PO, 0.1–0.2 mg/kg IV over 2 min in infants and 0.1–0.3 mg/kg IV over 2 min in children. *Contraindication:* Cardiogenic shock, AV block, age below 2 yr.

AGENTS FOR MYASTHENIA

Edrophonium chloride. Initial dose: 0.04 mg/kg dose IV, IM (maximum 1 mg for <30 kg). If no response after 1 min, may give 0.16 mg/kg/dose for a total of 0.2 mg/kg (total maximum dose is 5 mg for <30 kg). *Side effects:* Arrhythmias and bronchospasm.

Neostigmine bromide. Neonate: Initially, 0.05–0.1 mg IM or SC route, then PO 1 mg 30 min before feed. *Children:* 1–3 mg/kg/day PO q 4–6 hr or 0.01–0.04 mg/kg IV, IM or SC q 2–3 hr. Begin with lower dose and increase gradually till symptoms disappear. Use with atropine for nondepolarizing neuromuscular blocking agents. *Side effects:* Cholinergic crisis, bronchospasm, respiratory depression, hypotension, seizures, salivation, vomiting, diarrhea and lacrimation. Contraindicated in urinary and intestinal obstruction.

Pyridostigmine. For infants of myasthenic mothers: 0.05–0.15 mg/kg/dose q 4–6 hr IV or IM; then 7 mg/kg/day PO q 4–6 hr. Start at lower dose and increase gradually. *Side effects:* Cholinergic effect (same as neostigmine).

Physostigmine. 0.001–0.03 mg/kg/dose IM, SC, IV. Repeat q 15–20 min to desired effect or maximum dose of 20 mg. *Side effects:* Cholinergic effects (same as neostigmine).

ANTIBIOTICS

Penicillins

Penicillin may cause hypersensitivity reactions in about 1% of individuals. Acute symptoms include urticaria, angioneurotic edema, anaphylactic shock, asthma, laryngeal edema and hypotension. Delayed reactions are fixed drug eruption, serum sickness, hemolytic anemia and recurrent arthralgia. Sodium and potassium content of penicillin G is 0.3 mEq and 1.7 mEq per million units, respectively. Large doses may cause seizures (Table 29.2).

Cephalosporins

Approximately 10% patients with penicillin hypersensitivity show allergy to cephalosporin; fatal anaphylaxis may occur. Oral cephalosporins cause gastrointestinal symptoms such as loss of appetite, nausea, vomiting and diarrhea (Table 29.3).

Aminoglycosides

Aminoglycosides cause variable degrees of auditory and vestibular toxicity and reversible kidney dysfunction. Rashes and drug fevers occur in about 5% patients. Dosage should be reduced and interval between dosages increased in patients with impaired renal function. Administration of aminoglycoside dose once in 24 hr and as infusion reduces the risk of renal and auditory toxicity (Table 29.4).

Tetracyclines

Tetracyclines are deposited in growing teeth and bones; doxycycline does not bind as avidly. If used, between the

Table 29.2: Penicillins

Drug	*Dose**	*Route*	*Schedule*
Penicillin G aqueous	Routine dose: 100,000–400,000 U/kg Meningitis and endocarditis: 200,000–400,000 U/kg Prophylaxis of rheumatic fever: 200,000U/kg	IM or IV	4–6 hr
Benzathine penicillin	<30 kg: 0.6 million units >30 kg: 1.2 million units Prophylaxis of rheumatic fever <30 kg: 0.6 million units q 15 days >30 kg: 1.2 million units q 21 days	IM	2–3 weekly
Procaine penicillin G	Neonates: 50,000 U/kg/day 25,000–50,000 U/kg/day	IM	Single dose
Phenoxymethyl penicillin V	Infants: 62.5 mg–125 mg/dose Children <6 yr: 125 mg/dose 6–12 yr: 250 mg/dose Rheumatic fever prophylaxis: 250 mg	PO	12 hr
Methicillin sodium	150–400	IM or IV	6 hr
Oxacillin	50–200	PO, IM or IV	6 hr
Cloxacillin	50–100	PO or IV	4–6 hr
Ampicillin	100–200 Meningitis and enteric fever: 200–400	PO or IV IV	6 hr 4–6 hr
Amoxicillin	25–50	PO	8–12 hr
Coamoxiclav	25–40 100	PO IV	8–12 hr 8 hr
Ampicillin and sulbactam (in a ratio of 2:1)	100–400 (of ampicillin)	IM, IV	8 hr
Carbenicillin	30–50	PO	6 hr
Ticarcillin	200–300	IM or IV	4–6 hr
Ticarcillin (3 g) and clavulanate (100 mg)	240–320 (of ticarcillin)	IM or IV	4–6 hr
Piperacillin	100–300	IM or IV	4–6 hr
Piperacillin and tazobactam (in a ratio of 8:1)	300–400 (of piperacillin)	IV	6–8 hr

*Dose is (mg/kg/day) unless specified

Table 29.3: Cephalosporins

Drug	Dose (mg/kg/day)	Route	Schedule
First generation cephalosporins			
Cephalexin	25–100	PO	6 hr
Cefazolin	50–100	IM or IV	6–8 hr
Cefadroxil	30	PO	8–12 hr
Second generation cephalosporins			
Cefaclor	20–40	PO q	6–8 hr
Cefuroxime	75–150	IM or IV	6–8 hr
	20–40 (enteric fever)	PO	8–12 hr
Third generation cephalosporins (high CSF concentrations; widely used in meningitis)			
Cefotaxime	100–150	IM, IV	8–12 hr
Cefoperazone	100–150	IV	8–12 hr
Cefoperazone, sulbactum	40–80	IV	8–12 hr
Ceftriaxone	50–75	IV	12–24 hr
	100 (meningitis)	IV	12 hr
Ceftazidime	100–150	IV	8–12 hr
Ceftizoxime	100–200	IV or IM	6–8 hr
Cefixime	8–10; enteric fever: 20	PO	12 hr
Fourth generation cephalosporins			
Cefpirome	30–60	IM or IV	12 hr
Cefpodoxime	8–10	PO	12 hr
Cefepime	>2 months: 100–150 <2 months: 60	IV	8–12 hr

Table 29.4: Aminoglycosides

Drug	Dose (mg/kg/day)	Route	Schedule
Streptomycin	20–40	IM	12 hr
Gentamicin	5–7.5	IM, IV	8–12 hr
Amikacin	15–20	IM, IV	8–12 hr
Tobramycin	6–7.5	IM, IV	8–12 hr
Netilmicin	5–7.5	IM, IV	8 hr

ages of 2 months and 8 yr, both deciduous and permanent teeth may show irreversible staining, hypoplasia of enamel and caries. Prolonged use may lead to stunting. Tetracyclines are not recommended in children below 8 yr of age (Table 29.5).

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Chloramphenicol

It may cause idiosyncratic bone marrow depression and hypersensitivity reactions: like fever, rash, angioneurotic edema and GI disturbances. Neonates, especially premature, may show grey baby syndrome with abdominal distension, vomiting, refusal to suck, dyspnea, cyanosis, peripheral circulatory collapse and death (Table 29.6).

Table 29.5: Tetracyclines

Drug	Dose (mg/kg/day)	Route	Schedule
Tetracycline	25–50	PO	6 hr
	15–25	IM	8–12 hr
Doxycycline	2–5	PO	12–24 hr

Table 29.6: Chloramphenicol

	Dose (mg/kg/day)	Route	Schedule
Chloramphenicol	50–75	PO	6 hr
	100	IM or IV	6 hr

Ointment available as 0.5 and 1%

Macrolides

Macrolides may cause diarrhea, nausea, abnormal taste, raised transaminases and cholestatic jaundice. Clarithromycin has less abdominal discomfort; use with terfenadine, astemazole or cisapride may result in arrhythmias. Multiple drug interactions are noted (less with azithromycin) (Table 29.7).

Table 29.7: Macrolides

Drug	Dose (mg/kg/day)	Route	Schedule
Erythromycin	30–50	PO	6–8 hr
Azithromycin	10	PO	24 hr
	10 mg/kg on day 1; then 5 mg/kg for 4 more days		
Clarithromycin	15	PO	12 hr

Quinolones

Side effects: GI upset, renal failure, insomnia, dizziness and seizures; no concerns of arthropathy. Inhibit liver enzymes; elevated levels of theophylline. Rash, photosensitivity, raised transaminases and neutropenia (Table 29.8).

Table 29.8: Quinolones

Drug	Dose (mg/kg/day)	Route	Schedule
Nalidixic acid	50–60	PO	8 hr
Ciprofloxacin	20–30	PO	12 hr
	10–20	IV	12 hr
Gatifloxacin	10	PO	24 hr
Norfloxacin	10–15	PO	12 hr
Levofloxacin	10–15	PO, IV	24 hr
Ofloxacin	15	PO	12 hr
	5–10	IV	12 hr
Pefloxacin	12	PO	12 hr
Sparfloxacin	4	PO	24 hr

Sulfonamides

Side effects. Blood dyscrasias, exfoliative dermatitis, serum sickness and drug fever (Table 29.9).

Other antibiotics used commonly are listed in Table 29.10.

Antileprosy medications Refer to Chapter 25

Antitubercular medications Refer to Chapter 10

Table 29.9. Trimethoprim sulfamethoxazole (Cotrimoxazole)

Dose (mg/kg/day)	*Route*	*Schedule*
Trimethoprim 5–8; sulfamethoxazole 25–40	PO, IV	8–12 hr
Enteric fever: Trimethoprim 10; PO *Pneumocystis* pneumonia: Trimethoprim 20; PO		
Prophylaxis *Pneumocystis*: Trimethoprim 5 mg/kg alternate day; PO Urinary infections: 1–2; PO		

ANTIFUNGAL AGENTS

Amphotericin B. Test dose 0.1 mg/kg IV; then start 0.25 mg/kg/day; increase by 0.25 mg/kg daily, until dose of 1 mg/kg/day. Dilute in 5% dextrose, saline; protect from light. Total dose should not exceed 30–35 mg/kg over 4–6 weeks. *Side effects:* Febrile reactions, nephrotoxicity, hypokalemia and blood dyscrasias.

Liposomal Amphotericin B. 3–5 mg/kg/dose once daily; maximum 15 mg/kg/day. *Side effects:* as above.

Flucytosine. 50–150 mg/kg/day PO q 6 hr. *Side effects:* Neutropenia, thrombocytopenia, colitis and hepatotoxicity.

Griseofulvin. 10 mg/kg/day PO q 12 hr; double dose for extensive lesions. *Side effects:* Urticaria, paresthesia, proteinuria, leukopenia, photosensitivity; multiple drug interactions.

Griseofulvin. Microsize: Children >2 yr: 20–25 mg/kg/day q 8–12 hr. *Ultramicrosize:* Children >2 yr: 15 mg/kg/day q 8–12 hr.

Fluconazole. Loading dose 10 mg/kg IV/PO, then maintenance 3–6 mg/kg/day q 24 hr. *Side effects:* Dizziness, skin rash, hepatic dysfunction; drug interactions.

Ketoconazole. 3–6 mg/kg/day PO single dose. *Side effects:* Abdominal pain, headache, dizziness, somnolence, photophobia, thrombocytopenia, gynecomastia in adolescents and drug interactions.

Itraconazole. 3–5 mg/kg/day (oral thrush); 5–10 mg/kg/day (histoplasmosis); maximum 400 mg/day.

Prophylaxis in immunocompromised. 2–5 mg/kg/dose q 12–24 hr. *Side effects:* Hearing loss, arrhythmia, hepatotoxic; use cautiously in patients with liver disease and cardiac dysfunction.

Miconazole. 20–40 mg/kg/day PO q 8 hr; 2% local cream. *Side effects:* Pruritis, rash and thrombocytopenia.

Table 29.10: Other antibiotics

	Dose (mg/kg/day)	*Route*	*Schedule*	*Major side effects*
Aztreonam	90–120	IV, IM	6–8 hr	Low cross antigenicity with beta lactams, thrombophlebitis, leukopenia, eosinophilia, neutropenia, hypotension, seizures
Clindamycin	25–40 10–30	IV PO	6–8 hr 6–8 hr	Pseudomembranous colitis, rash, Stevens-Johnson syndrome, neutropenia, thrombocytopenia
Colistin	2.5–5 (colistin base) (50,000–75,000 U/kg/day)	IV	6–8 hr	Nephrotoxicity, neurotoxicity
Imipenem	60–100	IV	6 hr	Pruritis, urticaria, seizure, dizziness, hypotension, elevated liver enzymes
Meropenem	60–120	IV	8 hr	Nausea, vomiting, rarely seizures
Faropenem	15–40	PO	8 hr	Diarrhea, abdominal pain, nausea, and rash; safety in infants not established
Ertapenem	30	IV or IM	12 hr	Not approved for children less than 3 mo, diarrhea, nausea, headache
Vancomycin	40–60	IV	6–8 hr	Ototoxicity and nephrotoxicity (exacerbated with concomitant aminoglycosides); red man syndrome (associated with impure forms; rapid IV infusion)
Linezolid	20–30	IV or PO	8–12 hr	Bad taste in mouth; constipation, diarrhea, dizziness, headache, rarely anemia, leukopenia, thrombocytopenia
Teicoplanin	10 mg/kg 12 hr for 3 doses; then 6–10 mg/kg/day	IV, IM	24 hr	Long half-life. Less nephrotoxic; less catheter related phlebitis
Quinupristin/ Dalfopristin	22.5	IV	8–12 hr	Not FDA approved
Daptomycin	4–6	IV	24 hr	

Nystatin. 1–2 million units/day q 8 hr PO for diarrhea due to *Candida albicans.* For mucosal application: Dissolve 100,000 units nystatin per ml glycerine.

Terbinafine. Not recommended below 2 yr. For ≤20 kg: 62.5 mg q 24 hr; 20–40 kg: 125 mg q 24 hr; >40 kg: 250 mg q 24 hr for 2–6 weeks.

Voriconazole. 6 mg/kg/dose for 2 doses q 12 hr, then 3–4 mg/kg/dose 12 hr; 5–7 mg/kg/dose for invasive aspergillosis, oral: 3–5 mg/kg/dose 12 hr. *Side Effects*: Blurred vision, photophobia, photosensitivity, hepatic impairment and flu-like symptoms.

Caspofungin. <3 months: 25 mg/m^2/dose (max. 50 mg) once daily; older children: 70 mg/m^2 on day 1, followed by 50–70 mg/m^2 once daily (max. 70 mg). To be used cautiously in patients with liver disease. *Side effects*: Elevated transaminases, diarrhea, vomiting, flu-like symptoms and rash.

ANTHELMINTHICS

Albendazole. 1–2 yr: 200 mg single dose; >2 yr and adults: 400 mg single dose. *Side effects:* Anorexia, vomiting. *Strongyloides,* taeniasis, *H. nana*: 400 mg daily for 3 days. Hydatid cyst: 400 mg twice daily for 28 days (3 cycles at 14 days interval). Neurocysticercosis: 15–20 mg/kg/day for 2–3 weeks. Filaria: 400 mg single dose.

Diethylcarbamazine citrate. Filariasis: 6 mg/kg/day q 8 hr for 2 weeks; tropical eosinophilia: 10 mg/kg/day PO q 8 hr for 1 month; Loeffler syndrome: 15 mg/kg single dose for 4 days. *Side effects:* Gastrointestinal upset and drowsiness.

Ivermectin. Dose 200 µg/kg PO single dose. Contraindicated in children <5-yr-old.

Mebendazole. 100 mg PO twice daily for 3 days; repeat after two weeks.

Piperazine citrate. Enterobiasis: 50 mg/kg/day for 7 days; ascariasis: 150 mg/kg/PO single dose for 2 days. *Side effects:* Vomiting, blurred vision, uriticaria. Contraindicated in patients with epilepsy.

Praziquantel. Neurocysticercosis: 50 mg/kg/day q 8 hr PO for 10–14 days. Tapeworms: 10–20 mg/kg single dose. Liver fluke infestation: 75 mg/kg/day q 8 hr for 2 days.

Pyrantel pamoate. 10 mg/kg of pyrantel base, PO single dose with a maximum of 1 g. Repeat after one week.

Thiabendazole. 50 mg/kg/day q 12 hr up to a maximum dose of 3 g/day. Duration of therapy for *Strongyloides* 2 days, intestinal nematodes 2 days, cutaneous larva migrans 2–5 days, visceral larva migrans 5–7 days and trichinosis 2–4 days.

ANTIMALARIALS

Refer to Chapter 10

ANTIPROTOZOAL

Chloroquine. 10 mg/kg/day PO q 8 hr for 14–21 days for extraintestinal amebiasis. *Side effects:* Nausea, vomiting, itching. IV administration has been reported to cause hypotension, arrhythmias and cardiac depression.

Dehydroemetine dihydrochloride. 1–3 mg/kg/day PO q 8 hr for 10–15 days or 1 mg/kg/day IM for 7–10 days. *Side effects:* Renal and cardiac toxicity.

Diloxanide furoate. Luminal amebic infection, cysts: 20 mg/kg/day PO q 8 hr for 10 days. *Side effects:* Nausea and flatulence.

Metronidazole. Giardiasis: 10 mg/kg/day PO q 8 hr for 10 days. Amebiasis: 20 mg/kg/day PO q 8 hr for 21 days or 50 mg/kg/day PO q 8 hr for 7 days. *Side effects:* Diarrhea, leukopenia and metallic taste.

Pentamidine: Leishmaniasis: 4 mg/kg/day IM or slow IV infusion daily dose for 12 to 15 doses; a second course may be given after 2 weeks. *Side effects:* Breathlessness, tachycardia, dizziness, fainting, headache and vomiting.

Secnidazole. 30 mg/kg PO single dose. Hepatic amebiasis treatment for 5 days.

Sodium stibogluconate. Cutaneous leishmaniasis: 20 mg/kg/day IM, IV for 20 days; mucocutaneous leishmaniasis and systemic infection: treat for 30 days. *Side effects:* Nausea, vomiting, prolonged QT interval.

Tinidazole. 50 mg/kg/day PO for 2–3 days. *Side effects:* Same as for metronidazole. Giardiasis: 50 mg/kg single dose (*see* Chapter 10).

Nitazoxanide. 1–4 yr: 100 mg twice a day for 3 days; 4–12 yr: 200 mg twice a day for 3 days.

ANTIVIRAL AGENTS

Antiretroviral drugs. Drug doses are provided in Chapter 10.

Acyclovir. HSV encephalitis: 20 mg/kg/dose q 8 hr for 21 days; neonatal herpes simplex: 60 mg/kg/day q 8 hr IV. Herpes simplex: 1500 mg/m^2/day IV q 8 hr.

Varicella or varicella zoster: 80 mg/kg/day q 6 hr PO for 5 days (benefit if within 24 hr of onset of rash). Adolescents: 800 mg q 6 hr for 7 days. Immunocompromised hosts: 1500 mg/m^2/day IV q 8 hr, treated for 7–10 days.

Ribavirin. Respiratory syncytial virus: Ribavarin (6 g) diluted in 300 ml sterile water; nebulize 12–18 hr daily for 3–7 days.

Oral. 10 mg/kg/day q 6–8 hr (max dose 150 mg/d <10 yr; 200 mg/d >10 yr). *Side effects:* Seizures, congestive heart failure, urinary retention and leukopenia.

Ganciclovir. 10 mg/kg/day IV q 12 hr for 14–21 days; longterm 6 mg/kg/dose once daily for 5 days in a week. *Side effects:* Bone marrow depression, rash, fever and vomiting.

Valganciclovir. 450 mg/m^2/day or 30 mg/kg/day for 14–21 days.

Isoprinosine. Subacute sclerosing panencephalitis: 50–100 mg/kg/day q 12 hr oral.

INTERFERONS

Interferon alpha

Chronic hepatitis B: 3–10 million units/m^2 thrice a week SC for 24 weeks.
Chronic hepatitis C: Same dose with oral ribavirin for 24 weeks for genotypes 2 and 3; for 48 weeks for genotypes 1 and 4.

Pegylated interferon alpha 2b Chronic hepatitis C: 60 µg/m^2 once a week SC with ribavirin for 24 weeks in genotype 2 and 3; treatment for 48 weeks for genotypes 1 and 4.
Side effects: Flu-like symptoms, headache, bodyache, malaise, fever and chills, angioedema, urticaria, skin blistering or peeling; bone marrow depression; mood disorders; sepsis; seizures; arrhythmia and arthritis.

ANTICANCER DRUGS

The details are provided in Chapter 20.

ANTICOAGULANTS

Heparin. IV: 50 U/kg bolus; followed by 10–25 U/kg/hr as infusion or 50–100 U/kg/dose q 4 hr. *SC.* 25–50 U/kg q 12 hr. *Antidote. Protamine sulfate* (1 mg neutralizes 1 mg heparin) *Side effects:* Rash, alopecia, excessive bleeds and thrombocytopenia.

Enoxaparin. Infants <2 months: Prophylaxis: 0.75 mg/kg/dose q 12 hr; therapy: 1.5 mg/kg/dose q 12 hr. Older children. Prophylaxis: 0.5 mg/kg/dose q 12 hr; treatment: 1 mg/kg/dose q 12. Dosage titration with antifactor Xa level. *Side effects:* Bleeding, hypertension; use cautiously in patients with renal disease.

Warfarin. 0.05–0.34 mg/kg/day PO. Adjust dose to maintain international normalized ratio (INR) 2–2.5. *Side effects:* Bleeding, epistaxis and internal hemorrhage.

ANTICONVULSANTS

The details of doses are provided in Chapter 18.

ANTIDOTES

Ipecac syrup. Infants: 5–10 ml/dose; others 15–20 ml/dose. Do not use in semi-comatose child or after charcoal administration.

Deferoxamine. 20 mg/kg IM, IV; slow SC infusion q 6 hr. Dose adjusted based on response. *Side effects:* Hypotension, shock, cramps, diarrhea. Contraindicated in renal failure.

Dimercaprol. 2.5 mg/kg PO q 4 hr on first day, q 6 hr on next 2 days, q 12 hr for 10 days; and q 24 hr for 10 days. *Side effects:* Burning sensation, muscle aches, fever, hemolysis in G6PD deficiency.

Edetate, calcium disodium. 12.5–30 mg/kg/dose IV q 12 hr for 5 days. *Side effects:* Proteinuria and hematuria.

Methylene blue. 1–2 mg/kg/dose IV (in 5 min).

Nalorphine. 0.1 mg/kg/dose IM and IV.

Naloxone. 0.1 mg/kg/dose IM or IV; repeat if needed (maximum 2 mg).

Penicillamine. 20–40 mg/kg/day q 6–12 hr PO. *Side effects:* Nephrotoxic, hepatotoxic, leukopenia, thrombocytopenia, cataract and bleeding diathesis.

Digoxin specific Fab antibody. IV infusion; 60 mg binds 1 mg of digoxin approximately.

Pralidoxime. 25–50 mg/kg IM or IV as 5% solution over 15–30 min. The dose may be repeated at 1–2 hr and then at 10–12 hr intervals if cholinergic signs recur. For continuous infusion 9–19 mg/kg/hr after the initial bolus 25–50 mg/kg.

ANTIEMETICS AND GASTROINTESTINAL MEDICATIONS

Domperidone. 0.2–0.5 mg/kg/dose q 6–8 hr; do not exceed 2.4 mg/kg/day or 80 mg. *Side effects:* Extrapyramidal disorders; angioedema, urticaria; rarely agitation, nervousness, arrhythmias, gynecomastia and amenorrhea.

Metoclopramide. 0.1–0.2 mg/kg/dose q 6–8 hr orally or IV; maximum dose 10 mg. *Side effects:* Extrapyramidal disorders including oculogyric crisis, tardive dyskinesia and dystonia; drowsiness; allergic reactions.

Ondansetron hydrochloride. IV: 0.15–0.2 mg/kg/dose q 8–12 hr; oral: 1.2–4 mg/dose q 8–12 hr. *Side effects:* Headache, diarrhea, constipation, occasionally fever and rash.

Promethazine theoclate. Not approved for children below 2 yr. Children 2–5 yr: 5 mg q 6–8 hr; maximum daily dose 15 mg. Children 6–12 yr: 10 mg q 6–8 hr; maximum daily dose 25 mg. For motion sickness, administer 1–2 hr before travel. *Side effects:* Sedation, drowsiness, dry mouth, anorexia, blurred vision; rarely fever, jaundice, tremors, tinnitus, seizures, hallucinations and anxiety.

Ranitidine. 2 mg/kg/day PO, IM or IV q 12 hr. *Side effects:* Renal impairment.

Famotidine. 1–1.2 mg/kg/day, PO q 12 hr; maximum daily dose 40 mg.

Omeprazole. Children 5 to 10 kg: 5 mg OD, 10 to 20 kg: 10 mg OD, 20 kg or more: 20 mg OD. *Side effects*: Headache,

general feeling of being unwell, dizziness, confusion, lightheadedness and tiredness.

Lansoprazole. Less than 30 kg: 15 mg, more than/equal to 30kg: 30 mg. *Side effects:* Well tolerated, side effects as omeprazole.

Rabeprazole. Efficacy not established in pediatric patients. *Side effects:* Headache, nausea and vomiting, rarely rash, dizziness and seizures.

Sucralfate. 1 month–2 yr: 250 mg 4–6 hr; 2–12 yr: 500 mg 4–6 hr and 12–18 yr: 1 g 4–6 hr. *Side effects:* Constipation, headache, dizziness, insomnia and vomiting.

Lactulose. Constipation: 10–15 ml q 12–24 hr, less than 2 yr 2.5 ml/d PO, PR q 12 hr; more than 2 yr 5–10 ml PO, PR q 12 hr. *Side effects:* Diarrhea.

Bisacodyl. 5–10 mg bedtime. *Side effects:* Abdominal pain, diarrhea, muscle pain and dizziness.

Vasopressin. Bleeding esophageal varices: 20 U IV over 15 min, then 0.2 U/min or 0.33 U/kg/hr. *Side effects:* Hypertension, water intoxication and hyponatremia.

ANTIHISTAMINICS

Astemizole. 2 mg/10 kg/day taken half an hour before meals; not recommended <6 yr. *Side effects:* Weight gain with prolonged use.

Cetrizine. 0.2 mg/kg once daily. Levocetrizine has minimal effects on the central nervous system; 0.125 mg/kg once daily.

Clemastine. 1–3 yr: 0.25–0.5 mg BD; 3–6 yr: 0.5 mg BD; 6–12 yr: 0.5–1 mg BD; >12 yr: 1 mg BD. Useful for urticaria, contact dermatitis.

Chlorpheniramine maleate. 0.35 mg/kg/day q 4–6 hr. *Side effects:* Hypotension, sedation, urinary retention, oculogyric spasms with high doses and after few days of therapy.

Diphenhydramine hydrochloride. 5 mg/kg/day q 6 hr oral; maximum daily dose 300 mg. Anaphylaxis or phenothiazine overdose: 1–2 mg/kg IV slowly.

Fexofenadine. <12 yr: 30 mg q 12 hr; >12 yr: 60 mg q 12 hr or 120 mg once daily.

Hydroxyzine hydrochloride. 2 mg/kg/day q 6 hr; 0.5–1 mg/kg/dose q 4–6 hr IM.

Ketotifen. Prophylaxis of bronchial asthma; treatment of allergic rhinitis and conjunctivitis: Start at low dose; increase to 1 mg twice daily. *Side effects:* None.

Loratadine. 3–12: 5 mg/day; >12 yr: 10 mg/day.

Methdilazine hydrochloride. >3 yr: 4 mg q 6–12 hr

Pheniramine maleate. 0.5 mg/kg/day q 8 hr PO, IM, IV. *Side effects:* Same as chlorpheniramine.

Promethazine hydrochloride. 0.1 mg/kg/day q 6–8 hr; 0.5 mg/kg/dose bed time. Nausea, vomiting, sedation: 0.25–1 mg/kg/dose q 4 to 6 hr oral, IM, IV, PR. Motion sickness: 0.5 mg/kg/dose q 12 hr oral. *Side effects:* Same as chlorpheniramine.

Pseudoephedrine. <12 yr: 4 mg/kg/day q 6–8 hr oral; >12 yr: 30–60 mg/dose q 6–8 hr; maximum daily dose 240 mg.

ANTIHYPERTENSIVES

Details on therapy with antihypertensive agents are provided in Chapter 15.

ANTISPASMODICS

Dicyclomine hydrochloride. Infants below 6 months: 5–10 drops 15 min before feeds, 6–24 months: 10–20 drops 15 min before feeds; >2 yr: 1 ml q 6 hr. *Side effects:* Dry mouth and urinary retention.

Hyoscine butylbromide. 6–12 yr: 10 mg q 8 hr PO; 10–20 mg IV and IM bolus.

Oxyphenonium bromide. 0.8 mg/kg/day q 6 hr oral. Preschool children: 5–10 drops; older children: 10–20 drops q 6 hr. *Side effects:* Dry mouth, blurred vision, retention of urine, dizziness, fatigue and tremors.

Pipenzolate methylbromide. 2.5–5 mg q 8 hr

ANTITOXINS AND IMMUNOGLOBULINS

Anti-Rh D immunoglobulin. Antenatal prophylaxis: 300 µg IM at 28 weeks and 34 weeks gestation; or single dose within 72 hr of delivery. Twin pregnancy: Double the dose. Abortion, evacuation, trauma, other procedures (chorionic villus sampling, amniocentesis, external cephalic version): 250 µg IM.

Antisnake venom. Mixture of four enzyme-refined, lyophilized, polyvalent antisnake venom (common Krait, cobra, Russell viper and saw-scaled viper).

Dose. 5 vials (50 ml) for mild, 5–15 vials for moderate, 15–20 vials (150–200 ml) for severe features; smaller children may require 50% more dose. Exclude horse serum allergy (0.02 ml of 1:10 diluted antivenin intradermally); then infuse antivenin diluted in 250 ml N/5 saline (20 ml/kg/hr). Use steroids and antihistamines in addition. *Side effects:* Serum sickness and anaphylaxis.

Diphtheria antitoxin. Schick test positive. One dose of diphtheria toxoid; diphtheria antitoxin 500–2000 units IM in other arm. Second and third doses of toxoid are given at 4–6 week intervals for active immunization. Dose is not related to patient age and weight. Pharyngeal or laryngeal diphtheria of 48 hr duration: 20,000–40,000 units IV. Nasopharyngeal diphtheria: 40,000–60,000 units IV. Extensive disease of >3 days duration with neck swelling: 80,000–120,000 units IV. Antitoxin is diluted 1:20 in isotonic saline and administered at 1 ml/min.

Human normal immunoglobulin. Primary immunodeficiency: 0.2 ml/kg IM every 4 weeks. Attenuation of disease among

contacts of *measles:* 0.25 ml/kg IM within 6 days of exposure; *hepatitis A:* 0.02–0.04 ml/kg IM. *Side effects:* Coagulopathy, thrombocytopenia; contraindicated in IgA deficiency.

Hepatitis B (hepatitis B immune globulin). 0.06 ml/kg IM, maximum 3–5 ml within 7 days of exposure.

Human tetanus specific immunoglobulin. Prophylactic: 250 IU IM; therapeutic: 500 IU IM (maximum 3000–6000 IU).

Intravenous immunoglobulin (IVIG). 0.4 g/kg IV infusion daily for 5 days; 1 g/kg/day for 2 days or 2 g/kg in one day as IV infusion over 10–12 hr as single dose. Indications: (i) idiopathic thrombocytopenic purpura, (ii) Kawasaki disease, (iii) myasthenia gravis, (iv) Guillain-Barré syndrome, (v) systemic lupus erythematosus, (vi) juvenile idiopathic arthritis, (vii) autoimmune neutropenia, (viii) dermatomyositis, (ix) psoriasis, and (x) atopic allergy.

Human rabies specific immunoglobulin. If presents within 24 hr: 20 units/kg; one-half infiltrated at site of bite, other half IM in gluteal region. If presents between 1 and 7 days: Total dose given IM. Rabies vaccine is administered simultaneously.

Tetanus antitoxin. Prophylactic: 3,000–5,000 U SC, IM; Therapeutic: 10,000 U IM, IV; intrathecal: 250–500 U q 24 hr for 3 days. *Side effects:* Serum sickness, anaphylaxis. Varicella zoster immunoglobulin. 125 U/kg IM within 48–72 hr of exposure to varicella.

BRONCHODILATORS AND ANTIASTHMA AGENTS

Adrenaline. 0.01 ml/kg/dose (maximum 0.5 ml/dose) of 1 : 1000 solution SC; repeat after 15–20 min. *Side effects:* Tachycardia, palpitations and anxiety.

Aminophylline. Status asthmaticus: 5–7 mg/kg IV loading, followed by infusion at 0.5–1 mg/kg/hr. If already receiving oral aminophylline, do not use loading dose. Apneic spells in preterms: 5 mg/kg IV loading, followed by 1–2 mg/kg PO, IV q 8 hr. *Side effects*: Tachycardia, tremors, irritability and convulsions.

Beclomethasone dipropionate. MDI 50, 100, 200, 250 µg/puff: 100–1000 µg/day in 3 divided doses. Rotacaps 100, 200, 400 µg/cap: 100–1000 µg/day in 3 divided doses.

Budesonide. MDI 50, 100, 200 µg/puff, rotacaps 100, 200, 400 µg/cap: 200–800 µg/day in 1–2 divided doses. Respules 0.5 mg/ml, 1 mg/ml: 0.25–1 mg q 12 hr.

Ciclesonide. MDI 80, 160 µg/puff: 80–640 µg/day in 1–2 divided doses; not approved below 12 yr of age. Benefit of less oropharyngeal candidiasis and hypothalamo-pituitary axis suppression.

Formoterol fumarate. MDI 6 µg/puff, rotacap 12 µg/cap: 1–2 doses q 12 hr. Long acting selective β_2-adrenergic agonist; not recommended for monotherapy and <4 yr.

Fluticasone propionate. MDI 25, 50, 125 µg/puff, Rotacaps: 50, 100, 200 µg/puff: 100–1000 µg/day in 2 divided doses.

Ipratropium bromide. MDI 20 µg/puff: 2–4 puffs as needed; rotacap 40 µg/cap: 1–2 cap as needed; respules 0.5 mg/2 ml less than 1 yr: 125 µg/dose; >1 yr: 250 µg/dose, repeat q 20 min for 1 hr (during exacerbation); then q 6–8 hr.

Montelukast sodium. 1–5 yr: 4 mg PO once a day in evening; 6–14 yr: 5 mg once daily; >14 yr: 10 mg once daily. *Indications*: Exercise induced asthma, alternate to long-acting B2 agonists and allergic rhinitis.

Salbutamol. 0.15 mg/kg/dose PO q 8 hr. MDI 100 µg/dose: 2–4 puffs as needed q 20 min for 1 hr (during exacerbation), then q 6–8 hr. Nebulizer solution: 0.15 mg/kg/dose (minimum 1 mg as needed), q 20 min for 1 hr, followed q 6–8 hr. *Side effects*: Headache, tremor, irritability and hypokalemia.

Levosalbutamol. MDI 50 µg/puff: 2–4 puffs as needed. Salmeterol (long acting) 25 µg/puff MDI: 1–2 puffs twice a day; not for monotherapy and in <4-yr-old. *Side effects*: Tachycardia, tremors, headache and hypokalemia.

Sodium cromoglycate. MDI 5 mg/puff: 2 puffs 3–4 times a day; 4–6 weeks for clinical benefit. *Side effects:* Reflex coughing.

Terbutaline. 0.1–0.15 mg/kg/day q 8 hr PO. 0.005–0.01 mg/kg SC q 6 hr; IV 0.4–1.0 µg/kg/min followed by infusion of 1–10 µg/kg/hr. Nebulizer (10 mg/ml): 0.5–2 mg as needed. MDI 250 µg/puff: 2–4 puffs as needed. *Side effects*: Same as salbutamol.

Magnesium sulfate. Injection 25% (250 mg/ml), 50% (500 mg/ml): IV 25–100 mg/kg diluted in saline infused over 30 min (maximum 2 g). *Side effects:* Hypotension, respiratory depression and muscle weakness.

Note. Metered dose inhalers (MDI) should be used with large volume spacers. For infants, the spacer can be used with a face mask. Rotacap dose is double the inhaler dose; are administered using a rotahaler.

Nebulization. Final volume of 3–5 ml should be made by adding normal saline. Details on inhalant use and nebulization therapy with bronchodilators is provided in Chapter 14.

INOTROPIC AGENTS

Adrenaline. Cardiac arrest: 0.1 ml/kg/dose of 1:10,000 solution IV or intraosseous; endotracheal use: 0.1 ml/kg/dose of 1:1000 solution (flush with 5 ml saline, followed by 5 ventilations). In case of nonresponse, repeat same dose q 3–5 min.

Dobutamine. 2 to 25 µg/kg/min IV, available as 250 mg powdered form. Reconstitute ampoule with 10 ml saline to make 25 mg/ml. Dosage in mg for infusion: 15 mg × body weight dissolved in 24 ml of compatible solution (5% dextrose, 10% dextrose, 5% dextrose normal saline, normal saline), infusion of the above solution @0.5 ml/hr

delivers 5 µg/kg/min. *Side effects:* Hypotension if there is hypovolemia and tachycardia.

Dopamine. 2 to 20 µg/kg/min IV, available as 200 mg/5 ml ampoule, dosage in mg for infusion: 15 mg × body weight dissolved in 24 ml of compatible solution (5% dextrose, 10% dextrose, 5% dextrose normal saline, normal saline); Infusion of the above solution @ 0.5 ml/hr delivers 5 µg/kg/min. *Side effects:* Tachyarrhythmia, hypertension, vasoconstriction and vomiting. Extravasations may cause tissue necrosis.

Digoxin. Digitalizing dose: *premature neonates* 0.04 mg/kg/day; *term neonates* 0.06 mg/kg/day; *infants* 0.06–0.08 mg/kg/day; *older children* 0.04 mg/kg/day PO (parenteral dose is two-thirds of oral dose). One-half of the digitalizing dose is given stat, followed by one-quarter each after 8 and 16 hr. Maintenance dose is one-quarter of digitalizing dose; given once a day. *Side effects:* Nausea, vomiting; bigeminy pulse, extrasystoles, partial or complete heart block, sinus arrhythmia, atrial or ventricular tachycardia.

Milirinone. 50–75 µg/kg loading dose followed by 0.25 to 1.0 µg/kg/ min. *Side effects*: Extravasations may cause tissue necrosis, dizziness, headache, rarely severe allergic reactions.

Norepinephrine. 0.05 to 0.1 µg/kg/min titrate dose to desired effect (max. 2.0 µg/kg/min). *Side effects*: headache, bradycardia and hypertension.

Isoproterenol hydrochloride. 0.5 to 5.0 µg/kg/min. *Side effects:* Cardiac dysarrhythmias, rarely cardiac arrest, wheezing and bronchospasm.

Vasopressin. Catecholamine refractory vasodilatory septic shock: 0.3–2.0 mU/kg/minute IV infusion. *Side effects:* Hypertension, water intoxication and hyponatremia.

DIURETICS

Acetazolamide. Diuretic: 5 mg/kg/day PO q 8 hr. Hydrocephalus, epilepsy, glaucoma: 50–70 mg/kg/day PO q 8 hr. *Side effects:* Drowsiness, crystalluria, renal calculi, convulsion and acidosis.

Bumetanide. 0.01–0.02 mg/kg/dose; may be repeated q 6–12 hr. *Side effects:* Muscle cramps, nausea, vomiting, gynecomastia, leukopenia and thrombocytopenia.

Chlorthiazide. 20 mg/kg/day q 12 hr. *Side effects:* Hyperglycemia, glucosuria, neutropenia, neonatal thrombocytopenia, hypokalemia, hypotension.

Frusemide. 1–4 mg/kg/day PO in 1–4 divided doses; maximum 6 mg/kg. IV: 1–2 mg/kg/dose q 12 hr. Infusion: 0.1–0.4 mg/kg/hr. *Side effects:* Nausea, vomiting, hyponatremia, hypokalemia, metabolic alkalosis, hyperglycemia, hyperuricemia; occasionally hepatitis or pancreatitis, dizziness, vertigo, headache, tinnitus and hearing loss on prolonged use, rarely anemia, leukopenia or thrombocytopenia; systemic and cutaneous hypersensitivity reactions.

Human albumin. 1 g/kg/dose IV over 30–120 min for hypoproteinemia; administered in combination with frusemide to patients with nephrotic syndrome.

Hydrochlorthiazide. 1–2 mg/kg/day in two divided doses. *Side effects:* Almost similar to furosemide but less frequent.

Metolazone. 0.2–0.4 mg/kg/day. *Side effects:* Hypotension, palpitations and hypovolemia; syncope, dizziness, neuropathy, paresthesias, hepatitis, cholestasis, vomiting, anorexia, abdominal distension and pain, hypersensitivity, anemia, leukopenia and thrombocytopenia, hypokalemia, hyponatremia.

Spironolactone. Neonates: 1–3 mg/kg/day q 12–24 hr; Children: 1.5–3 mg/kg/day or 60 mg/m^2/day q 60–12 hr; not to exceed 100 mg/day. *Side effects*: Dry mouth, dizziness, headache, irregular periods, gynecomastia, hirsutism, erectile dysfunction and hyperkalemia.

Triamterene. 2–4 mg/kg/day q 12 hr. *Side effects:* Hyperkalemia, hyponatremia, dry mouth and headache.

Mannitol. 0.5–3 g/kg/dose IV given over 30–60 min.

MEDICATIONS FOR ENDOCRINOLOGICAL DISORDERS

Betamethasone. 0.1–0.2 mg/kg/day q 12 hr. (750 µg is equivalent to 5 mg prednisolone.) <1 yr: 1 mg, 1–5 yr: 2 mg, 6–12 yr: 4 mg daily. Adult dose: 0.5–6 mg/day. *Indications:* Congenital adrenal hyperplasia, brain edema, bronchial asthma, autoimmune disorders. For enhancing fetal lung maturity, when labor starts before 34 weeks, administer to mother 12 mg IM in 2 doses 24 hr apart.

Cortisone acetate. 0.7 mg/kg/day for physiological requirement. Therapeutic dose is 2.5–10 mg/kg/day q 8 hr. *Side effects: Immediate.* Moon facies, acne, increased appetite, reduced resistance to infections, headache, gastritis, hypertension, electrolyte disturbances, glaucoma, pseudotumor cerebri. *Prolonged therapy.* Myopathy, osteoporosis, growth retardation, cataract, adrenal cortical atrophy.

Dexamethasone. 0.05–0.5 mg/kg/day oral. Congenital adrenal hyperplasia: 0.5 to 1.5 mg/day. Adult: 10–50 mg stat then 4–8 mg q 4 hr; reduce 2 mg q 8 hr. For cerebral edema 0.5 mg/kg/dose q 6 hr IM or IV. Pulse dexamethasone: 5 mg/kg as slow infusion (maximum dose 100 mg).

Hydrocortisone. Status asthmaticus 4–8 mg/kg/dose q 4–6 hr IV; endotoxic shock: 50 mg/m^2 initial dose followed by 50–150 mg/m^2/day q 6 hr IV for 48–72 hr; acute adrenal insufficiency 1–2 mg/kg/dose IV, then 25–150 mg/m^2/day IV or IM.

Prednisolone. Dose one-fifth of cortisone; 2 mg/kg/day PO divided doses q 6–8 hr or single dose in the morning.

Methylprednisolone. 0.5 mg/kg/dose IM or IV. Emergency: 30 mg/kg IV bolus over 10–20 min; repeat after 4 hr if

necessary. Pulse corticosteroid therapy: 30 mg/kg daily for 3–5 days.

Triamcinolone. 24 mg/d PO in divided doses; deep IM 40 mg or intra-articular 2.5–15 mg; avoid <6 yr.

Note: Prednisolone, 5 mg = 0.75 mg betamethasone or dexamethasone, 4 mg methylprednisolone or triamcinolone, 20 mg hydrocortisone, and 25 mg cortisone acetate.

ACTH. 1.6 units/kg IM or IV single dose. Infantile spasms: 20–40 units/kg/day q 12 hr.

Vasopressin. Diabetes insipidus: 2.5–10 U q 6–12 hr SC or IM; 0.5–10 mU/kg/hr IV infusion. Catecholamine refractory vasodilatory septic shock: 0.3–2.0 mU/kg/minute IV infusion. *Side effects:* Hypertension, water intoxication, hyponatremia.

Desmopressin. Infants ≥3 months of age and children: 0.3 µg/kg IV by slow infusion over 15–30 min beginning 30 min before procedure; may repeat dose if needed. Children >12 yr of age: IV: 0.3 µg/kg once slowly over 15 to 30 min. Intranasal: body weight ≤50 kg 150 µg, >50 kg 150 µg; in each nostril. *Side effects*: Water intoxication, hyponatremia.

Growth hormone. 0.09–0.2 U/kg/d SC or IM till accepted height is achieved or bone fusion occurs. For Turner syndrome, dose might be increased to 0.11–0.14 U/kg/day.

Insulin. Details on insulin therapy are provided in Chapter 17.

Carbimazole. 1–2 mg/kg/day in 3 divided doses. *Side effects:* Urticaria, ageusia, pigmentation and bone marrow depression.

Thyroxine. 10–15 µg/kg/day in newborn babies, 5 µg/kg/day in children, single dose PO empty stomach in the morning.

Potassium iodide (SSKI) and Lugol's iodine. SSKI 5 drops q 6 hr: Lugol's iodine solution 4–8 drops q 6–8 hr oral. SSKI (1 g/ml) contains 76.4% iodine. Five drops four times a day (assuming 20 drops/ml) contain about 764 mg iodine. Lugol's solution (125 mg/ml of total iodine) contains, in each 100 ml, 5 g of iodine and 10 g of potassium iodide. Four drops given 4 times a day contain 134 mg of iodine.

Propylthiouracil. 1–4 mg/kg/day; <10 yr: 50–150 mg/day q 8 hr; >10 yr: 150–300 mg/day q 8 hr. Maintenance: 50 mg q 12 hr.

Erythropoietin. Anemia of prematurity: 25–100 U/ kg/dose SC or IV, 3 times a week. Chronic kidney disease: 50–150 U/kg/dose SC, 2–3 times a week. SC route requires lower doses than IV; rotated through arm, thigh and anterior abdominal wall.

Darbepoetin alpha. Prolonged half-life; administered less frequently. Pegylated forms not approved below 12 yr. *Side effects*: Hypertension, seizures, thrombosis of venous access.

Vitamin D: Dose for rickets (vitamin D_3, cholecalciferol): 60,000 IU PO daily for 10 days. The dosing of 1, 25-dihydroxyvitamin D (calcitriol) in patients with CKD stage 2–4 is based on body weight (*see* Chapter 16).

MICRONUTRIENTS

Magnesium sulfate (50% solution provides 4 mEq/ml). Protein energy malnutrition. 2–3 mEq/kg/day PO (maintenance requirement). Therapeutic (severe acute malnutrition): 0.5–1.0 ml/kg/day q 6 hr IM. 100 mg/kg/dose IV.

Zinc sulfate. Therapy of deficiency: 0.5 mg/kg/day for infants; 10 mg/day for <6 months, 20 mg >6 months. Acrodermatitis enteropathica: 6 mg/kg/day.

Parenteral iron therapy. Iron dextran: 4 mg/kg/dose (maximum 100 mg); slow IV push at 1 ml (50 mg) per minute. The first dose for iron dextran is 10 mg (weight <10 kg), 15 mg (weight 10–20 kg) or 20–25 mg for older children. Polynuclear ferric hydroxide sucrose or iron sucrose: 2 mg/kg (maximum 7 mg/kg); diluted 20-fold with normal saline; infused over 30 min; better side effect profile. *Side effects:* Hypersensitivity reactions (bronchospasm, angioedema, urticaria, hypotension); pain and muscle spasms. Severe or persistent symptoms require therapy with antihistaminics.

The dose required for correction of iron deficiency is calculated as:

Total iron deficit (mg) = Weight in kg × (target Hb – actual Hb in g/dl) × 2.4 + depot iron in mg

The depot iron is 15 mg/kg body weight for children <35 kg and 500 mg for >35 kg

Calcium gluconate (elemental calcium 9%). 1–2 ml/kg of 10% solution; slow IV infusion under cardiac monitoring.

Potassium chloride. 1–2 mEq/kg/day q 8 hr PO. Not to exceed 200 mEq/l in central line infusions.

Sodium bicarbonate. 1–2 mEq/kg/dose or calculated on basis of base deficit as follows: Base deficit × weight in kg × 0.6 = mEq, or ml of 7.5% solution of sodium bicarbonate required for correction.

SEDATIVES, HYPNOTICS AND ANTIDEPRESSANTS

Diazepam. Sedative and anxiolytic at doses of 2–5 mg PO. Anticonvulsant: 0.2 mg/kg/dose IV (maximum 10 mg); repeat in 15 min. Contraindicated in myasthenia gravis and acute narrow angle glaucoma.

Lorazepam. 0.1 mg/kg IV; repeat at 5 min; longer duration of action than diazepam. PO: 0.03–0.05 mg/kg/dose q 8–12 hr.

Clonazepam. 0.03 mg/kg/day q 8 hr; increase till maximum dose of 0.1–0.3 mg/kg/day.

Tricyclic antidepressants. 1.5 mg/kg/day single or divided doses. *Side effects:* Anticholinergic effects, dry mouth

constipation, urinary retention, blurred vision, tremors and hypotension.

Chloral hydrate. 5–10 mg/kg/dose for sedation; 20–75 mg/kg/dose for heavy sedation.

Chlorpromazine. 2.5–6 mg/kg/day q 6 hr oral.

Chorea. Start with 50 mg/day oral, increase by 25 mg/day till controlled; maximum dose 300 mg/day. Neonatal tetanus: 1–2 mg/kg per dose 2 to 4 hr.

Fluoxetine hydrochloride. 5–10 mg/day; maximum 20 mg/day.

Haloperidol. Psychotic disorder: 0.05–0.15 mg/kg/day q 8–12 hr; agitation: 0.01–0.03 mg/kg/day q 8–12 hr; chorea: 0.25 mg PO q 12 hr; 5–10 mg/day q 12 hr. *Side effects:* Extrapyramidal reactions and dyskinesia.

Ketamine. For IV induction: 0.5–2 mg/kg at a rate not to exceed 0.5 mg/kg/min; IM, oral, rectal: 3–10 mg/kg/dose; nasal and sublingual: 3–5 mg/kg/dose. Minor procedures 0.5–1.0 mg/kg; sedative dose 2 mg/kg. The concomitant use of midazolam is beneficial.

Midazolam. 0.07–0.2 mg/kg/dose IM or IV for preoperative sedation or conscious sedation during mechanical ventilation followed by 0.2–1 µg/kg/min for neonates and 0.5–3.0 µg/kg/min for infants and children. Status epilepticus: 0.2 mg/kg IV or IM followed by 0.1–0.2 mg/kg/hr. Intranasal 0.2 mg/kg may be used for acute seizure control. *Side effects*: Respiratory depression and shock.

Triclofos. 20 mg/kg/dose for sedation.

VASODILATORS

Isosorbide dinitrate: 0.1 mg/kg/D PO q 6–8 hr. *Side effects:* Flushing and headache.

Nifedipine. 0.3 mg/kg/dose oral q 6 hr

Prazosin. 5–25 µg/kg/dose q 6–8 hr (max. 0.1 mg/kg/U/dose. *Side effects:* Postural hypotension, dizziness, faintness, nasal stuffiness and priapism.

Tolazoline. 1–2 mg/kg IV over 10 min followed by 1–2 mg/kg/hr in continuous infusion. *Side effects:* Dizziness, faintness.

Sildenafil. 0.3–3 mg/kg/day divided in three doses. *Side effects*: Dizziness, lightheadedness.

Suggested Reading and Websites

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Integrated Management of Neonatal and Childhood Illness

30

AK Patwari, S Aneja

Child health has remained an essential component of most of the national health programs in India from Expanded Program of Immunization (EPI) in 1974 to the most recent National Rural Health Mission. Introduction of several new technologies in early 1980s made it possible to prevent major infectious diseases of childhood through mass immunization campaigns and treatment of diarrheal dehydration and malaria at low cost. However, the current child health scenario indicates that common childhood illnesses like acute respiratory infections, diarrhea, measles, malaria, and malnutrition continue to result in high mortality among children less than 5 yr of age. Integrated Management of Childhood Illness (IMCI) strategy optimizes public health approach for improving children's health through the delivery of essential child health interventions.

Why Integrated Management?

Many well-known interventions like universal immunization, essential newborn care, exclusive breastfeeding during first 6 months of life, appropriate complementary feeding, oral rehydration therapy, and timely and appropriate use of antibiotics in pneumonia have proven to be effective. While each of these interventions is successful, there is evidence to suggest that an integrated approach is needed to manage sick children. Sick children often present with overlapping signs and symptoms common to different illnesses and often suffer from more than one illness, which may necessitate different treatments. Another reason for integrated approach is the need for incorporating preventive strategies such as immunization and nutrition along with curative care.

INTEGRATED MANAGEMENT OF NEONATAL AND CHILDHOOD ILLNESS (IMNCI) STRATEGY

Integrated Management of Childhood Illness (IMCI) strategy, developed by World Health Organization in collaboration with UNICEF and many other agencies in mid-1990s, combines improved management of common childhood illnesses with prevention of diseases and promotion of health by including counseling on feeding and immunization. This strategy has been adapted and expanded in India to include neonatal care at home as well as in the health facilities and renamed as ***Integrated Management of Neonatal and Childhood Illness (IMNCI).***

Essential Components of IMNCI Strategy

The IMNCI strategy includes both preventive and curative interventions that aim to improve practices in health facilities, the health system and at home. At the core of the strategy is integrated case management of the most common neonatal and childhood problems with a focus on the most common causes of death in children <5 yr of age.

The strategy includes three main components:

i. Improvements in the case-management skills of health staff through use of locally adapted guidelines
ii. Improvements in the overall health system
iii. Improvements in family and community health care practices

This chapter elaborates the clinical guidelines for the treatment of sick children in an outpatient or primary care setting.

IMNCI Clinical Guidelines

The IMNCI clinical guidelines target children less than 5-yr-old, the age group that bears the highest burden of morbidity and mortality. The guidelines represent an evidence-based syndromic approach to case management that includes rational, effective and affordable use of drugs. Careful and systematic assessment of common symptoms, using selected reliable clinical signs, helps to guide rational and effective actions.

An evidence-based syndromic approach can be used to determine: (i) health problem(s) the child may have; (ii) severity of the child's condition; and (iii) actions that can be taken to care for the child (e.g. refer the child immediately, manage with available resources or manage

at home). In addition the guidelines suggest the adjustments required to manage with the capacity of health system and active involvement of family members in health care practices.

The Principles of Integrated Care

Depending on a child's age, various clinical signs and symptoms differ in their degrees of reliability and diagnostic value and importance. IMNCI clinical guidelines focus on children up to 5 yr of age. The treatment guidelines have been broadly described under two age categories:

1. Young infants age up to 2 months
2. Children age 2 months up to 5 yr

The IMNCI guidelines are based on the following principles:

- All children under 5 yr of age must be examined for conditions which indicate *immediate referral*
- Children must be *routinely assessed* for major symptoms, nutritional and immunization status, feeding problems and other problems
- Only a limited number of carefully *selected clinical signs* are used for assessment
- A combination of individual signs is used to classify the severity of illness which calls for specific action rather than a 'diagnosis'. Classifications are color-coded and suggest referral (*pink*), initiation of treatment in health facility (*yellow*) or management at home (*green*)
- IMNCI guidelines address *most common*, but not all pediatric problems
- IMNCI management protocols use a limited number of *essential drugs*
- Caretakers are *actively involved* in the treatment of children
- IMNCI includes counseling of caretakers about *home care* including feeding, fluids and when to return to health facility.

IMNCI Case Management Process (Fig. 30.1)

Steps of case management process are:
Step 1: Assess the young infant/child
Step 2: Classify the illness
Step 3: Identify treatment
Step 4: Treat the young infant/child
Step 5: Counsel the mother
Step 6: Followup care

Classification Tables

IMNCI classification tables describe the steps of case management process: Assess, classify and identify treatment (Chart 30.1). There are separate classification boxes for main symptoms, nutritional status and anemia. Classification tables are used starting with the *pink* rows. If the young infant or child does not have the severe classifications, look at the *yellow* rows. For the classification tables that have a *green* row, if the young infant or child does not have any of the signs in the pink or yellow rows, select the classification in the green row. If the young infant or child has signs from more than one row, the more severe classifications is selected. However, if the classification table has *more than one arm* (e.g. possible bacterial infection/jaundice, diarrhea in a sick child), one may have more than one classification from that box.

IMNCI classifications are not necessarily specific diagnoses, but they indicate what *action* needs to be taken. All classifications are color-coded: *pink* calls for hospital referral or admission, *yellow* for initiation of treatment, and *green* means that the child can be sent home with careful advice on when to return.

Effective Communication with the Care Provider

It is critical to communicate effectively with the infant's mother or caretaker. Proper communication helps to reassure the mother or caretaker that the infant will receive appropriate care. In addition, the success of home treatment depends on how well the mother or caretaker knows about giving the treatment and understands its importance.

OUTPATIENT MANAGEMENT OF YOUNG INFANTS AGE UP TO 2 MONTHS

Assess and Classify Sick Young Infants

Young infants (infants age <2 months) have special characteristics that must be considered when classifying their illness. They can become sick and die very quickly from serious bacterial infections. They frequently have only general signs such as few movements, fever or low body temperature. Mild chest indrawing is normal in young infants because their chest wall is soft. For these reasons, assessment, classification and treatment of young infant is somewhat different from an older infant or young child. The assessment procedure for this age group includes a number of important steps that must be followed by the health care provider, including: (i) history taking and communicating with the caretaker about the young infant's problem; (ii) checking for possible bacterial infection/jaundice; (iii) assessing for diarrhea if present; (iv) checking for feeding problem or malnutrition; (v) checking immunization status; and (vi) assessing other problems.

Checking for Possible Bacterial Infection/Jaundice

In the first step all sick young infants are first examined to assess for signs of possible bacterial infection and jaundice. The bacterial infection can be serious bacterial infection or a localized infection such as skin infection or ear infection.

The clinical signs which point to possible serious bacterial infection are: *Convulsions* (as part of the current illness); *fast breathing* (the cut-off rate to identify fast

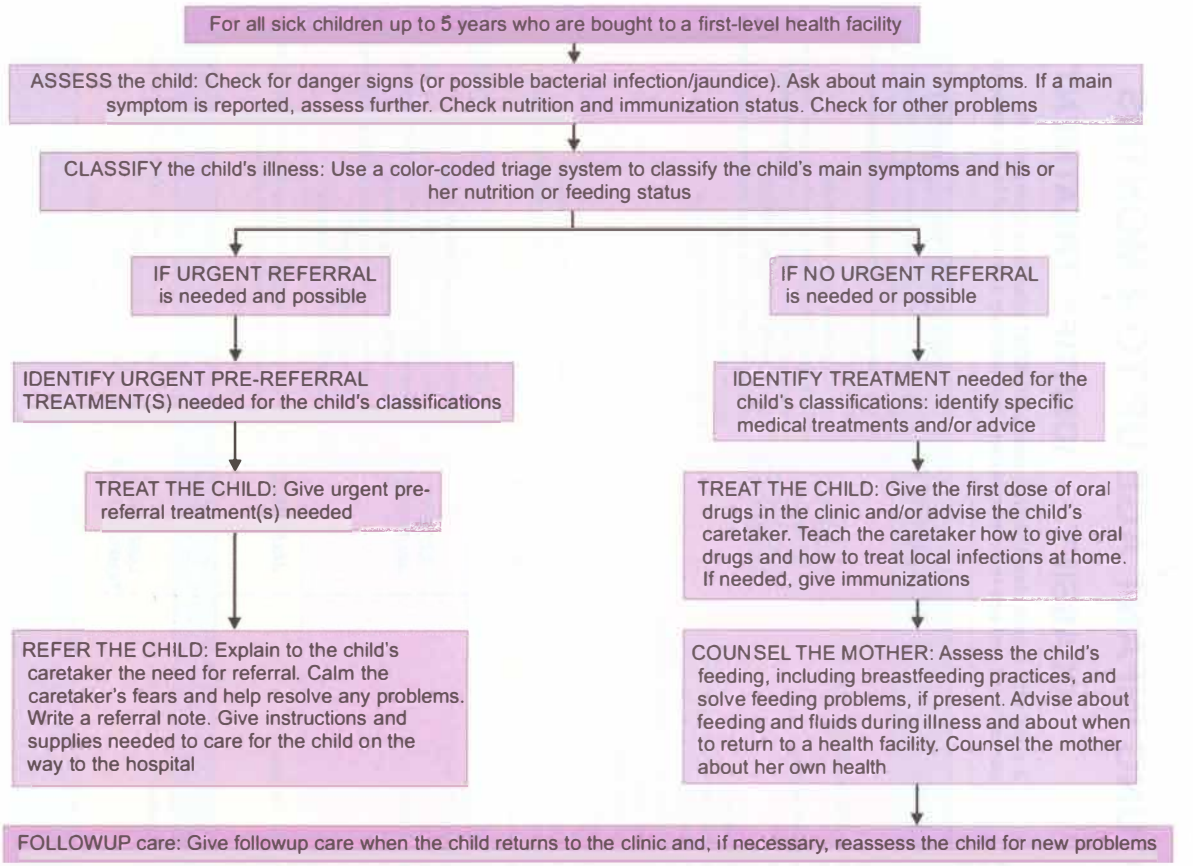

Fig. 30.1: IMNCI case management process

breathing in young infants is 60 breaths per minute or more; if the count is 60 breaths or more, the count should be repeated, because the breathing rate of a young infant is often irregular; if the second count is also 60 breaths or more, the young infant has fast breathing); *severe chest indrawing; nasal flaring; grunting; bulging fontanelle; >10 skin pustules; axillary temperature >37.5°C or <35.5°C; lethargy or unconsciousness;* and *less than normal movements.* Presence of any of these signs indicates possible serious bacterial infection which may be a part of sepsis or pneumonia. A young infant with possible serious bacterial infection is referred urgently to hospital after giving first dose of antibiotics. The mother is advised to continue breastfeeding and to keep the baby warm on the way to hospital.

Pus or redness around the umbilicus, presence of <10 skin pustules or pus draining from ear is classified as local bacterial infection and treated with oral antibiotics.

Jaundice is the visible manifestation of hyperbilirubinemia. Occurrence of jaundice within first 24 hr of birth or after 14 days of age, or deep jaundice visible as yellow palms and soles suggests pathological jaundice and is classified as a severe illness necessitating urgent referral to a hospital for evaluation. (Chart 30.1). An infant age 1–13 days who has jaundice but palms and soles are not yellow is advised home care but should be advised to come for followup after 2 days and advised when to return immediately.

In addition to possible bacterial infection and jaundice, sick young infants with temperature between 35.5 and 36.5°C are classified as low body temperature. This may be due to environmental factors or due to infection. Such infants are warmed using skin-to-skin contact and reassessed after 1 hr. If the temperature becomes normal and the infant has no other pink classification, he can be sent home after advising the mother on how to keep the baby warm. If the temperature is still below 36.5°C the infant should be referred to the hospital.

Assessing for Diarrhea

Diarrhea is a main symptom, which is assessed if the mother says it is present. Exclusively breastfed infants normally pass frequent soft stools. This should not be confused with diarrhea. A young infant is said to have diarrhea if the stools have changed from usual pattern and the child is passing many watery stools (more water than fecal matter).

Chart 30.1

ASSESS AND CLASSIFY THE SICK YOUNG INFANT AGE UP TO 2 MONTHS

ASSESS

ASK THE MOTHER WHAT THE YOUNG INFANT'S PROBLEMS ARE

- Determine if this is an initial or followup visit for this problem
  - if followup visit, use the followup instructions on the bottom of this chart
  - if initial visit, assess the young infant as follows:

USE ALL BOXES THAT MATCH INFANT'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS

CLASSIFY IDENTIFY TREATMENT

A child with a pink classification needs URGENT attention. Complete the assessment and pre-referral treatment immediately so referral is not delayed

CHECK FOR POSSIBLE BACTERIAL INFECTION/JAUNDICE

ASK: Has the infant had convulsions?

LOOK, LISTEN, FEEL:

- Count the breaths in one minute
  Repeat the count if elevated
- Look for severe chest indrawing
- Look for nasal flaring
- Look and listen for grunting
- Look and feel for bulging fontanel

YOUNG INFANT MUST BE CALM

- Look for pus draining from the ear
- Look at the umbilicus. Is it red or draining pus?
- Look for skin pustules. Are there 10 or more skin pustules or a big boil?
- Measure axillary temperature (if not possible, feel for fever or low body temperature)
- See if the young infant is lethargic or unconscious
- Look at the young infant's movements. Are they less than normal?
- Look for jaundice. Are the palms and soles yellow?

*#If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Young Infant and Counsel the Mother***

	SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent prereferral treatments are in bold print)
Classify ALL YOUNG INFANTS	• Convulsions or • Fast breathing ≥60 breaths per minute or more) or • Severe chest indrawing or • Nasal flaring or • Grunting or • Bulging fontanel or • ≥10 or more skin pustules or a big boil or • Axillary temperature 37.5°C or above (or feels hot to touch) or temperature less than 35.5°C (or feels cold to touch) or • Lethargic or unconscious or • Less than normal movements	**POSSIBLE SERIOUS BACTERIAL INFECTION**	➢ ***Give first dose of intramuscular ampicillin and gentamicin*** ➢ ***Treat to prevent low blood sugar*** ➢ ***Warm the young infant by skin to skin contact if temperature less than 36.5°C (or feels cold to touch) while arranging referral*** ➢ ***Advise mother how to keep the young infant warm on the way to the hospital*** ➢ ***Refer URGENTLY to hospital***
	• Umbilicus red or draining pus or • Pus discharge from ear or • <10 skin pustules	**LOCAL BACTERIAL INFECTION**	➢ ***Give oral amoxicillin for 5 days*** ➢ Teach mother to treat local infections at home ➢ Followup in 2 days
And if the infant has jaundice	• Palms and soles yellow or • Age < 24 hr or • Age 14 days or more	**SEVERE JAUNDICE**	➢ ***Treat to prevent low blood sugar*** ➢ ***Warm the young infant by skin to skin contact if temperature less than 36.5°C (or feels cold to touch) while arranging referral*** ➢ ***Advise mother how to keep the young infant warm on the way to the hospital*** ➢ ***Refer URGENTLY to hospital***
	Palms and soles not yellow	**JAUNDICE**	➢ Advise mother to give home care for the young infant ➢ Advise mother when to return immediately ➢ Followup in 2 days
And if the temperature is between 35.5 and 36.4°C	Temperature between 35.5 and 36.4°C	**LOW BODY TEMPERATURE**	➢ Warm the young infant using skin-to-skin contact for one hour and REASSESS If no improvement, refer ➢ Treat to prevent low blood sugar

Contd...

Chart 30.1 *(Contd.)*

THEN ASK:

Does the young infant have diarrhea?*

IF YES, ASK:

- For how long?
- Is there blood in the stool?

LOOK AND FEEL:

- Look at the young infant's general condition. Is the infant:
  - Lethargic or unconscious?
  - Restless and irritable?
- Look for sunken eyes
- Pinch the skin of the abdomen
  Does it go back:
  - Very slowly (longer than 2 seconds)?
  - Slowly?

Classify DIARRHEA

for DEHYDRATION

Two of the following signs: • Lethargic or unconscious • Sunken eyes • Skin pinch goes back very slowly	**SEVERE DEHYDRATION**	➢ ***Give first dose of intramuscular ampicillin and gentamicin*** ➢ ***If infant also has low weight or another severe classification:*** – ***Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way*** – ***Advise mother to continue breastfeeding*** – ***Advise mother how to keep the young infant warm on the way to the hospital*** ***OR*** ➢ If infant does not have low weight or any other severe classification: – Give fluid for severe dehydration (Plan C) and then refer to hospital after rehydration
Two of the following signs: • Restless, irritable • Sunken eyes • Skin pinch goes back slowly	**SOME DEHYDRATION**	➢ ***If infant also has low weight or another severe classification*** – ***Give first dose of intramuscular ampicillin and gentamicin*** – ***Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way*** – ***Advise mother to continue breastfeeding*** – ***Advise mother how to keep the young infant warm on the way to the hospital*** ➢ *If infant does not have low weight or another severe classification:* – Give fluids for some dehydration (Plan B) – Advise mother when to return immediately – Followup in 2 days
Not enough signs to classify as some or severe dehydration	**NO DEHYDRATION**	➢ Give fluids to treat diarrhea at home (Plan A) ➢ Advise mother when to return immediately ➢ Followup in 5 days if not improving

and if diarrhea 14 days or more

Diarrhoea lasting 14 days or more	**SEVERE PERSISTENT DIARRHEA**	➢ **Give first dose of intramuscular ampicillin and gentamicin if the young infant has low weight, dehydration or another severe classification** ➢ **Treat to prevent low blood sugar** ➢ **Advise how to keep infant warm on the way to the hospital** ➢ **Refer to hospital#**

and if blood in stool

Blood in the stool	**SEVERE DYSENTERY**	➢ **Give first dose of intramuscular ampicillin and gentamicin if the young infant has low weight, dehydration or another severe classification** ➢ **Treat to prevent low blood sugar** ➢ **Advise how to keep infant warm on the way to the hospital** ➢ **Refer to hospital#**

* ***What is diarrhea in a young infant?***

If the stools have changed from usual pattern and are many and watery (more water than fecal matter). The normally frequent or loose stools of a breastfed baby are not diarrhea

*If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Young Infant and Counsel the Mother***

Contd.

Chart 30.1 *(Contd.)*

THEN CHECK FOR FEEDING PROBLEM & MALNUTRITION:

ASK:

- Is there any difficulty feeding?
- Is the infant breastfed? If yes, how many times in 24 hr?
- Does the infant usually receive any other foods or drinks? If yes, how often?
- What do you use to feed the infant?

LOOK, FEEL:

Determine weight for age

IF AN INFANT: **Has any difficulty feeding, or**
Is breastfeeding less than 8 times in 24 hr, or
Is taking any other foods or drinks, or
Is low weight for age,

AND

Has no indications to refer urgently to hospital:

ASSESS BREASTFEEDING:

Has the infant breastfed in the previous hour?

If the infant has not fed in the previous hour, ask the mother to put her infant to the breast. Observe the breastfeed for 4 minutes
(If the infant was fed during the last hour, ask the mother if she can wait and tell you when the infant is willing to feed again)

- Is the infant able to attach?
  no attachment at all *not well attached* *good attachment*

TO CHECK ATTACHMENT, LOOK FOR:

- *Chin touching breast*
- *Mouth wide open*
- *Lower lip turned outward*
- *More areola visible above than below the mouth*

(All of these signs should be present if the attachment is good)

- Is the infant suckling effectively (that is, slow deep sucks, sometimes pausing)?
  not suckling at all *not suckling effectively* *suckling effectively*

Clear a blocked nose if it interferes with breastfeeding

- Look for ulcers or white patches in the mouth (thrush)

Does the mother have pain while breastfeeding?

If yes, look and feel for:
- Flat or inverted nipples, or sore nipples
- Engorged breasts or breast abscess

Classify FEEDING

• Not able to feed, or • No attachment at all, or • Not suckling at all, or • Severely underweight (<–3 SD)	**NOT ABLE TO FEED: POSSIBLE SERIOUS BACTERIAL INFECTION OR SEVERE MALNUTRITION**	➢ ***Give first dose of intramuscular ampicillin and gentamicin*** ➢ ***Treat to prevent low blood sugar*** ➢ ***Warm the young infant by skin-to-skin contact if temperature less than 36.5°C (or feels cold to touch) while arranging referral*** ➢ ***Advise mother how to keep the young infant warm on the way to the hospital*** ➢ ***Refer URGENTLY to hospital[¶]***
• Not well attached to breast, or • Not suckling effectively, or • Less than 8 breastfeeds in 24 hr, or • Receives other foods or drinks, or • Thrush (ulcers or white patches in mouth), or • Moderately underweight (<–2 to –3 SD), or • Breast or nipple problems	**FEEDING PROBLEM OR LOW WEIGHT FOR AGE**	➢ If not well attached or not suckling effectively, teach correct positioning and attachment ➢ If breastfeeding less than 8 times in 24 hr, advise to increase frequency of feeding ➢ If receiving other foods or drinks, counsel mother about breastfeeding more, reducing other foods or drinks, and using a cup and spoon ➢ If not breastfeeding at all, advise mother about giving locally appropriate animal milk and teach the mother to feed with a cup and spoon ➢ If thrush, teach the mother to treat thrush at home ➢ If low weight for age, teach the mother how to keep the young infant with low weight warm at home ➢ If breast or nipple problem, teach the mother to treat breast or nipple problems ➢ Advise mother to give home care for the young infant ➢ Advise mother when to return immediately ➢ Followup any feeding problem or thrush in 2 days ➢ Followup low weight for age in 14 days
Not low weight for age (≥–2SD) and no other signs of inadequate feeding	**NO FEEDING PROBLEM**	➢ Advise mother to give home care for the young infant ➢ Advise mother when to return immediately ➢ Praise the mother for feeding the infant well

[¶] *If referral is not possible, see the section* ***Where Referral Is Not Possible*** *in the module* ***Treat the Young Infant and Counsel the Mother***

Clinical Assessment and Classification

All infants with diarrhea should be assessed for presence of dehydration. A number of clinical signs are used to determine the level of dehydration: *infant's general condition* (lethargic or unconscious or restless/irritable); *sunken eyes* and elasticity *of skin* (skin pinch goes back very slowly, slowly or immediately). In addition the infant is assessed for persistent diarrhea and dysentery.

Persistent diarrhea is an episode of diarrhea, with or without blood, which begins acutely and lasts at least 14 days. Persistent diarrhea is usually associated with weight loss and often with serious nonintestinal infections. Persistent diarrhea in a young infant is considered as severe illness and requires urgent referral. Similarly, visible blood in stool in a young infant is classified as severe dysentery and the infant should be referred to hospital.

All young infants with diarrhea are classified for degree of dehydration and in addition may be classified if they have persistent diarrhea and /or dysentery. Young infants with severe dehydration will need IV fluids while those with some dehydration are treated as plan B with oral rehydration. Young infants with no dehydration will require more fluid to prevent dehydration (*see* Chapter on diarrhea).

Checking for Feeding Problems or Malnutrition

All sick young infants seen in outpatient health facilities should be routinely evaluated for adequate feeding and have their weight checked. Weight-for-age compares the young infant's weight with the infants of the same age in the reference population (WHO-NCHS reference). The *very low weight-for-age* or severely underweight identifies children whose weight is –3 standard deviations below the mean weight of infants in the reference population (Z score <–3). The *low weight for age* or moderately underweight identifies children whose weight is –2 standard deviations below the mean weight of infants in the reference population (Z score <–2). Infants who are very low weight for age are given pink classification and should be referred to a hospital. Infants who are low weight for age need special attention to how they are fed and on keeping them warm.

To assess the young infant for feeding problems the mother is asked specific questions about infant feeding to determine if the feeding practices are optimal. The weight of the child and feeding history is taken into consideration to determine if breast feeding technique needs to be checked. Thus an exclusively breastfed infant who is not low weight for age does not require any intervention and is therefore not observed for breastfeeding. If the mother gives history of feeding problem or the infant is low weight for age and has no indication for referral the mother is observed for breastfeeding. Breastfeeding is observed to see the signs of attachment and whether the infant is suckling effectively. Mothers of infants with problem in feeding are counseled appropriately. Infants who are not low weight for age and have no feeding problem are classified as 'no feeding problem' and counseled about home care of young infant.

Checking Immunization Status

Immunization status should be checked in all sick young infants. A young infant who is not sick enough to be referred to a hospital should be given the necessary immunizations before he is sent home.

Assessing Other Problems

All sick young infants need to be assessed for other potential problems mentioned by the mother or observed during the examination. If a potentially serious problem is found or there are no means in the clinic to help the infant, he should be referred to hospital.

Identify Treatment and Treat

The next step is to *identify treatment* required for the young infant according to the classification. All the treatments required are listed in the 'Identify Treatment' column of the *ASSESS and CLASSIFY THE SICK YOUNG INFANT*, Chart 30.1. If a sick young infant has more than one classification, treatment required for all the classifications must be identified. The first step is to determine if there is need to refer the child to hospital.

All infants and children with a severe classification (pink) are referred to a hospital as soon as assessment is completed and necessary pre-referral treatment is administered. Successful referral of severely ill infants to the hospital depends on effective counseling of the caretaker. The first step is to give urgent prereferral treatment (written in bold font in identify treatment section of chart). This may be:

- Administering first dose of antibiotic
- Treatment of severe dehydration
- Warming the young infant using skin-to-skin contact (kangaroo mother care) and keeping the infant warm on the way to the hospital
- Prevention of hypoglycemia with breastmilk; if young infant is not able to swallow give expressed breast milk/ appropriate animal milk with added sugar by nasogastric tube
- In young infants with diarrhea, giving frequent sips of ORS solution on the way to the hospital.

Treatment in Outpatient Clinic and at Home

Young infants who have local infection, feeding problem or low weight, or diarrhea with some dehydration should have treatment initiated in clinic which is to be continued at home (Table 30.1). Counseling a mother/caretaker is critical for home care. The health professional should use good communication skills while counseling the mother/ caretaker for treatment (Box 30.1).

Table 30.1: Treatment guidelines for managing sick young infant in outpatients and at home

Treatment of local infections
- Local bacterial infection: Give oral amoxicillin N cotrimoxazole or × 5 days (avoid cotrimoxazole in infants 1 month of age who are premature or jaundiced)
- Skin pustules or umbilical infection: Teach to apply gentian violet paint twice daily at home.
- Discharge from ear: Teach to dry the ear by wicking

Some and no dehydration
- Treat dehydration as per WHO guidelines for treatment of dehydration.

Feeding problem or low weight
- Skin pustules or umbilical infection: Teach to apply gentian
- Teach correct positioning and attachment for breastfeeding
- Teach the mother to manage breast and nipple problems
- Treat thrush: Tell the mother to paint the mouth of the young infant with gentian violet 0.25% twice daily
- Feeding with a cup and spoon: Wherever indicated teach the mother correct technique of feeding
- Counsel the mother/caretaker about other feeding problems.

Keep the young infant warm
- Teach the mother how to keep the young infant with low weight or low body temperature warm (do not bathe the young infant but sponge with lukewarm water to clean, provide skin to skin contact; keep the room warm: clothe the baby in 3–4 layers properly covering the head with a cap and hands and feet with gloves and socks respectively, cover the baby and the mother with additional quilt or shawl, especially in cold weather).

Box 30.1: Effective communication and counseling–APAC

- *Ask and listen:* Ask the mother/caretaker and listen carefully to find out the young infant/child's problems and what the mother/caretaker is already doing for the young infant/child
- *Praise:* Praise the mother/caretaker for what she has done well
- *Advise and teach:* Advise the mother/caretaker how to take care of young infant/child at home (for tasks which require mother/caretaker to carry out treatment at home: give information, show an example, and let her practice)
- *Check:* Before the mother/caretaker leaves, always check her understanding by asking questions to find out what she understands and what needs further explanation

30

OUTPATIENT MANAGEMENT OF SICK CHILD AGE 2 MONTHS UP TO 5 YEARS

Assess and Classify Sick Child

The assessment procedure is similar to that of young infant including: (i) history taking and communicating with the caretaker about the child's problem; (ii) checking for general danger signs; (iii) checking main symptoms; (iv) checking for malnutrition; (v) checking for anemia; (vi) assessing the child's feeding; (vii) checking immunization status; and (viii) assessing other problems (Chart 30.2).

Checking for General Danger Signs

A sick child brought to an outpatient facility may have signs that clearly indicate a specific problem. For example, a child may present with cough and chest indrawing which indicate severe pneumonia. However, some children may present with serious, nonspecific signs called *General Danger Signs* that do not point to a particular diagnosis. For example, a child who is lethargic or unconscious may have meningitis, severe pneumonia, cerebral malaria or any other severe disease. Great care should be taken to ensure that these general danger signs are not overlooked because they suggest that a child is severely ill and needs urgent attention. The following general danger signs should be routinely checked in all children: (i) history of convulsions during the present illness, (ii) unconsciousness or lethargy, (iii) inability to drink or breastfeed when mother tries to breastfeed or to give the child something to drink, and (iv) child vomits everything.

If a child has *one or more* of these signs, he must be considered *seriously ill* and will almost always need referral. In order to start treatment for severe illnesses without delay, the child should be quickly assessed for the main symptoms and malnutrition and referred urgently to a hospital.

Assessing for Main Symptoms

After checking for general danger signs, the health care provider must enquire about the following main symptoms: (i) cough or difficult breathing; (ii) diarrhea; (iii) fever; and (iv) ear problems. If the symptom is present the child is evaluated for that symptom (Chart 30.2).

Cough or difficult breathing A child with cough or difficult breathing may have pneumonia or severe respiratory infection. In developing countries, pneumonia is often due to bacteria. The most common are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Many children are brought to the clinic with less serious respiratory infections. Most children with cough or difficult breathing have only a mild infection. They do not need treatment with antibiotics. Their families can manage them at home. Very sick children with cough or difficult breathing need to be identified as they require antibiotic therapy. Fortunately, one can identify almost all cases of pneumonia by checking for these two clinical signs: fast breathing and chest indrawing. Chest indrawing is a sign of severe pneumonia.

Clinical assessment and classification. A child presenting with cough or difficult breathing should first be assessed for general danger signs. This child may have pneumonia or another severe respiratory infection. Three key clinical signs are used to assess a sick child with cough or difficult breathing: *fast breathing* (cut-off respiratory rate for fast breathing is 50 breaths per minute or more for a child 2 months up to 12 months, and 40 breaths per minute or more for 12 months up to 5 yr); *lower chest wall indrawing and stridor in a calm child*. Based on a combination of the above clinical signs, children presenting with cough or difficult

Chart 30.2

ASSESS AND CLASSIFY THE SICK CHILD AGE 2 MONTHS UP TO 5 YEARS

ASSESS

CLASSIFY

IDENTIFY TREATMENT

ASK THE MOTHER WHAT THE CHILD'S PROBLEM ARE?

- Determine if this is an initial or followup visit for this problem
  If follow-up visit, use the followup instructions on *TREAT THE CHILD* chart
  If initial visit, assess the child as follows:

CHECK FOR GENERAL DANGER SIGNS

ASK:	***LOOK:***
• Is the child able to drink or breastfeed? • Does the child vomit everything? • Has the child had convulsions?	See if the child is lethargic or unconscious

A child with any general danger sign needs URGENT attention; complete the assessment and any pre-referral treatment immediately so referral is not delayed

USE ALL BOXES THAT MATCH THE CHILD'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS

THEN ASK ABOUT MAIN SYMPTOMS:

Does the child have cough or difficult breathing?

IF YES, ASK: For how long?

LOOK, LISTEN:
- Count the breaths in one minute
- Look for chest indrawing
- Look and listen for stridor

CHILD MUST BE CALM

Classify COUGH or DIFFICULT BREATHING

If the child is:	Fast breathing is:
2 months up to 12 months	50 breaths per minute or more
12 months up to 5 years	40 breaths per minute or more

SIGNS	CLASSIFY AS	IDENTIFY TREATMENT (Urgent pre-referral treatments are in bold print)
• Any general danger sign, or • Chest indrawing, or • Stridor in calm child	**SEVERE PNEUMONIA OR VERY SEVERE DISEASE**	➢ ***Give first dose of injectable chloramphenicol (If not possible give oral amoxicillin)*** ➢ ***Refer URGENTLY to hospital #***
Fast breathing	**PNEUMONIA**	➢ ***Give Amoxicillin for 5 days*** ➢ Soothe the throat and relieve the cough with a safe remedy if child is 6 mo or older ➢ Advise mother when to return immediately ➢ Followup in 2 days
No signs of pneumonia or very severe disease.	**NO PNEUMONIA: COUGH OR COLD**	➢ If coughing more than 30 days, refer for assessment ➢ Soothe the throat and relieve the cough with a safe home remedy if child is 6 mo or older ➢ Advise mother when to return immediately ➢ Followup in 5 days if not improving

*#If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child***

Contd.

Chart 30.2 *(Contd.)*

Does the child have diarrhea?

IF YES, ASK:

- For how long?
- Is there blood in the stool?

LOOK AND FEEL:

- Look at the child's general condition
  - Is the child:
    - Lethargic or unconscious?
    - Restless and irritable?
- Look for sunken eyes
  - Offer the child fluid
  - Is the child:
    - Not able to drink or drinking poorly?
    - Drinking eagerly, thirsty?
- Pinch the skin of the abdomen
  - Does it go back:
    - Very slowly (longer than 2 seconds)?
    - Slowly?

Classify DIARRHEA

for DEHYDRATION		
Two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink, or drinking poorly • Skin pinch goes back very slowly	**SEVERE DEHYDRATION**	➢ If child has no other severe classification: – Give fluid for severe dehydration (Plan C) ➢ ***If child also has another severe classification:*** ***Refer URGENTLY to hospital*** with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding ➢ ***If child is 2 years or older and there is cholera in your area, give doxycycline for cholera***
Two of the following signs: • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly	**SOME DEHYDRATION**	➢ Give fluid and food for some dehydration (Plan B) ➢ ***If child also has a severe classification:*** ***Refer URGENTLY to hospital*** with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding ➢ Advise mother when to return immediately ➢ Followup in 5 days if not improving
Not enough signs to classify as some or severe dehydration	**NO DEHYDRATION**	➢ Give fluid, zinc supplements and food to treat diarrhea at home (Plan A) ➢ Advise mother when to return immediately ➢ Followup in 5 days if not improving
and if diarrhea 14 days or more		
Dehydration present	**SEVERE PERSISTENT DIARRHEA**	➢ **Treat dehydration before referral unless the child has another severe classification** ➢ **Refer to hospital***
No dehydration	**PERSISTENT DIARRHEA**	➢ Advise the mother on feeding a child who has PERSISTENT DIARRHEA ➢ ***Give single dose of vitamin A*** ➢ Give zinc supplements daily for 14 days ➢ Followup in 5 days
and if blood in stool		
Blood in the stool	**DYSENTERY**	➢ ***Treat for 3 days with ciprofloxacin*** ➢ ***Treat dehydration*** ➢ Give zinc supplements daily for 14 days ➢ Followup in 2 days

*If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child***

Contd.

Chart 30.2 *(Contd.)*

Does the child have fever?

(by history or feels hot or temperature 37.5°C* or above)

IF YES:
Decide Malaria Risk: High or Low

THEN ASK:

- Fever for how long?
- If more than 7 days, has fever been present everyday?
- Has the child had measles within the last 3 months?

LOOK AND FEEL:

- Look or feel for stiff neck
- Look and feel for bulging fontanelle
- Look for runny nose

Look for signs of MEASLES

- Generalized rash and
- One of these: cough, runny nose, or red eyes

If the child has measles now or within the last 3 months:

- Look for mouth ulcers Are they deep and extensive?
- Look for pus draining from the eye
- Look for clouding of the cornea

Classify FEVER

High Malaria Risk

Low Malaria Risk

If MEASLES Now or within last 3 months, Classify

HIGH MALARIA RISK

• Any general danger sign, or • Stiff neck, or • Bulging fontanel	**VERY SEVERE FEBRILE DISEASE**	➢ ***Give first dose of IM quinine after making a blood smear / RDT*** ➢ ***Give first dose of IV or IM chloramphenicol (If not possible, give oral amoxicillin)*** ➢ ***Treat the child to prevent low blood sugar*** ➢ ***Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above)*** ➢ ***Refer URGENTLY to hospital#***
Fever (by history, or feels hot, or temperature 37.5°C or above)	**MALARIA**	➢ ***Give oral antimalarials for HIGH malaria risk area after making a blood smear*** ➢ ***Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above)*** ➢ Advise mother when to return immediately ➢ Followup in 2 days if fever persists ➢ If fever is present everyday for more than 7 days, refer for assessment

LOW MALARIA RISK

• Any general danger sign, or • Stiff neck, or • Bulging fontanel	**VERY SEVERE FEBRILE DISEASE**	➢ ***Give first dose of IM quinine after making a blood smear*** ➢ ***Give first dose of IV or IM chloramphenicol (If not possible, give oral amoxicillin)*** ➢ ***Treat the child to prevent low blood sugar*** ➢ ***Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above)*** ➢ ***Refer URGENTLY to hospital#***
• NO runny nose, and • NO measles, and • NO other cause of fever	**MALARIA**	➢ ***Give oral antimalarials for LOW malaria risk area after making a blood smear / RDT*** ➢ ***Give one dose of paracetamol in clinic for high fever (temp. 38.5°C or above)*** ➢ Advise mother when to return immediately ➢ Followup in 2 days ➢ If fever is present everyday for more than 7 days, refer for assessment
• Runny nose PRESENT or • Measles PRESENT or • Other cause of fever PRESENT**	**FEVER: MALARIA UNLIKELY**	➢ ***Give one dose of paracetamol in clinic for high fever (temp.38.5°C or above)*** ➢ Advise mother when to return immediately ➢ Followup in 2 days ➢ If fever is present everyday for more than 7 days, refer for assessment

• Any general danger sign, or • Clouding of cornea, or • Deep or extensive mouth ulcers	**SEVERE COMPLICATED MEASLES*** **	➢ ***Give first dose of vitamin A*** ➢ ***Give first dose of injectable chloramphenicol (if not possible give oral amoxicillin)*** ➢ ***If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment*** ➢ ***Refer URGENTLY to hospital***
• Pus draining from the eye, or • Mouth ulcers	**MEASLES WITH EYE OR MOUTH COMPLICATIONS*** **	➢ ***Give first dose of vitamin A*** ➢ If pus draining from the eye, treat eye infection with tetracycline eye ointment ➢ If mouth ulcers, treat with gentian violet ➢ Followup in 2 days
Measles now or within the last 3 months	**MEASLES**	***Give first dose of vitamin A***

** This cut off is for axillary temperatures, rectal temperature cutoff is approximately 0.5°C higher*
*** Other causes of fever include cough or cold, pneumonia, diarrhea, dysentery and skin infections*
**** Other important complications of measles – pneumonia, stridor, diarrhea, ear infection, and malnutrition – are classified in other tables*

If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child

Contd.

Chart 30.2 *(Contd.)*

Does the child have an ear problem?

IF YES, ASK:

- Is there ear pain?
- Is there ear discharge? If yes, for how long?

LOOK AND FEEL:

- Look for pus draining from the ear
- Feel for tender swelling behind the ear

Classify EAR PROBLEM

Tender swelling behind the ear	**MASTOIDITIS**	➢ ***Give first dose of injectable chloramphenicol (if not possible give oral amoxycillin)*** ➢ ***Give first dose of paracetamol for pain*** ➢ ***Refer URGENTLY to hospital#***
• Pus is seen draining from the ear and discharge is reported for less than 14 days, or • Ear pain	**ACUTE EAR INFECTION**	➢ ***Give Amoxicillin for 5 days*** ➢ Give paracetamol for pain ➢ Dry the ear by wicking ➢ Followup in 5 days
Pus is seen draining from the ear and discharge is reported for 14 days or more	**CHRONIC EAR INFECTION**	➢ Dry the ear by wicking ➢ Topical ciprofloxacin ear drops for 2 weeks ➢ Followup in 5 days
• No ear pain, and • No pus seen draining from the ear	**NO EAR INFECTION**	No additional treatment

*#If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child***

Contd.

THEN CHECK FOR MALNUTRITION

LOOK AND FEEL:

- Look for visible severe wasting
- Look for oedema of both feet
- Determine weight for age

Classify NUTRITIONAL STATUS

• Visible severe wasting, or • Oedema of both feet	**SEVERE MALNUTRITION**	➢ ***Give single dose of vitamin A*** ➢ ***Prevent low blood sugar*** ➢ ***Refer URGENTLY to hospital**** ➢ ***While referral is being organized, warm the child*** ➢ ***Keep the child warm on the way to hospital***
Very low weight for age	**VERY LOW WEIGHT**	➢ Assess and counsel for feeding – If feeding problem, followup in 5 days ➢ Advise mother when to return immediately ➢ Followup in 30 days
Not very low weight for age and no other signs of malnutrition	**NOT VERY LOW WEIGHT**	➢ If child is less than 2 yr old, assess the child's feeding and counsel the mother on feeding according to the FOOD box on the *COUNSEL THE MOTHER* chart – If feeding problem, followup in 5 days ➢ Advise mother when to return immediately

THEN CHECK FOR ANEMIA

LOOK:

- Look for palmar pallor. Is it:
  - Severe palmar pallor?
  - Some palmar pallor?

Classify ANEMIA

Severe palmar pallor	**SEVERE ANEMIA**	➢ ***Refer URGENTLY to hospital****
Some palmar pallor	**ANEMIA**	➢ Give iron folic acid therapy for 14 days ➢ Assess the child's feeding and counsel the mother on feeding according to the FOOD box on the *COUNSEL THE MOTHER* chart – If feeding problem, followup in 5 days ➢ Advise mother when to return immediately ➢ Followup in 14 days
No palmar pallor	**NO ANEMIA**	➢ Give prophylactic iron folic acid if child 6 mo or older

THEN CHECK THE CHILD'S IMMUNIZATION *, PROPHYLACTIC VITAMIN A & IRON-FOLIC ACID SUPPLEMENTATION STATUS

IMMUNIZATION SCHEDULE:

AGE	VACCINE
Birth	BCG + OPV-0
6 weeks	DPT-1 + OPV-1 (+ HepB-1**)
10 weeks	DPT-2 + OPV-2 (+ HepB-2**)
14 weeks	DPT-3 + OPV-3 (+ HepB-3**)
9 mo	Measles
16–18 mo	DPT Booster + OPV
60 mo	DT

PROPHYLACTIC VITAMIN A

Give a single dose of vitamin A:

100,000 IU at 9 mo with measles immunization
200,000 IU at 16–18 mo with DPT Booster
200,000 IU at 24 mo and every 6 mo till 60 mo of age

PROPHYLACTIC IFA

Give 20 mg elemental iron +100 mcg folic acid (one tablet of Pediatric IFA or 5 ml of IFA syrup or 1 ml of IFA drops) for a total of 100 days in a year after the child has recovered from acute illness **if:**

➢ The child 6 mo of age or older, and
➢ Has not received Pediatric IFA tablet/syrup/drops for 100 days in last one year

*** A child who needs to be immunized should be advised to go for immunization the day vaccines are available at AW/SC/PHC**
**** Hepatitis B to be given wherever included in the immunization schedule**

ASSESS OTHER PROBLEMS

MAKE SURE CHILD WITH ANY GENERAL DANGER SIGN IS REFERRED after first dose of an appropriate antibiotic and other urgent treatments
Exception: Rehydration of the child according to Plan C may resolve danger signs so that referral is no longer needed

*****If referral is not possible, see the section **Where Referral Is Not Possible** in the module **Treat the Child***

breathing can be classified into one of the three categories. A child with general danger sign or chest indrawing or stridor is classified as severe pneumonia or very severe disease and merits urgent referral to the hospital. A sick child with cough who has fast breathing is classified as pneumonia and his treatment initiated in clinic with oral antimicrobials. A child with cough with none of these signs is classified as cough and cold and given home remedies to soothe throat and counseled for home care.

A child with cough or cold normally improves in one or two weeks. However, a child with chronic cough (more than 30 days) needs to be further assessed (and, if needed, referred) to exclude tuberculosis, asthma, whooping cough or any other problem).

Diarrhea A child with diarrhea passes stools with more water than normal. A child with diarrhea may have (i) acute watery diarrhea (including cholera); (ii) dysentery (bloody diarrhea); or (iii) persistent diarrhea (diarrhea that lasts 14 days or more).

Most diarrheal episodes are caused by agents for which antimicrobials are not effective and therefore antibiotics should not be used routinely for treatment of diarrhea. Antidiarrheal drugs do *not* provide practical benefits for children with acute diarrhea, and some may have dangerous side effects. Therefore these drugs should never be given to children.

Clinical assessment and classification. *All* children with diarrhea should be assessed for dehydration based on the following clinical signs: *child's general condition* (lethargic or unconscious or restless/irritable); *sunken eyes*; *child's reaction when offered to drink* (not able to drink or drinking poorly or drinking eagerly/thirsty or drinking normally) and *elasticity of skin* (skin pinch goes back very slowly, slowly or immediately). In addition a child with diarrhea should be asked how long the child has had diarrhea and if there is blood in the stool. This will allow identification of children with persistent diarrhea and dysentery.

Children with severe dehydration require immediate IV infusion according to WHO treatment guidelines described in plan C. Children with some dehydration require active oral treatment with ORS as per plan B. Patients with diarrhea and no dehydration are advised to give more fluid than usual to prevent dehydration according to WHO treatment plan A.

All children with persistent diarrhea are classified based on presence or absence of dehydration. Children with persistent diarrhea and dehydration are classified as severe persistent diarrhea and need to be referred to hospital after treatment of dehydration. Children with persistent diarrhea and no dehydration can be safely managed on outpatient basis with appropriate feeding. Children with dysentery are given effective antibiotics for shigellosis.

Fever Fever is a very common condition and is often the main reason for bringing children to the health center. It may be caused by minor infections, but may also be the most obvious sign of a life-threatening illness, e.g. *P. falciparum* malaria or meningitis. When diagnostic capacity is limited, it is important first to identify those children who need urgent referral with appropriate prereferral treatment (antimalarial or antibacterial). *All* sick children should be assessed for fever if it is reported by mother or fever is present on examination.

Clinical assessment and classification. In endemic areas the risk of malaria transmission is defined by areas of high and low malaria risk in the country. National Anti Malaria Program (NAMP) has defined areas depending on malaria risk. A child presenting with fever is assessed and classified depending on risk of malaria. History of duration of fever is important in evaluating fever. If fever has persisted daily for more than seven days the child needs to be referred to hospital for assessment and diagnostic tests. The other signs looked for in a child with fever include general danger signs (assessed earlier) and signs of meningitis, e.g. *bulging fontanel and stiff neck*. Besides these, signs of measles and runny nose are also looked for.

If the child has measles currently or within the last three months, he should be assessed for possible complications. Some complications of measles are assessed as main symptoms, e.g. cough/difficult breathing, diarrhea and ear infections. Clouding of cornea and mouth ulcers are assessed along with measles. Clouding of cornea is a dangerous eye complication. If not treated, cornea can ulcerate and cause blindness. An infant with corneal clouding needs urgent treatment with vitamin A.

Before classifying fever, one should check for other obvious causes of fever.

Children with fever are classified based on the presence of any of the general danger signs, stiff neck, level of malaria risk in the area and presence/absence of symptoms like runny nose, measles or clinical signs of other possible infection. In high malaria risk area all children with fever need to get antimalarial treatment as per NAMP guidelines. In areas with low malaria risk children with fever with no other obvious cause are classified as malaria and should be evaluated with blood smear and treated with oral antimalarial drugs (chloroquine). In low malaria risk area children with fever with another cause of fever (e.g. cough and cold or ear infection or diarrhea) are classified as fever, malaria unlikely and given symptomatic treatment for fever. Since the malaria risk may change with time malaria is treated as per national guidelines.

Ear problems A child with an ear problem may have otitis. It may be acute or chronic infection. If the infection is not treated, the ear drum may perforate. Ear infections are the main cause of deafness in low-income areas, which in-turn leads to learning problems. The middle ear infection can also spread from the ear and cause mastoiditis and/or meningitis. The sick child is assessed for ear infection if any ear problem is reported.

Clinical assessment and classification. The mother is asked about history of ear *pain* and ear *discharge or pus*. The child is examined for tender *swelling behind the ear*. Based on these clinical findings a child can be classified as mastoiditis, acute ear infection, chronic ear infection or no ear infection. Children with mastoiditis are classified as severe illness and referred urgently to hospital. Children with acute ear infection are given oral antibiotics and those with chronic ear infection are advised to keep the ear dry by wicking.

Checking for Malnutrition

After assessing for general danger signs and the four main symptoms, *all children should be assessed for malnutrition*. There are two main reasons for routine assessment of nutritional status in sick children: (i) to identify children with severe malnutrition who are at increased risk of mortality and need urgent referral to provide active treatment; and (ii) to identify children with suboptimal nutritional status resulting from ongoing deficits in dietary intake plus repeated episodes of infection and who may benefit from nutritional counseling.

Clinical Assessment and Classification

Visible severe wasting. This is defined as severe wasting of the shoulders, arms, buttocks, and legs, with ribs easily seen, and indicates presence of marasmus. When wasting is extreme, there are many-folds of skin on the buttocks and thigh. It looks as if the child is wearing baggy pants. The face of a child with visible severe wasting may still look normal. The child's abdomen may be large or distended.

Edema of both feet. The presence of edema in both feet may signal kwashiorkor.

Weight-for-age. Plotting weight for age in the growth chart, based on reference population, helps to identify children with *low* (Z score less than –2) or *very low* (Z score less than –3) weight for age, those who are at increased risk of infection and poor growth and development.

Classification of nutritional status. Using a combination of the simple clinical signs above, children can be classified as *severe malnutrition* (visible wasting with or without edema), *very low weight* or *not very low weight*.

Checking for Anemia

All children should also be assessed for anemia. The most common cause of anemia in young children in developing countries is nutritional or because of parasitic or helminthic infections.

Clinical assessment and classification: Palmar pallor can help to identify sick children with severe anemia. Wherever feasible, diagnosis of anemia can be supported by using a simple laboratory test for hemoglobin estimation. For clinical assessment of anemia the color of the child's palm is compared with examiner's own palm. If the skin of the child's palm is pale, the child has *some palmar pallor*. If the skin of the palm is very pale or so pale that it looks white, the child has *severe palmar pallor*. Based on palmar pallor it is classified as severe anemia, anemia or no anemia.

Assessing the Child's Feeding

All children *less than 2-yr-old* and *all children classified as anemia or very low weight* need to be assessed for feeding even if they have a normal Z score. Feeding assessment includes questioning the mother or caretaker about feeding history. The mother or caretaker should be given appropriate advice to help overcome any feeding problems found.

To assess feeding, ask the mother: does she breastfeed her child (how many times during the day and night), does the child take any other food or fluids (what food or fluids, how many times a day, how the child is fed, how large are the servings, does the child receive his own serving, who feeds the child) and during the illness, has the child's feeding changed (if yes, how?)

Identify feeding problems When counseling a mother about feeding, one should use good communication skills. It is important to complete the assessment of feeding by referring to age appropriate feeding recommendations and identify all the feeding problems before giving advice. In addition to differences from the feeding recommendations, some other problems may become apparent from the mother's answers. Other common feeding problems are: *Difficulty breastfeeding, use of feeding bottle, lack of active feeding and not feeding well during illness.* IMNCI guidelines recommend locally acceptable, available and affordable foods for feeding a child during sickness and health. A sample of such recommendations is given in the IMNCI chart which needs to be adapted to local conditions.

Checking Immunization, Vitamin A and Folic Acid Supplementation Status

The immunization status of ***every sick child*** brought to a health facility should be checked. Children who are well enough to be sent home can be immunized.

After checking immunization status, determine if the child needs vitamin A supplementation and / or prophylactic iron folic acid supplementation.

Assessing other Problems

The IMNCI clinical guidelines focus on five main symptoms. In addition, the assessment steps within each main symptom take into account several other common problems. For example, conditions such as meningitis, sepsis, tuberculosis, conjunctivitis, and different causes of fever such as ear infection and sore throat are routinely assessed within the IMNCI case management process. If the guidelines are correctly applied, children with these conditions will receive presumptive treatment or urgent referral. Nevertheless, health care providers still need to consider other causes of severe or acute illness.

Identify Treatment and Treat

All the treatments required are listed in the Identify Treatment column of the *Assess and Classify the Sick Child Age 2 Months up to 5 Years* (Chart 30.2). *All sick children* with a severe classification (pink) are referred to a hospital as soon as assessment is completed and necessary pre-referral treatment is administered. If a child only has severe dehydration and no other severe classification, and IV infusion is available in the outpatient clinic, an attempt should be made to rehydrate the sick child. The principles of referral of a sick child are similar to those described for a sick young infant.

Referral of Children Age 2 Months up to 5 Years

Possible prereferral treatment(s) includes:

- For *convulsions* diazepam IV or rectally. If convulsions continue after 10 min give a second dose.
- First dose of appropriate intramuscular antibiotic—chloramphenicol or ampicillin + gentamicin or ceftriaxone (for *severe pneumonia or severe disease; very severe febrile disease; severe complicated measles; mastoiditis*). Give oral antibiotic if injectable antibiotics are not available.
- First dose of quinine (for *severe malaria*) as per national guidelines.
- Vitamin A (*persistent diarrhea, measles, severe malnutrition*).
- Prevention of hypoglycemia with breast milk or sugar water.
- Oral antimalarials as per guidelines.
- Paracetamol for high fever (38.5°C or above) or pain.
- Tetracycline eye ointment (if clouding of the cornea or pus draining from eye).
- Frequent sips of ORS solution on the way to the hospital in sick children with diarrhea.

If a child does not need *urgent* referral, check to see if the child needs *nonurgent referral* for further assessment; for example, for a cough that has lasted more than 30 days, or for fever that has lasted seven days or more. These referrals are not as urgent, and other necessary treatments may be done before transporting for referral.

Treatment in Outpatient Clinics and at Home

Identify the treatment associated with each nonreferral classification (*yellow and green*) in the IMNCI chart. Treatment uses a minimum of affordable essential drugs. Following guidelines for treatment need to be followed:

- Counseling a mother/caretaker for looking after the child at home is very important. Good communication skills based on principles of *APAC* are helpful for effective counseling.
- Give appropriate treatment and advice for 'yellow' and 'green' classifications as detailed in Table 30.2.

Table 30.2: Treatment guidelines for managing sick child in outpatients and at home

Pneumonia, acute ear infection: Give the first dose of the antibiotics in the clinic and teach the mother how to give oral drugs, cotrimoxazole
Dysentery: Give the first dose of the antibiotic in the clinic and teach the mother how to give oral drug, ciprofloxicin for 3 days
Cholera: In areas where cholera can not be excluded, children more than 2-year-old with severe dehydration should be given a single dose of doxycycline
Dehydration and persistent diarrhea: Treat 'some' and 'no' dehydration and persistent diarrhea as per standard WHO guidelines
Persistent diarrhea and severe malnutrition, give single dose of vitamin A in the clinic
Measles, give two doses (first dose in clinic and give mother one dose to give at home the next day)
Malaria: Treat as per recommendations
Anemia: Give iron folic acid for 14 days
Cough and cold: If the child is 6 months or older use safe home remedies (continue breastfeeding, use honey, tulsi, ginger and other safe local home remedies)
Local infection: Teach the mother or caretaker how to treat the infection at home. Instructions may be given about how to: Treat eye infection with tetracycline eye ointment; dry the ear by wicking to treat ear infection; treat mouth ulcers with gentian violet
For acute diarrhea, persistent diarrhea and dysentery, give zinc (10–20 mg) supplements for 14 days

Counseling a Mother or Caretaker

A child who is seen at the clinic needs to continue treatment, feeding and fluids at home. The child's mother or caretaker also needs to recognize when the child is not improving, or is becoming sicker. The success of home treatment depends on how well the mother or caretaker knows how to give treatment, understands its importance and knows when to return to a health care provider. Some advice is simple; other advice requires teaching the mother or caretaker how to do a task. When you teach a mother how to treat a child, use three basic teaching steps: *give information; show an example; let her practice.*

- Advise to continue feeding and increase fluids during illness
- Teach how to give oral drugs or to treat local infection;
- Counsel to solve feeding problems (if any)
- Advise when to return (Table 30.3). Every mother or caretaker who is taking a sick child home needs to be advised about when to return to a health facility. The health care provider should (i) teach signs that mean to return immediately for further care, (ii) advise when to return for a followup visit, and (iii) schedule the next well-child or immunization visit.

Table 30.3: Counsel mother when to return

Mother should report immediately if she notices following symptoms

Young infant (age 0–2 mo)	*Sick child (2 mo–5 yrs)*
Breastfeeding or drinking poorly	*Any child*
Becomes sicker	Not able to drink or breastfeed
Develops fever or cold to touch	Becomes sicker
	Develops fever
Fast/difficult breathing	*Child with cough and cold*
Blood in stools (if infant has diarrhea)	Develop fast/difficult breathing
Yellow palms and soles (if jaundiced)	*Child with diarrhea*
	Has blood in stool
	Drinking poorly

Mother should bring infant for followup visit *
Mother should come for scheduled immunization visit
**See* section on identify treatment

REVISION IN IMNCI GUIDELINES

IMNCI strategy recommends adaptation of clinical and management guidelines based on the local epidemiologic scenario and management guidelines, which are evidence-based, pertain to majority of common childhood illnesses, are locally relevant and feasible. Evaluation and providing justification for revision of these guidelines is a continuous process. With the availability of more epidemiological data on common childhood illnesses in India, there is a possibility of future inclusion of conditions like HIV/AIDS, dengue fever and asthma at national or state level revision of IMNCI guidelines.

Suggested Reading

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31 Rights of Children

Rajeev Seth

The Constitution of India guarantees equality before the law to all citizens and pledges special protection for children. In 1992, India accepted the obligations of the UN Convention on the Rights of the Child (CRC). In the last two decades, the government has taken several steps towards publicly advancing children's rights. These include the formation of the National Commission for Protection of Child Rights (2005), a National Plan of Action for Children (2005) and advancing various legislations such as Right to Education (2009) to protect, promote and defend child rights in the country. Physicians need to be familiar with child rights in order to ensure advocacy for children and their families.

United Nations Convention on the Rights of the Child

The United Nations Convention on the Rights of the Child (UN CRC) is the first legally binding international instrument to incorporate civil, cultural, economic, political and social rights for children. It sets out these rights in 54 articles and two optional protocols. Table 31.1 provides articles of UN CRC that apply to child health. There is sufficient evidence globally to acknowledge that the UN CRC has influenced childrens access to health and well-being.

Every pediatrician can, and should have, adequate knowledge of the rights of children in domains of child survival, identity, development, protection and participation. They should understand the broad social determinants of child health, become trained in the use of CRC, align themselves with like-minded organizations in efforts at advocacy, and lobby their local, state and national elected representatives to advance child rights.

Promotion and Protection of Child Rights in India

In 2006, the Government of India upgraded to an independent status the Ministry of Women and Child Development, in order to focus on issues concerning the welfare of women and children. The National Commission

Table 31.1: Articles of the UN Convention on the Rights of the Child that apply to child health

Article	*Purpose*
Article 2	Protection from discrimination
Article 3	Best interests of the child are a primary consideration: The institutions, services and facilities responsible for the care or protection of children shall conform to the standards established by competent authorities
Article 5	Parents are responsible for ensuring that child rights are protected
Article 6	Right to survival and development
Article 9	Right of the child who is separated from one or both parents to maintain personal relations and direct contact with both parents on a regular basis
Article 12	Right of a child to express his/her views, considering the maturity of the child
Article 14	Freedom of expression including seeking, receiving and imparting information
Article 16	Protection of privacy
Article 17	Access to information from mass media, with protection from material injurious to the child's well-being
Article 18	Assistance to parents with child rearing responsibilities
Article 19	Protection from physical and mental violence, abuse or neglect
Article 20	Special protection to children deprived of their families
Article 22	Protection of children seeking refugee status
Article 23	Rights of disabled children to special care
Article 24	Right to health and access to health care
Article 27	Right to an adequate standard of living
Article 28	Right to education
Article 30	Right to the child's own culture and religion
Article 31	Participation in leisure and play
Article 34	Protection from sexual exploitation

or Protection of Child Rights, constituted in 2007, provides for setting up of state level Commissions meant for protection and promotion of child rights in the country. Besides the institutional, administrative and legislative framework, India has a strong presence of non-Governmental organizations (NGOs) that, along with the media, act as watchdogs to protect human and child rights.

Measures for Implementation

Several policies, laws and programs have been introduced to implement the national commitment to child rights. These include:

National Policy for Children (1974). This policy declared children as being a supreme national asset.

National Charter for Children (2003). The charter emphasizes the Government's commitment to rights of children, while enumerating children's duties towards their families, society and nation.

National Plan of Action for Children (2005). This plan commits to ensuring rights of all children by creating an enabling environment for their survival, growth, development and protection.

National Policy for Persons with Disabilities (2006). The policy recognizes that a majority of persons with disabilities can lead a better quality of life if they have access to equal opportunities and effective rehabilitation measures.

Policy Framework for Children with AIDS in India (2007). This policy seeks to address the needs of children affected by HIV/AIDS, by integrating services for them within the existing development and poverty reduction programs.

National Rehabilitation and Resettlement Policy (2007). Under this policy, no project involving displacement of families can be undertaken without a detailed assessment of social impact on the lives of children.

National Urban Housing and Habitat Policy (2007). The policy seeks to promote sustainable development of habitat and services at affordable prices in the country and thereby provide shelter to children from disadvantaged families.

National Legislation

The legislative framework for children's rights is being strengthened by the formulations of new laws and amendments in old laws. These include the Food Security bill (2011), Right to Free and Compulsory Education Act (2009), Prohibition of Child Marriage Act (2006), the Commissions for Protection of Child Rights Act (2005), Amendments to Juvenile Justice (Care and Protection of Children) Act (2006), Right to Information (2005), the Goa Children (amendment) Act (2005), the Child Labor (Prohibition and Regulation) Act (1986) and Information and Technology (amendment) Act (2008). Two notifications in 2006 and 2008 expanded the list of banned and hazardous processes and occupations. New legislations include the Bill for Prevention of Offences against the Child and the HIV/AIDS bill.

National Programs

The Government of India is implementing several programs on social inclusion, gender sensitivity, child rights, participation and protection. These programs include: Integrated Child Development Services (ICDS), *Kishori Shakti Yojana* and Nutrition Program for Adolescent Girls, Rajiv Gandhi Crèche Scheme for children of working mothers, *Sishu Grah* (scheme for assistance to homes for children to promote in-country adoption), *Dhanalakshmi* (conditional cash transfer schemes for the girl child), Program for Juvenile Justice, Child Line (outreach services for children in need of care and protection through 24 hr toll free number 1098), Integrated Child Protection Scheme, Integrated Program for Street Children, *Ujjawala* (scheme for prevention of trafficking and rescue, rehabilitation, reintegration and repatriation), *Sarva Shiksha Abhiyan* (scheme to address educational needs of 6 to 14-yr-old and bridge social, gender and regional gaps with active community participation), National Program for Education of Girls at elementary level (*Kasturba Gandhi Balika Vidyalaya*), National Rural Health Mission, Mid-day Meal Program, Jawaharlal Nehru National Urban Renewal Mission, Universal Immunization Program (UIP) and Integrated Management of Neonatal and Childhood Illness (IMNCI).

Role of Pediatricians in Realizing Child Rights

The most basic and crucial child rights are survival and early childhood care, including health care, nutrition, growth, development and education. Prevention of neglect and protection from exploitation (street children, child labor, trafficking) are complex issues. Parents are often illiterate and ignorant of the rights of their children; awareness of these rights is essential so that they can fight to obtain them.

Pediatricians should join hands with committed groups of multidisciplinary child health professionals, nurses, teachers, social workers, psychologist, lawyers, police, judiciary, child rights activists and community leaders in order to work together and monitor governmental efforts in promotion and protection of various child rights. They should be able to gather and collate available indicators of national child health, address key issues and concerns and facilitate children's participation in projects and policy development. Pediatricians should collaborate with national and international NGOs to initiate advocacy campaigns and media releases in order to change policy, legislations and practice in accordance with the UN CRC.

CHILD ABUSE AND NEGLECT

The term child abuse has different connotations in different cultural milieu and socioeconomic situations. The World Health Organization (WHO) defines child abuse or

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maltreatment as forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial exploitation that results in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power. Major types of child abuse by caregiver or other adults include:

Physical abuse. Acts of commission by a caregiver that cause actual physical harm or have the potential for harm.

Sexual abuse. Those acts where a caregiver uses a child for sexual gratification.

Emotional abuse. The failure of a caregiver to provide an appropriate and supportive environment, including acts that have an adverse effect on the emotional health and development of children.

Neglect. The failure of a parent or guardian to provide for the development of the child, where he/she is in a position to do so, in one or more of the following areas: health, education, emotional development, nutrition, shelter and safe living conditions. Neglect is thus distinguished from circumstances of poverty, in that neglect can occur only in cases where reasonable resources are available to the caregiver.

Manifestations

Injuries inflicted by a caregiver on a child can take many forms. Patterns of injury to the skin are noted. Skeletal manifestations of abuse include multiple fractures at different stages of healing. Death in abused children is most often the consequence of a head injury or injury to internal organs. About one-third of severely shaken infants die and the majority of survivors suffer from longterm consequences such as mental retardation, cerebral palsy or blindness. Children who have been sexually abused may exhibit symptoms of infection, genital injury, abdominal pain, constipation, chronic or recurrent urinary tract infections or behavioral problems. Many children will disclose abuse to caregivers or others spontaneously, although there may be additional direct physical or behavioral signs. Emotional and psychological abuse has received less attention globally due to cultural variations in different countries. Corporal punishment of children, in the form of slapping, punching, kicking or beating, is a concern in schools and other institutions. Child neglect can manifest as failure to thrive, failure to seek basic health care, immunization and deprivation of education and basic nutrition needs. A neglected child is exposed to environmental hazards, substance abuse, inadequate supervision, poor hygiene and abandonment.

Strategies to Reduce Child Abuse and Neglect

Preventing child abuse and neglect should be part of national agenda. In India, abuse and neglect of children is a major social and public health problem, especially among socially marginalized and economically backward groups, such as children in urban slums, street and work children and children of construction workers. While child labor cannot be abolished in the presence of abject poverty, the Government should ensure that working children are not exploited. Protection of children against all forms of abuse and exploitation is a basic child right. The employer must provide for health care for children and ensure that they get time for education.

A comprehensive approach to child protection services in rural areas should involve the established system of *Panchayati Raj*. The *panchayat* officials should be responsible for ensuring basic education, nutrition, health care and sanitation for every child in the village. It should be binding on the *panchayat* to ensure that each child attends school and is protected from agrarian and allied rural occupations as a part of family or individual child labor.

Pediatricians have a significant role in recognizing, responding to and reporting child abuse. They are often the first point of contact of a child with abuse and the best advocates for protection of their rights. While Indian laws do not make it mandatory to report child abuse and neglect, pediatricians should seek assistance from Special Juvenile Police units, Child Welfare Committees, Child Line (an emergency toll-free phone service for children in distress), National and state Commissions for Protection of Child Rights (NCPCR) and NGOs, and direct families to these services. Pediatricians can work with the community, NGOs and governmental administrators to reach out to neglected, deprived and abused children.

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ADOPTION

Adoption is an important option for the rehabilitation of destitute and abandoned children or those who cannot be brought up by their parents due to social reasons. Medical practitioners play a vital role in influencing health and social decisions of their adoptive patients and should work closely with counselors and health professionals.

Legal Aspects

'Right to a family' is proposed as a fundamental right by the United Nations. Adoption agencies should ensure that these rights are protected. In India, only agencies recognized by

the Government can deal with adoption placement. Private adoptions, including direct placement by hospitals, maternity and nursing homes, are illegal. Prior to 2000, adoption was allowed to Hindus under the Hindu Adoption and Maintenance Act; other religious groups were governed by the Guardianship and Wards Act. The Juvenile Justice (Care and Protection of Children) Act, passed by the parliament in 2000, enables citizens of all religions the freedom to adopt a minor child, irrespective whether he/she is a single parent. Such adoptive parents may adopt a child of the same sex, irrespective of the number of living biological sons or daughters.

Procedure of Adoption

A child, who has been relinquished by his/her biological parents or found abandoned, must first be presented to the Child Welfare Committee. Under the current law, this committee has the sole authority to declare the child available for adoption. After due investigations, the committee declares the child as destitute and available for adoption. In case the biological parents want to relinquish a child, they have to execute a document in favor of the adoption agency, witnessed by any authority of the hospital and a relative. A waiting period of two months is given to biological parents to reconsider the decision, following which the child is free for adoption.

Prospective Adoptive Parents

A child can be adopted by a married couple with infertility or those voluntarily opting for adoption. Even single persons are eligible to adopt. Couples who have taken a decision to adopt should go to an agency licensed by the state government and the Central Adoption Resource Authority, an autonomous body in the Ministry of Women and Child Development. Only recognized placement agencies can process the application of abandoned Indian children for in-country and inter-country adoptions. Applications for inter-country adoption of a child born in India should be forwarded by an accredited agency of the country of the adoptive parents, to an agency in India, along with all documents to the Central Adoption Resource Authority.

A social worker from the adoption agency performs pre-adoption counseling, which includes providing guidelines and support to pre-adoptive parents, helping them make informed decisions. A home study is conducted by a professional social worker. Additionally, parents are required to submit a document regarding their health and financial status. Once the application is approved, a suitable child is shown to them. After they accept the child, placement is legalized. The placement is followed up to a period of 3 yr or such time until legal adoption is complete. The adoptive parents are assured confidentiality and provided support as needed.

Role of the Pediatrician

Families often take pediatricians into confidence and seek their advice. Additionally, babies in placement agencies are usually taken for a second opinion to a pediatrician. Pediatricians can counsel and teach families about the process of adoption. A supporting and understanding attitude encourages adoptive parents to overcome their fears. The physician should examine the child carefully and explain to the adoptive parents the diagnoses, if any, and their prognosis. They should ensure that all essential tests (such as HIV, hepatitis B) with a window period are repeated at 3 and 6 months before placement. Parents who wish to relinquish their children due to any reason should be counseled about the correct procedure so as to ensure that children are not left in public places or unhealthy surroundings, which may be unsafe and traumatizing.

Suggested Reading

Central Adoption Resource Agency; www.adoptionindia.nic.in

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