Preface

All you need to know to ace the exam—in one place!

The purpose of this book is to serve as a review text before pediatric finals for rapid review of *high yield* pediatrics-oriented topics for final year MBBS students, USMLE step 2, and other board exams. All details, facts and figures are according to standards and correct to the best of my knowledge.

Numerous mnemonics and memory aids (labeled as: *aide mémoire)* are spread throughtout the text to help easy memorization of difficult facts.

The book has been broken down into small chapters to facilitate easy, and quick reading and memorization of topics without getting bogged down on too much unnecessary details.

Bonus chapters have been added to help difficult concepts of dysmorphology and morphological features. These particularly help in pleasing senior pediatrics teachers during ward postings.

It is recommended that the reader study this book thoroughly and cover-to-cover to ensure all topics are covered which may be dispersed for the sake of easier contextual learning.

—Ali SW,

March, 2015.

Acknowledgements

All the *credit* goes to God, mum, dad, my computer and so *none is left in my phone*!

Contents

CHAPTER 1 GROWTH & DEVELOPMENT

(I) Normal Growth

An accurate measurement of length/height, weight, and head circumference should be obtained at every health supervision visit and plotted on statistical on growth charts. Serial measurements are more useful than a single measurement. Recognizing the pattern helps define whether growth is within acceptable limits or warrants evaluation.

Height is a measure of a single tissue (i.e. bone) and hence is the best index for long-term growth. It has three phases:

Phases of growth in height	Factors involved
Infantile phase	Nutrition
Childhood phase (~18 months of age)	Growth hormone
Pubertal phase	Sex hormones

Body Mass Index (BMI) is used to classify adiposity and is recommended as a screening tool for children and adolescents to identify that are overweight or at risk for being overweight.

When caloric intake is inadequate, the weight percentile falls first, then the height, and the head circumference is last. Caloric intake may be poor due to inadequate feeding or attention and stimulation (nonorganic failure to thrive.

An increasing weight percentile in the face of a falling height percentile suggests hypothyroidism.

Head circumference may be disproportionately large when there is familial megalocephaly, hydrocephalus, or merely catch-up growth in a neurologically normal prema- ture infant.

A child is considered microcephalic if the head circumference is less than the third percentile, even if length and weight measurements also are proportionately low.

Serial measurements of head circumference are crucial during infancy, a period of rapid brain development, and should be plotted regularly until the child is 2 years of age. Size of the brain at birth is 25% of adult size, 90% at 5 years and 95% at 10 years.

Lymphoid tissue differs, gaining maximum at adolescense and decline later.

Table. Rules of Thumb for Growth
Weight
Weight loss in first few days: 5%–10% of birth weight
Return to birth weight: 7–10 days of age
Daily weight gain:
20–30 g for first 3–4 months
15–20 g for rest of the first year
Height
Average length: 20 in. at birth, 30 in. at 1 year
At age 4 years, the average child is double birth length or 40 in.
Head circumference (hc)
Average HC: 35 cm at birth (13.5 in.)
HC increases: 1 cm per month for first year (2 cm per month for first 3 months, then slower)

(II) Factors affecting growth

- Genetics
- Environmental factors
  - Nutrition
  - Disease
  - Socioeconomic class
  - Psychological stress
  - Seasons: Height increases most in spring, Weight increases fastest in autumn.
  - Secular trend: growth parameters progressively increasing over the last century, mostly due to improved nutrition
  - Endocrine factors
    - Growth hormone,
    - Thyroxine,
    - Cortisol,
    - Androgens,
    - Estrogen

(III) Assessment of growth

i) Weight

Decreases by 10% of birth weight during first few weeks. Then increases 25-30 g/day for up to 3 months. Then increases 400 g/month up to 1st year.

- Doubles the birth weight by 5 months.
- Triples the birth weight by 1 year.
- Quadruples (x4) by age of 2 years.
- Quintuples (x5) by 3 years.
- Sextuples (x6) by **5 years**.
- Decuples (x10) by 10 years.

From age 2 years to adolescence (age ~13 years), annual weight gain is 5 pounds/year (=2.27 kg/year).

ii) Length/Height

- Increases by 50% at 1st year of age.
- Doubles at 4 years of age, and
- Triples at 13 years of age.
- Height gain from age 2 years to adolescence is 5 cm/year (~2 inch)

From 2 years to 12 years of age, use formula: [(Age x 6) + 77]

iii) Head Circumference

- Increments in the first year
  - 5 cm in the first 3 months
  - 4 cm in the next 3 months
  - 2 cm in the next 3 months
  - 1 cm in the next 3 months

***Aide mémoire:* '3' and '9' and multiples of '5':**	
Birth	35 cm
3 months age	40 cm
9 months age	45 cm
3 years age	50 cm
9 years age	55 cm

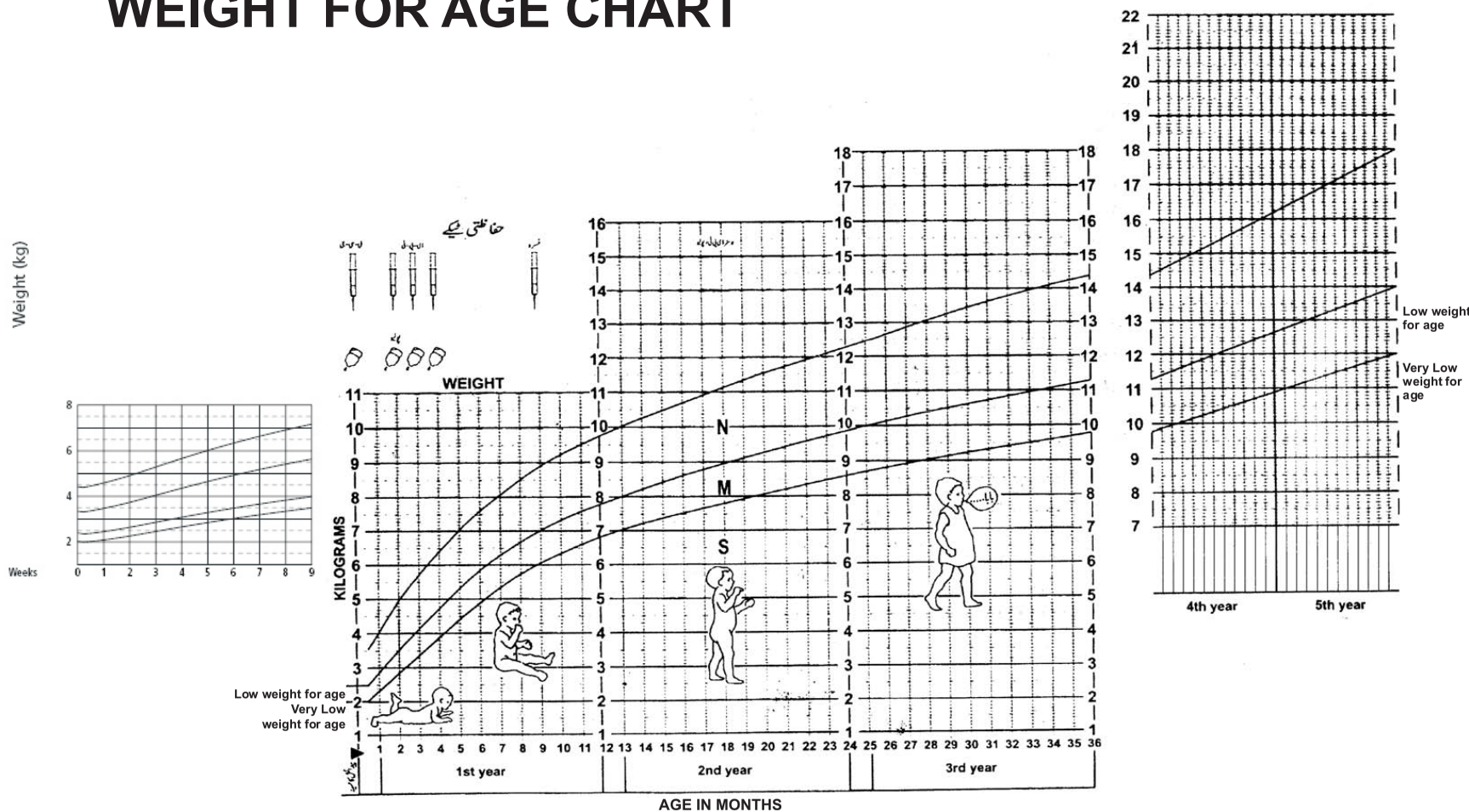
- Usually increases by 50% of birth FOC at the end of first year.

iv) Mid-Upper Arm Circumference

MUAC is normal if between 13.5 to 16 cm from age 1 year to 5 years.

- Normally
  - At birth: 11 cm
  - At 1 year: 16 cm
  - At 5 years: 17 cm
- Abnormal if age 1 year to 5 years:
- 12.5-13.5 cm: Borderline Malnutrition
- <12.5 cm: Severe Malnutrition

WEIGHT FOR AGE CHART



(IV) Abnormal Growth

Weight does not follow a normal distribution, therefore 3rd and 97th percentiles doe not correspond to ±2SD.

The most common reasons for deviant measurements are technical. Hence, repeat the measurement.

Separate growth charts should be used for dysmorphology syndromes (e.g. Turner syndrome, Down syndrome, achondroplasia etc.).

Newborns' heads are significantly larger in proportion to the rest of their body. The head circumference to mid-chest circumference ratio is equal to 1 around 1 year of age, after which it progressively decreases.

Certain growth disturbances result in characteristic changes in the proportional sizes of the trunk, extremities, and head:

Table. Patterns of growth abnormalities and their initial workup

Pattern	Diagnoses to consider	Further evaluation
Weight, Length, and Head circumference all < 5th percentile	• Constitutional short stature • Familial short stature • Genetic abnormality • Intrauterine insult	• Midparental heights, • Evaluation of pubertal development, • Examination of prenatal records, • Chromosome analysis
Discrepant percentiles (e.g., weight 5th, length 5th, head circumference 50th, etc)	Normal variant (familial or constitutional), endocrine growth failure, caloric insufficiency	Mid-parental heights, thyroid hormone, growth factors, growth hormone testing, evaluation of pubertal development
Declining percentiles	Catch-down growth, Caloric insufficiency, endocrine growth failure, endocrine growth failure	Complete history and physical examination, Dietary and social history, growth factors, growth hormone testing

Infants born small for gestational age, or prematurely, ingest more and exhibit catch-up growth in the first 6 months. These infants should be fed on demand and provided as much as they want unless they are vomiting (not just spitting up).

Growth of the nervous system is most rapid in the first 2 years, correlating with increasing physical, emotional, behavioral, and cognitive development. There is again rapid change during adolescence.

An evaluation for primary amenorrhea should be considered for any female adolescent who has not reached menarche by 15 years or has not done so within 3 years of thelarche. Lack of breast development by age 13 years also should be evaluated.

The growth pattern of a child with low weight, length, and head circumference is commonly associated with familial short stature. These children are genetically normal but are smaller than most children.

For further evaluations, parental heights may be useful, although there are many exceptions.

For a girl, midparental height is calculated as follows: $\frac{\text{Paternal Height (in.)}+\text{Maternal Height (in.)}}{2} - 2.5$

For a boy, midparental height is calculated as follows: $\frac{\text{Paternal Height (in.)}+\text{Maternal Height (in.)}}{2} + 2.5$

Many children assume a lower percentile between 6 and 18 months (after starting out in high

percentiles) until they match their genetic programming, then grow along new, lower percentiles.

They usually do not decrease > 2 standard deviations (SD) and have normal developmental, behavioral, and physical examinations. These children with catch-down growth should be followed closely, but no further evaluation is warranted.

i) Diagnostic approach to short stature

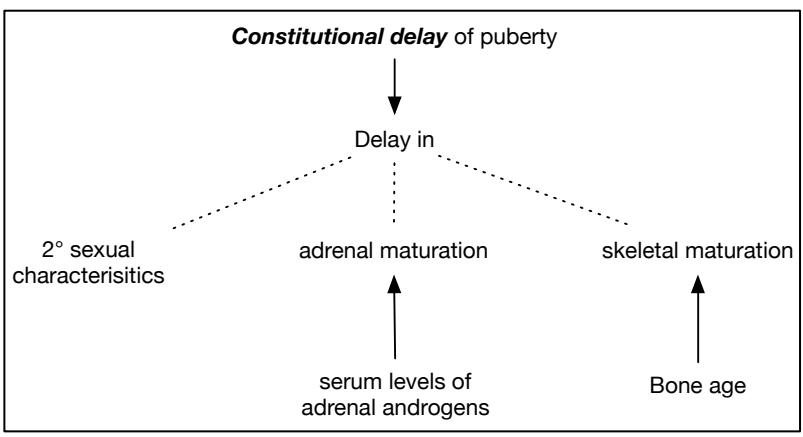
Short stature: A height below the 3rd percentile for individuals of that sex and chronological age in the population.

The most common causes are genetic (i.e. familial) and constitutional delay of growth—

Growth hormone deficiency
Laron syndrome (growth hormone resistance)
Somatomedins (IGF-1/IGF-2) binding protein defidency •
Constitutional delay of puberty (aka maturational growth delay, MGD)
Genetic (familial) short stature
Nutritional dwarfing
Chronic systemic diseases
Emotional deprivation
Dwarfing syndromes: Seckel syndrome Russelt-Silver syndrome •

a) Constitutional delay of puberty

The lack or late appearance of secondary sexual characteristics, delayed skeletal maturation and delayed adrenarche:



b) Genetic short stature

- Genetic short stature is associated with a bone age that is consistent with chronological age and predicts adult short stature.
- In contrast, constitutional delay is associated with a bone age that is delayed for chronological age and predicts normal adult stature.

	Constitutional delay	**Genetic short stature**
Bone age	Delayed	Normal
Outcome in adulthood	*Normal*	*short* stature

c) Investigations

- Routine Laboratory Screening: CBC, ESR, etc.
- Bone age in children:
    - Bone age can determine if there is more potential for growth and can be used to predict final height.
    - X ray *left wrist* determines bone age (for age group 2 to 8 years) can be determined by:
    - The number of carpal bones and their appearance are noted. The *non-dominant* left hand is chosen to avoid abnormal shadows due to injuries that are more likely to occur in *dominant hands*.
    - ***Bone age= No. of ossification centers on xray – 1***

Ossification centers	Bone age in years
2	1
3	2
4	3
5	4
6	5
7	6

    - Age of appearance of epiphysis can also help determine bone age:

Epiphysis	Age of appearance
Capitullum	2 years
Radial head	4 years
Internal epicondyle	6 years
Trochlea	8 years
Olecranon	11 years
External epicondyle	13 years

- Midparental Height Calculation: It is also useful to obtain the parents' heights and calculate a midparental height.
    - Although there are many genes involved in stature, and an offspring's height frequently varies considerably from midparental height, the midparental or target height can still give a good clue that the short stature is genetic.
- Karyotyping
- Other tests may be indicated depending on clinical suspicion may include:
    - Central imaging studies
    - Celiac diseae workup with antibody testing
    - Endocrine studies:
        - Serum levels of insulin-like growth factor I (IGF-I, previously called somatomedin C), and insulin-like growth factor-binding protein 3 (IGFBP-3).
        - Thyroid function testing.
        - GH stimulation testing

d) Diagnosis

Table. Typical Relationships between Bone Age, Height Age, and Chronological Age for Causes of Delayed Puberty or Short Stature	
Relationship	**Cause**
HA < BA = CA	Genetic short stature
HA ≤ BA < CA ***or*** BA < HA < CA	Skeletal dysplasia
HA = BA < CA	Constitutional delay
HA ≤ BA < CA	Hypopituitarism
BA < HA < CA	Hypothyroidism
BA ≤ HA < CA	Hypogonadism
BA = HA < CA	Systemic illness, e.g. malnutrition

These relationships between chronological age (CA), height age (HA), and bone age (BA) can help narrow down the differential diagnoses.

e) Treatment

The treatment is individualized for each case, and requires expert specialist opinion.

ii) Obesity

Children born to obese mothers are three to five times more likely to be obese in childhood. Some small for gestational age (SGA) newborns also have higher risks for abnormal postnatal weight gain and diabetes.

a) Assessment

Early recognition is essential because the early interventions are more likely to be successful.

A BMI for age and gender above the 95th percentile is strongly associated with excessive body fat and is associated with multiple cardiovascular disease risk factors.

The diagnosis of obesity depends on the measurement of excess body fat. Body Mass Index (BMI) is a convenient screening tool.

$$\text{BMI} = \frac{\text{Weight in Kg}}{\text{Height in meters}^2}$$

Table. Body Mass Index (BMI) Interpretation	
BMI/Age Percentile	**Interpretation**
<5th	Underweight
5th–85th	Normal
85th–95th	Overweight
>95th	Obese

Anthropometric data, including weight, height, calculation of BMI and its plotting on growth charts helps to recognize pattern of disease.

b) Investigations

- These are generally reserved for children who have a BMI > 95th percentile, have evidence of comorbidities, or both.
- Useful laboratory tests may include hemoglobin A_{1c}, fasting lipid profile, fasting glucose levels, liver function tests, and thyroid function tests (if there is a faster increase in weight than height).

c) Clinical Features

- Hypertension
- Adipose tissue deposition pattern (central or generalized).
- Signs of associated conditions (acanthosis nigricans, hirsutism, genetic diseases etc).

Table. Some Diseases Associated with Childhood Obesity	
Syndrome	**Features**
Cushing syndrome	Adrenal hyperplasia or pituitary tumor
Prader-Willi syndrome	Neonatal hypotonia, normal growth immediately after birth, small hands and feet, mental retardation, hypogonadism; some have partial deletion of chromosome 15
Pseudohypoparathyroidism	Variable hypocalcemia, cutaneous calcifications
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck; XO chromosome

d) Complications

- Complications of obesity in children and adolescents can affect virtually every major organ system.
- High BMI increases the risk of metabolic and cardiovascular diseases and some cancers; it is also the **most important modifiable risk factor for glycemia and diabetes**.
- Obesity is associated with the presence of precursors of coronary heart disease that are already evident in 12- and 13-year-old children.

Table. Complications of Obesity	
Complication	**Effects**
Psychosocial	Peer discrimination, teasing, isolation, depression, eating disorders (binge-eating)
Growth	Advance bone age, increased height, early menarche
CNS	Pseudotumor cerebri
Respiratory	Obstructive sleep apnea
Cardiovascular	Hypertension, cardiac hypertrophy, arrhythmias, ischemic heart disease
Orthopedic	Slipped capital femoral epiphysis, Blount disease
Metabolic	Insulin resistance, type 2 diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, gout, ∗ hepatic steatosis, polycystic ovary disease, cholelithiasis

e) Treatment

Using the mneumonic described, the clinician should guide the patient who seeks weight reduction to create SMART goals: Specific, Measurable, Attainable, Realistic, and Timely. Setting up specific goals is most important.

Surgical treatment may be advocated as a preferred and cost-effective solution for certain children and adolescents but is controversial.

The existing evidence suggests that bariatric surgery in severely obese adolescent results in significant weight loss and improvements in comorbidities and quality of life.

CHAPTER 2 NORMAL DEVELOPMENT

(I) Physical Development

i) Newborn Period

Any asymmetric movement or altered muscle tone and function requires further evaluation.

Primitive neonatal reflexes are unique in the newborn period and can further elucidate or eliminate concerns over asymmetric function. The most important reflexes to assess during the newborn period are:

The Moro reflex is elicited by allowing the infant's head to gently move back suddenly (from a few inches off of the mattress onto the examiner's hand), resulting in a startle, then abduction and upward movement of the arms followed by adduction and flexion. The legs respond with flexion.

The rooting reflex is elicited by touching the corner of the infant's mouth, resulting in lowering of the lower lip on the same side with tongue movement toward the stimulus. The face also turns toward the stimulus.

The sucking reflex occurs with almost any object placed in the newborn's mouth. The infant responds with vigorous sucking. The sucking reflex is replaced later by voluntary sucking.

The grasp reflex occurs when placing an object, such as a finger, onto the infant's palm (palmar grasp) or sole (plantar grasp). The infant responds by flexing fingers or curling the toes.

Placing the infant supine and turning the head to the side elicit the asymmetric tonic neck reflex. This placement results in ipsilateral extension of the arm and the leg into a "fencing" position. The contralateral side flexes as well.

A delay in the expected disappearance of the reflexes may also warrant an evaluation of the central nervous system.

ii) Later Infancy

With the development of gross motor skills, the infant is first able to control his or her posture, then proximal musculature, and last, distal musculature.

When a joint held in an abnormal fashion can be moved passively into the proper position, there is a high likelihood of resolving with the progression of gross motor development. Fixed deformities warrant immediate pediatric orthopedic consultation.

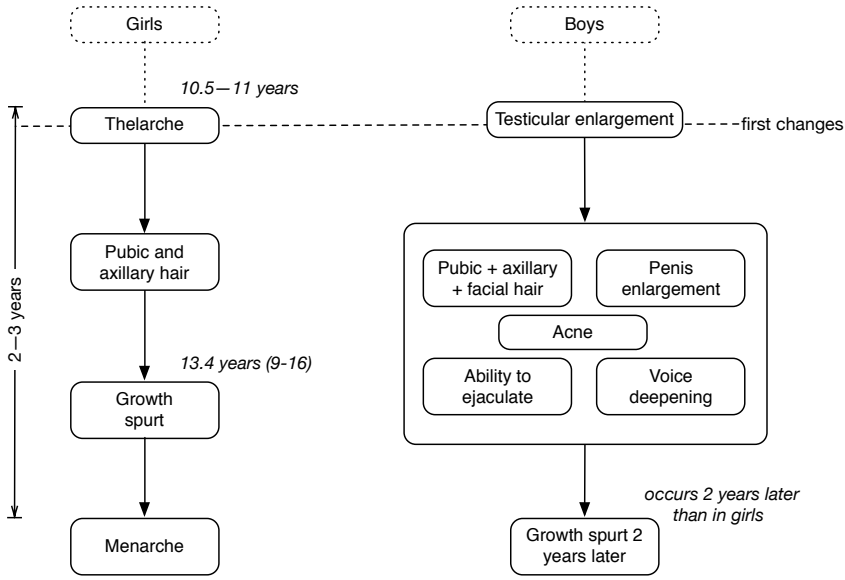
Evaluation of vision and ocular movements is important to prevent the serious outcome of strabismus. The cover test and light reflex should be performed at early health maintenance visits; **interventions after age 2 decrease the chance of preserving binocular vision or normal visual acuity**.

iii) Adolescence

Adolescence is the time between the beginning of sexual maturation (puberty) and adulthood. it is the time period between age 13 and 19 according.

a) Puberty

Puberty is the time in which child's sexual and physical caracteristics mature. It occurs due to hormone changes that lead to body changes and development of 2° sexual characterisitics.



b) Delayed puberty

It is defined as the the onset of puberty after 14 years in girls and 14.5 years in boys.

Causes include:

- Endocrine, genetic or metabolic disorders,
- Constitutional delay, or
- Psychosocial retardation.
- Chronic illness, e.g.
    - Chronic renal failure
    - Cystic fibrosis
    - Anorexia nervosa

c) Precocious puberty

- It is defined as onset of secondary sexual characterisitics before 9 years of age in boys and 8 years of 8 in girls. It is more common in girls.
- It is associated with intracranial tumors in male children, while it is usually idiopathic in females.

(II) Developmental milestones

Easily measured developmental milestones are well established through age 6 years only.

(III) Psychosocial assessment

i) Bonding and Attachment in Infancy

The terms bonding and attachment describe the affective relationships between parents and infants. Bonding occurs shortly after birth and reflects the feelings of the parents toward the newborn (unidirectional). Attachment involves reciprocal feelings between parent and infant and develops gradually over the first year.

ii) Stranger anxiety

Stranger anxiety develops between 9 and 18 months of age, when infants normally become insecure about separation from the primary caregiver.

iii) Separation anxiety

Toddlers build on attachment and in times of stress, toddlers often cling to their parents, known as **Separation anxiety.**

iv) Adolescence

It spans from about age 10 to 25 years. Better characterized by the developmental stages (early, middle, and late adolescence) that all teens must pass through. Late adolescence usually is marked by formal operational thinking, including thoughts about their future.

(IV) Modifying psychosocial behaviors

- Many common behavioral problems of children can be improved by the four major methods of operant conditioning. These are positive reinforcement, negative reinforcement, extinction, and punishment.
- Positive reinforcement increases the frequency of a behavior by following the behavior with a favorable event (e.g., admiring a child for excellent school performance).
- Negative reinforcement usually decreases the frequency of a behavior by removal, cessation, or avoidance of an unpleasant event.
- Extinction occurs when there is a decrease in the frequency of a previously reinforced behavior because the reinforcement is withheld. Extinction is the principle behind the common advice to ignore behavior such as crying at bedtime or temper tantrums, which parents may unwittingly reinforce through attention and comforting. Punishment decreases the frequency of a behavior through unpleasant consequences.
- Positive reinforcement is more effective than punishment. Punishment is more effective when combined with positive reinforcement.

CHAPTER 3 DISORDERS OF DEVELOPMENT

(I) Normal developmental milestones

Table. Developmental Milestones

Age	Gross motor	Fine motor	Social	Language	Other
2 wk	Moves head side to side		Regards face	Alerts to bell	
2 mo	Lifts shoulder while prone	Tracks past midline	Smiles responsively	CooingSearches for sound with eyes	
3 mo	Neck holding achieved	Follows moving objects in a circular fashion, converges and focuses			Reaches for familiar people or objects,
4 mo	Lifts up on handsRolls front to backIf pulled to sit from supine, no head lag	Reaches for object Raking grasp	Looks at handBegins to work toward toy	Laughs and squeals	
6 mo	Sits alone	Transfers object hand to hand	Feeds self Holds bottle	Babbles	
9 mo	Pulls to standGets into sitting position	Starting to pincer grasp Bangs two blocks together	Waves bye-bye Plays pat-a-cake	Says *Dada* and *Mama*, but nonspecificTwo-syllable sounds	
12 mo	WalksStoops and stands	Puts block in cup	Drinks from a cup Imitates others	Says *Mama* and *Dada*, specificSays one to two other words	
15 mo	Walks backward	ScribblesStacks two blocks	Uses spoon and fork Helps in housework	Says three to six words Follows commands	
18 mo	Runs	Stacks four blocks Kicks a ball	Removes garment “Feeds” doll	Says at least six words	
2 yr	Walks up and down stairs Throws overhand	Stacks six blocks Copies line	Washes and dries hands Brushes teeth. Puts on clothes	Puts two words together Points to pictures Knows body parts	Understands concept of *today*
3 yr	Walks steps alternating feet Broad jump	Stacks eight blocks Wiggles thumb	Uses spoon well, spilling little Puts on T-shirt	Names picturesSpeech understandable to stranger 75%Says three-word sentences	Understands concepts of *tomorrow* and *yesterday*

Age	Gross motor	Fine motor	Social	Language	Other
4 yr	Balances well on each foot Hops on one foot	Copies O, maybe + Draws person with three parts	Brushes teeth without helpDresses without help	Names colors Understands adjectives	
5 yr	Heel-to-toe walks	Copies □		CountsUnderstands opposites	
6 yr	Balances on each foot 6 sec	Copies Δ, Can draw a person with six parts		Defines words	Begins to understand *right* and *left*

(II) Copying shapes

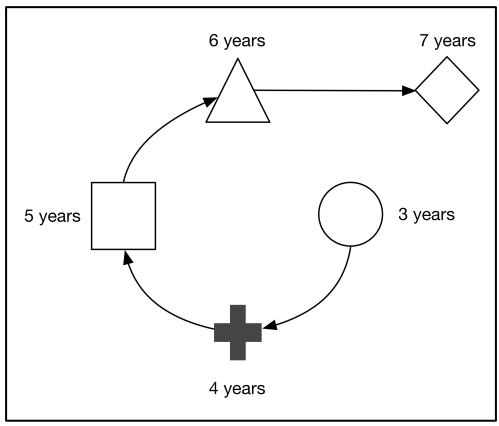


Figure. Approximate ages for copying shapes. *Aide mémoire*: the shapes hold a similar position in the illustration as on the famous gaming consoles game pads like Xbox, and PlayStation.

For development assessment two scales used frequently are:

- Griffith Scale (Birth – 8 years age)
- Denver Developmental Screening test

The Denver Developmental Screening Test II was the classic test used by general pediatricians. It assesses the development of children from birth to 6 years of age in the following four domains:

Griffith Scale	Denver Developmental Screening
A. Locomotor	1. Personal-social
B. Personal-social	2. Fine motor–adaptive
C. Hearing and Speech	3. Language
D. Eye and Hand coordination	4. Gross motor
E. Performance	
F. Practical reasoning (older children)	

(III) Intellectual Development

Intelligence tests best assess intellectual capability at various stages, comparing it with chronological age to give 'Intelligence quotient', expressed as a percentage. $\text{I. Q} = \frac{\text{Intellectual age}}{\text{Chronological age}} \text{ x } 100$

(IV) Delayed Development

- Psychosocial, emotional deprivation
- Idiopathic
- Mental handicap
- Specific abnormality likes blindness and deafness
- Intercurrent illness and hypothyroidism give rise to arrested or deteriorating development

Language screening correlates best with cognitive development in the early years.

Table. Rules of Thumb for language development and expressive language

Age (yr)	Speech production	Articulation	Following commands
1	One to three words		One-step commands
2	Two- to three-word phrases	½	Two-step commands
3	Routine use of sentences	¾	
4	Routine use of sentence sequences; conversational give-and-take	Almost all	
5	Complex sentences; extensive use of modifiers, pronouns, and prepositions	Almost all	
Articulation: amount of speech understood by a stranger			

Most changes in language development in the first years involve recognition and understanding (receptive language).

Table. Conditions considered high risk for associated hearing deficit
Congenital hearing loss in first cousin or closer relative
Bilirubin level of ≥20 mg/dL
Congenital rubella or other nonbacterial intrauterine infection
Defects in the ear, nose, or throat
Birth weight of ≤1500 g
Multiple apneic episodes
Exchange transfusion
Meningitis
Five-minute Apgar score of ≤5
Treatment with ototoxic drugs (e.g., aminoglycosides and loop diuretics)

Whenever there is a speech and/or language delay, a hearing deficit must be considered.

CHAPTER 4 EVALUATING A WELL CHILD

Following screening tests are recommended: newborn metabolic screening with hemoglobin electrophoresis, hearing and vision evaluation, anemia and lead screening, and tuberculosis testing.

Infants with sickle cell disease may begin receiving oral penicillin prophylaxis *to prevent sepsis*, the major cause of mortality in these infants.

(I) Anemia Screening

Children are screened for anemia at ages when there is a higher incidence of iron deficiency anemia:

- Healthy term infants usually are screened at 12 months of age because this is when a high incidence of iron deficiency is noted.
- Additionally, Infants are screened at birth and again at 4 months if there is a documented risk, such as low birth weight or prematurity.

When iron deficiency is strongly suspected, a therapeutic trial of iron may be used.

(II) Tuberculosis Screening

In general the standardized purified protein derivative intradermal test is used with evaluation by a health care provider 48 to 72 hours after injection. The size of induration denotes a positive test:

- For most patients, 10 mm of induration is a positive test.
- For HIV-positive patients, those with recent tuberculosis contacts, patients with evidence of old healed tuberculosis on chest film, or immunosuppressed patients: 5 mm is a positive test.

(III) Immunizations

Immunization records should be checked at each office visit, regardless of the reason. Appropriate vaccinations should be administered. Refer to following chapter on Immunizations.

(IV) Nutritional Assessment

Plotting a child's growth on the standard charts is a vital component of the nutritional assessment. A dietary history should be obtained.

(V) Dentition

Dentition is not a reliable index of development.

Table. Primary Teeth

	Maxillary	Mandibular
Central incisors	7 months	6 months
Lateral incisors	8 months	9 months
Canine	18 months	18 months
First molars	15 months	15 months
Second molars	2 years	2 years

Table. Permanent teeth	
First molars	6 years
Central and lateral incisors	8 years
First premolars	9 years
Second premolars	10 years
Canines	11 years
Second molars	12 years
Wisdom teeth	~22 years

- Dental health care visits should include instruction about preventive care practiced at home.
- In infants, rubbing gums with a wet washcloth can be the first step in oral hygiene.
- Other prophylactic methods shown to be effective at preventing caries are concentrated fluoride topical treatments (dental varnish) and acrylic sealants on the molars.
- Fluoridation of water or fluoride supplements in communities that do not have fluoridation are important in the prevention of cavities.

(VI) Anticipatory Guidance

The "Back to Sleep" initiative has reduced the incidence of sudden infant death syndrome (SIDS). American Academy of Pediatrics recommendeds that *babies should be laid on their backs when putting to sleep.*

There has been a considerable decrease in SIDS since this initiative.

CHAPTER 5 IMMUNIZATIONS AND PROPHYLAXIS

(I) Definitions

i) Active Immunity

It is the induction of immunity through the administration of a vaccine or toxoid (inactivated toxin).

ii) Passive Immunity

This short-lived form of immunity occurs when an individual receives prepared antibodies: e.g.

- Transplacental transfer of maternal antibodies
- Passage of IgA from mother to newborn during breast-feeding
- Administration of antibody, either as immunoglobulin or monoclonal antibody.

iii) Herd Immunity

Herd immunity is bases on the notion that if a herd (a population or group) is protected from a disease by immunization then the chance that a major epidemic will occur is limited. This concept has been utilized for small pox vaccination in the past.

(II) Vaccines

- Transplacentally transferred maternal antibodies (predominantly IgG) protect the infant for upto 3-4 months, which can neutralize vaccines till this age.
- BCG vaccination is associated with cell mediated immunity and so, it can be given at birth.
- Antibodies against measles persist upto 6-9 months of age if mother has been vaccinated or suffered from measles. So measles vaccination is given after that age.
- Immunization of preterm infants should begin at the same chronological age as recommended for term.
- There is a small rise of antibody level with 1st two doses, but with 3rd dose, there is a tremendous antibody rise, which is called "**Booster dose**".
- First two doses are called **sensitizing doses** and subsequent doses as Recall Booster.
- Small pox vaccination is not recommended these days.

i) Recommendations

- Deep injection and gentle massage reduces the risk of antigenic cysts.
- Live attenuated vaccine should be delayed for approx. 6 weeks after, if a polyvalent immune globulin has been given.

ii) Conditions which are not contraindications to vaccination

- Minor illnesses, e.g. upper ARI, diarrhea, or fever <38.5°C.
- Allergy, hay-fever (allergic rhinitis), asthma.

- Prematurity, small for date infants
- Malnutrition
- Child being breast fed
- Family history of convulsions
- Treatment with antibiotics, low dose corticosteroids or locally acting steroids (e.g. topical or inhaled).
- Dermatitis, eczema, or localized skin infections.
- Chronic diseases of the heart, lung, kidney and liver.
- Stable neurological conditions such as cerebral palsy, and Down's syndrome.
- History of jaundice after birth.
- Immunization should be delayed only in case of high-grade fever so that any sign of illness will not be attributed to vaccination.
- *A child with diarrhoea who is due to receive oral polio vaccine should be given a dose, but this dose should not be counted in the schedule*. Administer an extra dose, i.e***. that is, a fifth dose*** at least four weeks after he or she has received the last dose in the schedule.

iii) Vaccine safety

a) Heat sensitive vaccines

Range	Vaccine
most sensitive  least sensitive	OPV
	Measles, MMR
	DTP, DTP-HepB, DTP-Hib, DTP-HepB+Hib, YF
	BCG
	Hib, DT
	Td, TT, HepB, JE

b) Freeze sensitive vaccines

- Most vaccines recommended for children in Pakistan, (BCG, DTP, HiB, MMR, Hep B) are to be kept at 2-8°C (fridge section) and not frozen.
- Only Oral Polio vaccine should be kept in freezer i.e. 0°C.

iv) Contraindications to vaccination

- Live vaccines should not be given to immunocompromised.
- Do not give DPT-2 or -3 to a child who has had convulsions or shock within 3 days of the most recent dose.
- Do not give DPT to a child with recurrent convulsions or an active disease of the central nervous system.
- Do not give BCG or yellow fever vaccine to a child with symptomatic HIV infection or AIDS, but do give the other vaccines.

v) Vaccine Vial Monitor (VVM)

It is a temperature & time-sensitive coloured label, which provides an indication of the appro-

ximate amount of heat to which the vial has been exposed:

Colour changes of VVM	Interpretation
Inner square lighter than outer circle	Vaccine can be used (if within expiry date).
Inner square colour same or darker than outer	Vaccine should be discarded

vi) Types of Vaccines

Type of Vaccine	Examples	
Live vaccines These produce active immunity by causing mild infection	**Bacterial**	**Viral**
	BCG	MMR Polio Yellow fever
Killed/inactivated vaccines These are prepared from virulent organisms or preformed antigen inactivated by heat, phenol, formaldehyde or some other means	**Bacterial**	**Viral**
	Perussis Cholera	Influenza Injectable polio (Salk)
Toxoids These are toxins which have been rendered non-toxic by treatment with formaldehyde but their antigenicity is maintained	Diphtheria Tetanus	
Polysaccharide vaccines A T-cell-dependent response in infants can be induced by conjugation to a protein carrier (e.g. tetanus toxoid), without which these are poor immunogens in less than 2 year olds.	Pneumococcal Meningococcal Hemophilus influenza B	
Recombinant vaccines	Hepatitis B Human Papilloma virus	

(III) Expanded Program of Immunization (EPI)

Age	Vaccine	Dose	Route
At birth	BCG	0.05 ml	I/D (Right deltoid)
	OPV (0)	2 drops	Oral
6 weeks	OPV (1)	2 drops	Oral
	Petavalent (1)	0.5 ml	I/M
	PCV (1)	0.5 ml	I/M
10 weeks	OPV (2)	2 drops	Oral
	Petavalent (2)	0.5 ml	I/M
	PCV (2)	0.5 ml	I/M
14 weeks	OPV (3)	2 drops	Oral
	Petavalent (3)	0.5 ml	I/M
	PCV (3)	0.5 ml	I/M
9 months	Measles (1)	0.5 ml	S/C
15 months	Measles (2) (optional MMR)	0.5 ml	S/C
5 years	DT booster	0.5 ml	I/M
	OPV booster	2 drops	Oral
10 years	Td booster	0.5 ml	I/M

Source: http://epi.punjab.gov.pk/Home.aspx. Pneumococcal Conjugate Vaccine (PCV) introduced n 2012.

i) Routine for missed immunizations

a) 2-5 year age group

BCG	1 dose	
DTP	2 doses	4 weeks interval
Polio	2 doses	

b) > 5 years age group

BCG	1 dose	
TT or Td (adult)	2 doses	4 weeks interval
DTaP	2 doses	

ii) Vaccines included in EPI

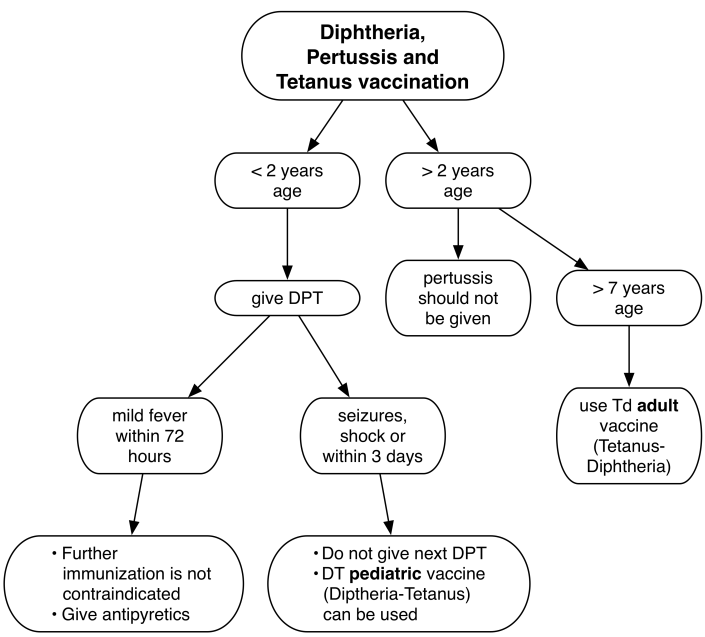
iii) Poliomyelitis

a) Supplementary immunization with OPV

A key strategy for polio eradication large scale campaigns (National Immunization Days) are conducted where two doses of OPV, one month apart, are given to all children under five years of age regardless of how many doses they have received in the past.

Many rounds of National immunization days maybe conducted in a country however there is no risk associated with receiving multiple doses of OPV.

iv) DPT vaccine



v) Measles

Infants at high risk (HIV-infected, in closed communities such as refugee camps, or in the presence of an outbreak) may receive a dose at 6 months of age followed by an extra dose at 9 months.

Type of vaccine	BCG Live bacterial	Live oral polio vaccine (OPV)	Pentavalent vaccine	Measles Live attenuated viral
Number of doses	One	Four in endemic countries (including birth dose)	Three	One dose.
Schedule	At or as soon as possible after birth	At birth 6, 10, 14 weeks	6, 10, 14 wks	At 9–11 months of age
Booster	None	18 months, 5 years and supplementary immunization	18 months (DPT only), 5 years (DT only), 10 years (Td only)	15 months (optional MMR)
Contraindications	Symptomatic HIV infection	None	Do not use as a birth dose	Severe reaction to previous dose; pregnancy; congenital or acquired immune disorders **(not HIV infection)**
Adverse Reactions	Local abscess, regional lymphadenitis; osteomyelitis, disseminated disease	Vaccine associated paralytic polio (approximately 1 in 6 million vaccinations)	Mild local and systemic reactions are common	Malaise, fever, rash 5–12 days later; idiopathic thrombocytopenic purpura; rarely, encephalitis, anaphylaxis
Special precautions	A special syringe and needle is used for correct administration of BCG vaccine	Children known to have congenital immune deficiency syndromes should receive IPV rather than OPV.	Do not use as a birth dose, usually not given over 6 years of age	None
Dosage	0.05 to 0.1ml	2 drops	0.5 ml	0.5ml
Injection site	Right deltoid	–	Vastus lateralis muscle	Outer mid-thigh/upper arm depending on the age
Injection type	Intradermal	–	Intramuscular	Subcutaneous
Storage	Store between 2°C–8°C (vaccine can frozen for long-term storage)	Store between 2°C and 8°C (maybe frozen for long-term storage)	Store between 2°C–8°C. Never freeze	Store between 2°C–8°C (vaccine maybe frozen for long-term storage but not the diluent)

(IV) Non-EPI vaccines

i) Schedule of Non-EPI vaccinations

Table. Schedule of non-epi vaccinations			
Age (approx.)	Vaccine	Dose	Route
10 weeks	Rotavirus (1)	0.5 ml	Oral
14 weeks	Rotavirus (2)	1 ml	Oral
12 months	Hepatitis-A (1)	0.5 ml	IM
	Chickenpox	0.5 ml	SC
15 months	PCV booster	0.5 ml	IM
18 months	Hepatitis-A (2)	0.5 ml	IM
> 2 years	Typhoid	0.5 ml	IM
4-5 years	Chickenpox	0.5 ml	SC
5-7 years	MMR	0.5 ml	SC
Numerals in parenthesis represent chronological order of dose.			

ii) Meningococcus

Type of vaccine	**Purified bacterial capsular polysaccharide (A, C, W135, Y)**
Number of doses	One
Schedule	Not less than three months; older than three years recommended
Booster	Every three to five years
Contraindications	Severe adverse reaction to previous dose
Adverse Reactions	Occasional mild local reaction, mild fever
Special precautions	Children aged under two years of age are not protected by the vaccine
Dosage	0.5 ml
Injection site	Upper arm
Injection type	Subcutaneous
Storage	Store between 2°C–8° C

iii) Pneumococcus

It is recommended to give a dose of vaccine to children > 2 years at high risk, i.e. those with:

- Sickle cell anemia,
- Chronic renal failure,
- Immunosuppression from organ transplantation,
- Leaks of CSF, and
- HIV infection.

iv) Rabies

a) Active Immunization

Pre-exporsure prophylaxis:

- Dose is 1 ml by S/C or I/M injection
- 2 doses are given at interval of 4 weeks
- Then booster dose after 1 year
- Afterwards, booster dose 3-4 yearly if needed

Post-exposure prophylaxis

- Dose is 1 ml by S/C or I/M injection
- 4 doses on days 0, 3, 7, 14, and 28

b) Passive Immunization

Human Rabies Immunoglobulin:

- Used if HDCV is not available
- It is given 20 IU/kg, half of which is infiltrated into wound site

Rabies Anti-serum

- It is for passive immunization when Human Rabies Immunoglobulin is not available.
- Dose is 40 IU/kg by IM injection. Part of it is infiltrated around wound site.

CHAPTER 6 BEHAVIORAL DISORDERS

(I) Head rolling and banging

Common in infants who are left in cribs for long periods

(II) Thumb sucking

Provides a satisfying outlet for the child.

(III) Teeth grinding

Tension and repressed anger are the causes. Praise and emotional support is required.

(IV) Trichotillomania (Hair Pulling)

It is also known as hair pulling. Excessive swallowing of broken hairs gives rise to bezoars.

(V) Breath holding

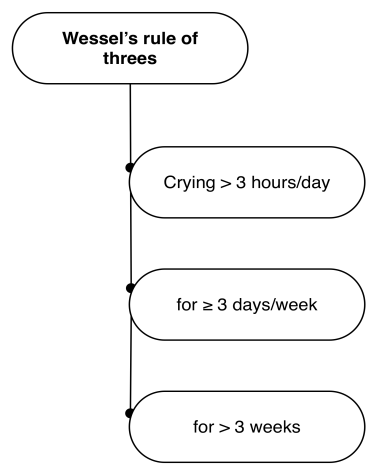
During crying child holds his breath, may become cyanosed and even develop a convulsion. Parents should remain calm, put the child flat on bed or on the side with the head somewhat low. Any demads that provoked this behavior should not be met after recovery. Usually the child has forgotten about it after he recovers.

(VI) Dysfluency (Stuttering)

Begins during development of speech. It is common in 3- to 4-years age. Lack of confidence and anxiety cause aggravation. Speech therapy is advised for persistent cases.

Unless the dysfluency is severe, is accompanied by tics or unusual posturing, or occurs after 4 years of age, parents should be counseled that it is normal and transient and to accept it calmly and patiently.

(VII) Crying and Colicky babies



Crying is best understood by the characteristics of timing, duration, frequency, intensity, and modifiability of the cry. Most infants cry little during the first 2 weeks of life, gradually increasing to 3 hours per day by 6 weeks and decreasing to 1 hour per day by 12 weeks.

Colic often is diagnosed using Wessel's rule of threes — crying for more than 3 hours per day, at least 3 days per week, for more than 3 weeks.

The limitations of this definition include the lack of specificity of the word "crying" and the necessity to wait 3 weeks to make a diagnosis in an infant who has excessive crying.

Colicky crying is often described as paroxysmal and may be characterized by facial grimacing, leg flexion, and passing flatus.

i) Etiology

- The etiology of colic is unknown
- It is considered an extreme of the normal phenomenon of infant crying. Girls and boys are equally affected.
- The clinician who evaluates a crying infant must differentiate serious disease from colic, which has no identifiable etiology.
- Attention to the feeding history can reveal feeding-related problems, e.g.
    - hunger,
    - air swallowing (worsened by crying),
    - gastroesophageal reflux, and
    - food intolerance.

ii) Diagnosis

The diagnosis of colic is **made only when the physical examination reveals no organic cause** for the infant's excessive crying. The examination includes;

- Vital signs,
- Weight, length, and head circumference,
- Signs of systemic illness
- Skin lesions, insect bites, corneal abrasions, hair tourniquets, skeletal infections

There may be undiagnosed neurologic conditions, such as perinatal brain injuries, as the cause of irritability and crying.

Investigations are reserved for infants in whom there are history or physical examination findings suggesting an organic cause for excessive crying.

iii) Differential Diagnosis

The differential diagnosis for colic is broad and includes any condition that can cause pain or discomfort in the infant.

- Cow's milk protein intolerance,
- maternal drug effects (including fluoxetine hydrochloride via breastfeeding), and

In most cases, the cause of crying in infants is unexplained.

Diagnosis of colic is indicated if
1. Began before 3 weeks' corrected age
2. Crying has a diurnal pattern consistent with colic (afternoon & evening)
3. Infant otherwise healthy and thriving

iv) Treatment

- Parental education and demystification. Learning about the temporal pattern of colic can be reassuring; the mean crying duration begins to decrease at 6 weeks of age and decreases by half by 12 weeks of age. Colic does not always resolve by 3 months of age (15 %).
- Techniques for calming infants include soothing vocalizations or singing, swaddling, slow rhythmic rocking, walking, white noise, and gentle vibration.

- Medications are of no benefit in reducing colic and should be avoided.
- It may be effective to switch to a non-cow's milk formula or mother can eliminate dairy products from her diet if the infant has signs of cow's milk protein colitis.

v) Prevention

- Education of parents about the normal pattern of infant crying.
- Increased contact and carrying of the infant in the weeks before the onset of colic may decrease the duration of crying episodes.
- Soothing strategies may be more effective if the infant has experienced them before the onset of excessive crying.

(VIII) Temper Tantrums

A temper tantrum is an out-of-control and violent or frustrated behavior seen when the young child experiences frustration, anger, or is unable to cope with a situation.

Temper tantrum behaviors
Screaming
Stomping
Hitting
Head banging
Falling down
Breath-holding
Vomiting
Biting.

Temper tantrums can be considered normal behavior in 1- to 3-year-old children, when the temper tantrum period is of short duration and the tantrums are not manipulative in nature.

i) Etiology

Temper tantrums are believed to be a normal human developmental stage. Child temperament may be a determinant of tantrum behavior.

ii) Epidemiology

This behavior is common in children 18 months to 4 years of age.

Tantrums occur equally in boys and girls during the preschool period. These behaviors appears to peak late in the third year of life.

iii) Clinical Features

- Temper tantrums are common in 2- and 3-year-old children. They may occur once a week or more, lasting is 2 to 5 minutes, and duration increases with age.
- The coexistence of other behavioral problems, e.g. sleep problems, learning problems, and social problems, suggests the possibility of a more serious mental health disorder.
- Dysmorphic features may reveal a genetic syndrome.
- Behavioral observations reveal a child's ability to follow instructions, play with age-appropriate toys, and interact with parents and the clinician.
- Laboratory studies screening for lead exposure are important.

- Children who behave well all day at day care and exhibit temper tantrums at home in the evening may be signaling fatigue or need for parental attention.
- In some cases, parents inadvertently reinforce tantrum behavior by complying with the child's demands. The child's behavior can be seen as manipulative or simply as learned behavior from a prior successful experience.

iv) Differential Diagnosis

- Most children who have temper tantrums have no underlying medical problem.
- Hearing loss and language delay may be associated with temper tantrums.
- Children with brain injury and other brain disorders are at increased risk for prolonged temper tantrum behavior (increased duration of episodes and expanded normal tantrum age).
- Congenital adrenal hyperplasia and precocious puberty, also may present with severe and persistent tantrums.

v) Treatment

- Intervention begins with parental education about temper tantrums, stressing that tantrums are a normal developmental phase.
- Review of the child's daily routine to understand essential unmet needs and identify the underlying stress, which is the cornerstone of treatment.
- Distraction can short-circuit an impending tantrum.
- Recommended behavioral strategies include behavior modification with positive and negative reinforcement or extinction.
- During the first week of any behavioral intervention, tantrum behavior may increase. Parents must be warned that it will probably get worse before it gets better.

(IX) PICA

- It is an eating disorder typically defined as the persistent eating of non-nutritive substances for a period of atleast one month, at an age in which this behavior is considered developmentally inappropriate (e.g. >18-24 months).

Ingestions related to PICA
Clay
Dirt
Sand
Pebbles
Finger nails
Chalk

- Deficiencies in minerals (iron, calcium, zinc), vitamins (thiamine, niacin, Vitamin C and D), insufficient parent-child interactions, malnutrition are all associated with pica.
- Presents with signs and symptoms of toxic ingestions (e.g. lead), their complications, or infections.
- A multidisciplinary approach (Psychologists, social workers, and physicians) and focus on associated nutritional deficiencies is also part of management.

(X) Attention-Deficit/Hyperactivity Disorder

Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder defined by symptoms of inattention, hyperactivity, and impulsivity.

Clinical guidelines emphasize the use of the Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition, criteria to diagnose ADHD.

<table>
<tr><th colspan="3">DSM-V Guidelines for diagnosing ADHD</th></tr>
<tr><th colspan="2">For Age ≤ 16 years</th><th>For Age ≥ 17 years</th></tr>
<tr><td>≥ 6 inattention symptoms
or
≥ 6 hyperactivity-impulsivity symptoms</td><td>≥ 6 months in
≥ 2 environments.</td><td>≥ 5 inattention symptoms
or
≥ 5 hyperactivity-impulsivity symptoms</td></tr>
<tr><td colspan="3">In addition, several symptoms must have been present prior to 12 years of age; evidence of significant impairment in social, academic, or work settings must occur; and other mental disorders must be excluded.</td></tr>
</table>

- Symptoms of inattention include: failing to pay close attention to details, appearing to not listen when spoken to directly, becoming easily distracted etc.
- Symptoms of hyperactivity include: being restless, talking excessively, running or climbing excessively inappropriately.
- Symptoms of impulsivity include: blurting out answers before a question has been completed, frequent interruptions, difficulty awaiting turn etc.

i) Etiology

- ADHD is multifactorial in origin, with genetic, neural, and environmental contributions. Dopaminergic and noradrenergic neurotransmitter genes are believed to play a role.
- Neuroimaging studies (functional magnetic resonance imaging and positron emission tomography, commonly recognized as fMRI and PET, respectively) may show structural and functional differences in frontal lobes, inferior parietal cortex, basal ganglia, corpus callus, and cerebellar vermis.
- Prenatal exposure to substances (e.g., nicotine, alcohol) and damage to the CNS from trauma or infection increase the risk of ADHD.

ii) Epidemiology

- Boys have predominant hyperactive/impulse type.
- Girls are more likely to present with inattentive symptoms.
- Symptoms of ADHD, particularly impulsivity and inattention, persist into adolescence and adulthood in 60% to 80% of patients.

iii) Clinical Features

- ADHD is diagnosed clinically by history.
- A physical examination is essential to provide an alternative explanation for the child's behaviors including medical or developmental problems that may underlie or coexist (psychiatric conditions in 60%).
- Consider thyroid function studies, blood lead levels, genetic studies, and brain imaging studies if indicated by medical history, environmental history, or physical examination to rule out differentials.

- Children with ADHD can typically focus without hyperactivity in environments with low stimulation and little distraction (e.g., clinician's office).

iv) Investigations

- Other medical conditions should be invetigated, e.g. hyperthyroidism, lead intoxication, and sensory deficits, should be considered.
- Liver function tests before start of therapy, as the medications used are metabolized by the liver.

v) Treatment

- Management begins with parental education about ADHD as a chronic condition.
- Foods containing colors and preservatives are sometimes incriminated in causing ADHD and excluded from diet.
- Children with ADHD respond to behavioral management, including structure, routine, and consistency in adult responses to their behaviors.
- Stimulant medications are the first-line agents for treatment of ADHD due to extensive evidence of effectiveness and safety.
- Nonstimulant medications may be helpful in situations, e.g.
    - Nonresponse to stimulant medication,
    - Family preference,
    - Concerns about medication abuse, and
    - Coexisting tic or sleep problems

Table. Medications for Attention-Deficit/Hyperactivity Disorder

Medications			**Side effects**
Stimulants (first-line)	Mixed amphetamine salts Methylphenidate Dexmethylphenidate Lisdexamfetamine		Apetite suppression, Sleep disturbance, ⇧-risk of sudden cardiac death
Non-stimulants	Norepinephrine-Reuptake Inhibitor	Atomoxetine	GI symptoms
	Alpha Agonists	Clonidine	Sedation
		Guanfacine	

(XI) Prevention

- Promoting calm environments and opportunities for age-appropriate activities that require increasing levels of focus may be helpful.
- Limiting TV and rapid-response video games that reinforce short attention span.
- Secondary disabilities can be prevented appropriate behavioral and pharmaceutical interventions.

CHAPTER 7 ELIMINATION DISORDERS

(I) Normal Development

Toilet training usually begins after the second birthday and is achieved at about 3 years of age.

(II) Enuresis

Enuresis is urinary incontinence in a child who is adequately mature to have achieved continence. Daytime and nighttime dryness is expected by approximate 4 and 6 years of age, respectively (according to U.S. standards).

- Primary incontinence: a child who has never achieved dryness.
- Secondary incontinence: a child who has been dry for at least 6 months).

i) Etiology

- Lack of a nocturnal vasopressin peak
- Involuntary contractions of the detrusor muscle
- Reduced bladder capacity (dilated distal colon due to chronic constipation impinges on the bladder).

Enuresis is often associated with a positive family history (primary form) and high arousal threshold during sleep. Stressful life events can also trigger loss of bladder control.

ii) Epidemiology

- Boys are more likely to have nocturnal enuresis.
- Girls are more likely to have diurnal enuresis.

iii) Clinical Manifestations

Enuresis may be:

- Nocturnal (night-time, 85%) or
- Diurnal (daytime).

The physical examination includes special attention is paid to the abdominal, neurologic, and genital, rectal (constipation), and lumbosacral (dysraphism, tethered cord) examinations.

iv) Investigations

- Clean catch urine D/R and C/S to look for chronic urinary tract infection (UTI), renal disease, and diabetes mellitus.
- Renal sonogram and a voiding cystourethrogram for
    - Recurrent UTIs,
    - Severe voiding dysfunction or
    - Neurologic findings

v) Differential Diagnosis

Secondary diurnal and nocturnal enuresis are more likely to have an organic etiology:

- UTI
- Diabetes mellitus
- Diabetes insipidus,

vi) Treatment

- Treatment begins with treating any diagnosed underlying organic causes of enuresis. **Elimination of underlying chronic constipation is often curative.**
- The most commonly used treatment options are conditioning therapy and pharmacotherapy.
- Preservation of the child's self-esteem.
- The most widely used conditioning therapy for nocturnal enuresis is the enuresis alarm. Enuresis alarms have an initial success rate of 70% (after 3-5 months) with a relapse rate of 10%.
- Pharmacotherapy for nighttime enuresis includes desmopressin acetate (ADH analog) and rarely tricyclic antidepressants (Imipramine). It has high relapse rate on discontinuation.

vii) Complications

- Psychological effects on child's self esteem
- Cardiac arrhythmias may occur with use of Tricyclic antidepressants.

(III) Constipation

- Constipation is decreased frequency of bowel movements usually associated with a hard stool consistency.
- Soiling is the escape of stool into the underclothing often associated with fecal impaction. It is usually liquid stool that seeps around a hard faecal mass (*spurious diarrhoea*).
- Encopresis is the *voluntary or involuntary* passage of stool in socially unacceptable places, e.g. behind furniture after 4 years of age. ***Encopresis without constipation*** *is uncommon and may be a symptom of oppositional defiant disorder or other psychiatric illness.*
- Normally, bowel habits decline between birth and 4 years of age, starting with greater than four stools per day to about once a day.

i) Etiology

- Low-fiber diet
- Painful anal lesion/ chronic withholding of bowel movements
- Other anatomic, and systemic causes include:
    - Anal stenosis
    - Hirschsprung's disease
    - Hypothyroidism
- About 95% of children referred to a subspecialist for encopresis have no other underlying pathologic condition.

ii) Clinical Features

- Continuous or frequent soiling by liquid stools.
- Children younger than 3 years of age often present with painful defecation, impaction, and withholding.
- A detailed history and thorough examination may give clues to an underlying local causes, or gastrointestinal, endocrine, and neurologic disorders.
- A rectal examination helps in assessing sphincter tone, size of the rectal vault and firm stools.

iii) Investigations

- Abdominal x-ray is not required.
- Barium enema and rectal biopsy may be carried out on grounds of clinical findings.

iv) Treatment

Table. Clean out/disimpaction methods and maintaince for constipation

	Clean-Out Disimpaction		**Maintenance Medications**
Infants	Glycerin suppositories Enema		Oral Medications Lactulose Glycerin suppository
Children	***Rapid Cleanout*** Enema Mineral oil Normal saline Hypertonic phosphate Polyethylene glycol	***Slower Cleanout*** Oral high-dose mineral oil Magnesium citrate	Oral Medications Osmotics Mineral oil Lactulose Bisacodyl Glycerin suppository

- The treatment depends on the causative factors:
  - Dietary advice for increased fibre and a good fluid intake.
  - Withholding due pain of anal fissure can be relieved by local anaesthetic gel.
  - Treatment of hirschsprung disease is surgery
  - Child psychiatrist should be involved in the managing behavioral problems.
- Excessive fecal load or the stool impaction may be treated with clean-out disimpaction methods:
  - Enemas alone or combinations of enema, suppository, and oral laxatives.
  - Occasionally manual evacuation under general anaesthesia may be needed and rectal biopsies may be considered at the same time.
  - In a chronically distended rectum, bowel stimulants (e.g. senna) may improve contractility and should be used for short duration only.
- Once the bowel has been cleared, regular bowel habit should be maintained with regular toileting together with stimulant and softening laxatives.
  - Successful treatment requires 6 to 24 months.
  - Parental education and counselling

CHAPTER 8 PEDIATRIC SLEEP & DISORDERS

Sleep is a complex behavioral and physiologic process characterized by a reversible state of partial unresponsiveness and disengagement from the environment.

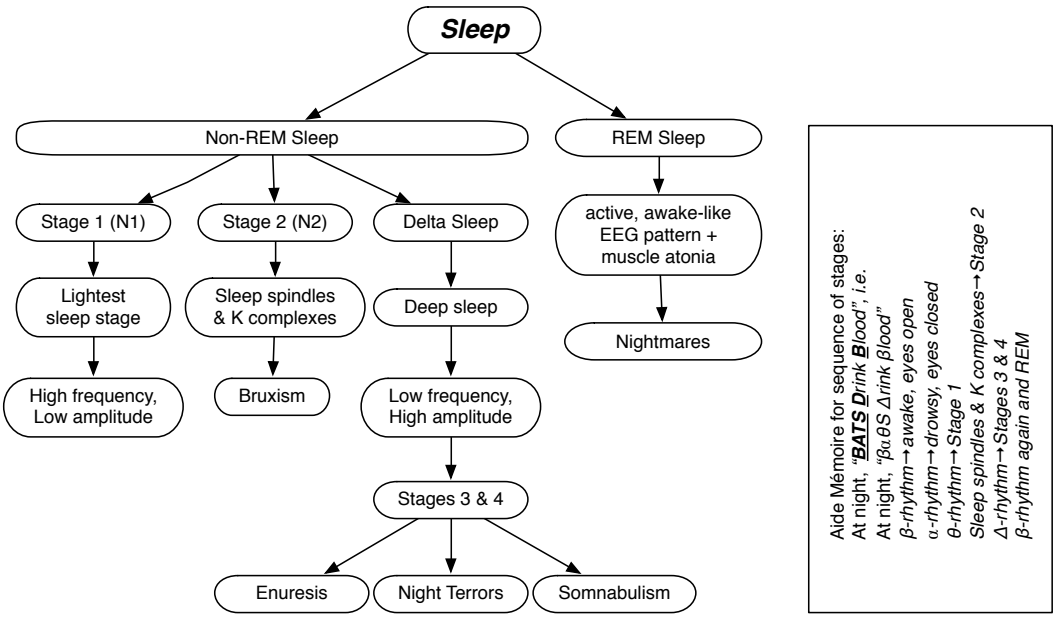


Figure. Sleep Stages

- Sleep architecture changes from fetal life through infancy and childhood. Sleep cycles last approximately 60 minutes in newborns and gradually lengthen to 90 minutes in children and adults. Neonates typically begin their sleep cycle in REM sleep, whereas older children and adults begin sleep in NREM sleep.
- REM sleep in neonates is termed active sleep, and frequent muscle twitches and facial grimaces are common. REM sleep comprises up to 50% of total sleep time in newborns and gradually decreases to 25% to 30% by adolescence. Slow-wave sleep is not seen before 3 to 6 months of age. Beginning from 6 to 12 months and continuing through adulthood, the amount of REM sleep shifts toward the last third of the night, while NREM sleep predominates during the first third of the night.

The timing and duration of sleep also change with age. Sleep patterns become more diurnal and total daily sleep time gradually decreases.

- Full-term infants sleep on average 16 to 18 hours per day in fragmented intervals throughout the day and night. One-year-old children sleep on average 10 to 11 hours per night and nap for 2 to 3 hours during the day.
- Naps decrease from two naps to one during the second year of life.

(I) Sleep Disorders

- Numerous sleep disorders exist, including behavioral insomnias, parasomnias, and circadian rhythm disorders.
- Sleep disorders due to organic pathology, e.g. obstructive sleep apnea (OSA) and other illnesses should also be considered.

Table. Childhood Sleep Disruption Disorders			
Type	**Symptoms**	**Cause**	**Treatment**
Behavioral Insomnias			
Behavioral insomnia of childhood *Sleep-onset association subtype*	Frequent or prolonged night wakenings requiring intervention	Child falls asleep in conditions different from those of the rest of the night	Put child to bed drowsy but awake; allow to fall asleep independently
Behavioral insomnia of childhood *Limit-setting subtype*	Bedtime resistance/refusal Excessive expression of "needs" by child	Parental anxiety, unwillingness/inability to enforce bedtime rules and limits	Modify parental behavior to improve limit-setting (provide rewards/positive reinforcement).
Parasomnias			
Sleepwalking Night terrors Confusional arousals	Awakening 1–3 h after falling asleep with characteristic behaviors	Stage N3 (deep) sleep instability Genetic predisposition	Reassurance Protective environment Scheduled awakenings
Sleep enuresis	Bed-wetting	Stage N3 instability. Metabolic disease (e.g., diabetes) Urinary tract infection Urinary anatomic anomaly	Reassurance, Fluid limitation, Pre-bed voiding, **Behavioral approaches (bell and pad)** Emotional support Medication (e.g. Desmopressin, imipramine)
Circadian rhythm disorder			
Irregular sleep-wake pattern	Variable waking and sleeping	No defined sleep schedule	Regularize schedule
Delayed sleep phase	Not sleepy at bedtime Sleep onset at a consistently late time Morning/daytime sleepiness	Shift in sleep-wake schedule with resetting of circadian rhythm	Enforce wake-up time, Move bedtime earlier or keep awake overnight to create drowsy state, Melatonin
Organic causes			
Obstructive sleep apnea (OSA)	Frequent snoring, gasps/snorts, episodes of apnea, labored breathing during sleep, daytime sleepiness, attention and/or learning problems	Adenotonsillar hypertrophy, obesity, allergic rhinitis, craniofacial abnormalities, Neuromuscular diseases	Polysomnography (for diagnosis) Adenotonsillectomy Weight loss Nasal steroids Continuous positive airway pressure (CPAP)
Illness	Painful crying out	Any chronically irritating disorder (e.g., otitis, asthma, or esophageal reflux)	Treat disease symptomatically
Neurodevelopmental and central nervous system disorders	Variable sleep disruptions	Variable; rule out seizures, OSA	Evaluate environment Sleep hygiene Sedatives as last resort

(II) Clinical Features

Some children present with daytime behavioral problems, including inattentiveness, hyperactivity, or irritability rather than overt sleepiness.

A complete physical examination is important to rule out:

- Medical causes of sleep disturbance, such as conditions that cause pain,
- Neurologic conditions that could be associated with seizure disorder, and other CNS disorders (ADHD),
- Signs of upper airway obstruction (e.g. enlarged tonsils or adenoids or other).

(III) Investigations

- A polysomnogram is used to detect Obstructive Sleep Apnea (OSA), excessive limb movements, and seizure disorder.
    - It consists of all-night observation and recording performed in a sleep laboratory.
    - Polysomnography is not indicated in children with primary insomnia (difficulty initiating or maintaining sleep), circadian rhythm disorders, uncomplicated parasomnias, or behaviorally based sleep problems.
- Children with frequent or prolonged parasomnias may need a sleep study to evaluate for possible coexisting sleep disorders or nocturnal seizures.

(IV) Differential Diagnosis

- Parasomnias are unusual or abnormal behaviors of nervous system that manifest during sleep. These include sleepwalking; sleep terrors, and confusional arousals. These occur during NREM sleep and are more likely during the first ⅓ of the night.
- Sleepwalking is common and benign but may be with agitation or dangerous behaviors. Sleep terrors consist of an abrupt awakening with a loud scream, agitation, and unresponsiveness to caregivers' attempts to console.

Table. Night terrors versus nightmares

Features	Night terrors	Nightmares
Sleep stage	Non-REM—Delta sleep	REM sleep
Physiologic arousal	Extreme	Elevated
Recall upon awakening	No	Yes
Associations	Positive family history Temporal lobe epilepsy	-

- Confusional arousals are similar to sleep terrors, tend to be less dramatic but last longer.
- Circadian rhythm disorders consist of an exaggerated delayed sleep phase, leading to the inability to arouse in the mornings and failure to meet sleep requirements. These are most common during adolescence. Sleep deprivation leads to problems with cognition and emotional regulation.
- Obstructive sleep apnea in childhood is often not easy to diagnose. OSA is commonly caused by tonsillar or adenoidal hypertrophy. Obesity is a risk-factor.
    - History of snoring; some children may have
    - Excessive daytime sleepiness.

- Poor growth (toddlers)
- Cognitive difficulties.
- Hyperactivity is more common in such children

- Primary sleep disorders must be differentiated from sleep disorders associated with psychiatric and medical disorders.

(V) Treatment and prevention

Table. Bedtime practices and prevention of pediatric behavioral sleep disorders
Consistent and appropriate bedtime and wake-up time
Consistent bedtime routine (~30 min) to cue sleep
Consistent ambient noise, light, temperature in bedroom
Adequate food, hydration, socialization, and physical activity during the day
No television or other electronics in bedroom
Avoidance of naps (unless developmentally appropriate)
Caffeine avoidance Child feels safe and protected
Child allowed to develop self-soothing strategies
Parents are comfortable setting limits/boundaries

- Starts with parental education. Some infants may not sleep through the night before 6-18 months of age. Infrequent or nonintrusive parasomnias do not need treatment beyond education and reassurance.
- Behavioral interventions:
  - Infants should be put in bed drowsy, but still awake, after they have had a diaper change, food, and comfort.
  - Systematic ignoring consists of not responding to a child's demands for parental attention at bedtime.
  - Unmodified extinction ("cry it out"): putting the child to bed and then ignoring the child's demands until the next morning.
  - Graduated extinction: waiting progressively longer periods of time before briefly checking on the child.
  - Reinforcing feelings of safety are best for children with night terrors.
  - Circadian rhythm disorders are treated by ensuring sleep hygiene practices and gradual resetting of the biologic clock with bedtime fading (gradually advancing the bedtime forward over the course of several weeks).
- Pharmacology is rarely indicated for insomnias.
  - Melatonin has sleep-inducing properties useful in treating **delayed sleep phase syndrome** .
  - The centrally acting α_2-agonist clonidine can be used in refractory sleep difficulties in children.

(VI) Complications

- Impairment of cognitive functions and emotional regulation.
- Acute illnesses
- Psychiatric disorders

CHAPTER 9 DIET OF A NORMAL INFANT

(I) Principles of feeding of an infant

1. Feed according to expected weight
2. Give 110 kcal/kg/day
3. Give 5 oz/kg milk feeding per day
4. Water requirement is 150 ml/kg/day
5. Milk should not be diluted after 3 months of age
6. No sugar should be added to bottle feed if baby is also breast fed
7. Weaning should be started at 4-6 months of age

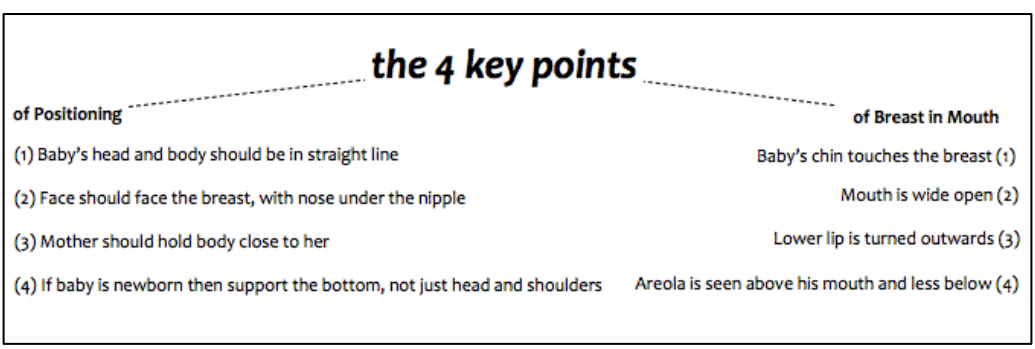
(II) Sources of caloric supply

Biomolecule	**Caloric supply**
Carbohydrate	50-55%
Fat	30-35%
Protein	10-15%

(III) Breastfeeding

Human milk and breastfeeding are the ideal and normative standards for infant feeding and nutrition.

WHO recommends exclusive breastfeeding in the first 6 months of life, with continued intake for the first year, and as long as desired thereafter.

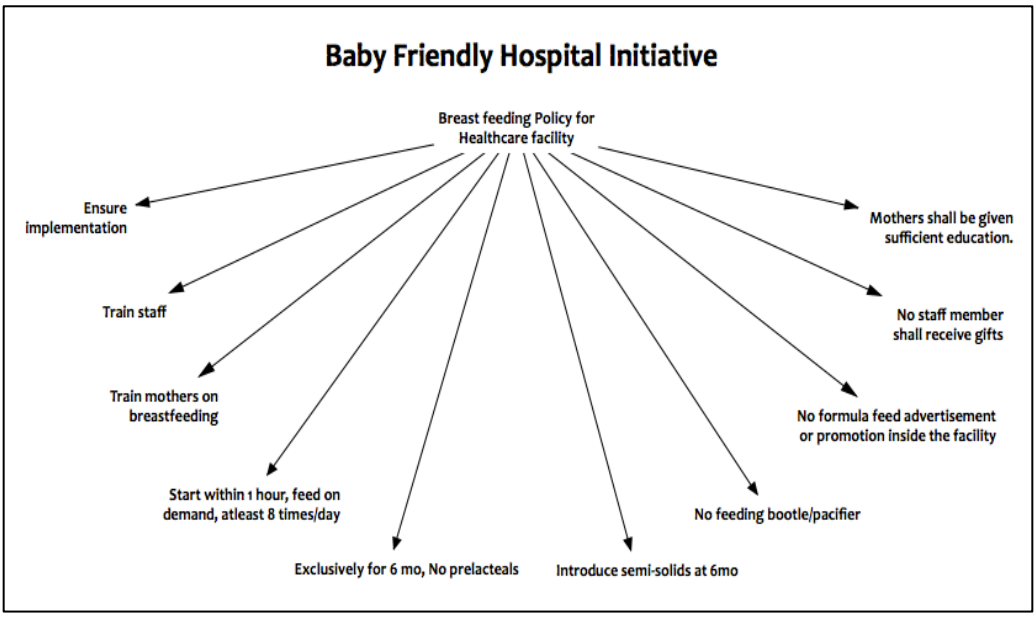


i) Physiology

When baby suckles on the breast, oxytocin and prolactin from pituitary gland are secreted. More prolactin is produced at night, so breastfeeding at night helps to keep up the milk supply. Oxytocin, involved in milk let-down reflex, is stimulated by sight and sound of baby, and inhibited by maternal anxiety, pain, embarrassment or lack of confidence.

There is greater emphasis to improve and standardize hospital practices with "Baby Friendly" programs for breastfeeding support.

ii) 'Baby Friendly Hospitals' Initiative



Breast milk is the ideal food for babies. The health care facility should do the following to protect, promote and support breastfeeding:

1. All health facility sstaff incluing doctors, health technicians, lady health visitors, vaccinators, and community health workers shall work together to ensure the implementation of the breastfeeding policy.
2. All relevant health care staff shall be trained in the skills necessary to implement this policy.
3. Health facility staff shall ensure that all expectant motherts, at clinic visits or during outreach activities, receive education on the benefits and management of breast feeding, the dangers of bottle feeding, and the dietary needs during pregnancy and lactation, prenatal exams shall include breast examination.
4. At delivery, newborn infants, including premature infants, shall be put on the breast within one hour of delivery. Babies should be fed on demand, every 2-3 hours for a minimum of eight feedings within 24 hours.
5. Exclusive breast-feeding shall be promoted from birth to 4-6 months. No water, ghutti, fresh animal milk, infant formula or other liquid is to be given to an exclusively breast fed inant. Trained health care staff shall help mothers having breastfeeding problems to continue to breastfeed.
6. Staff shall promote the introduction of semi-solid foods at 4-6 months with continued breastfeeding upto 2 years.
7. No feeding bottles and pacifiers shall be allowed in the health facility.
8. No promotional materials about formula, feeding bottles and pacifiers, such as posters, free samples or gift items shall be allowed in the facility nor shall they be given to the mother.
9. No health care staff shall receive gifts, free samples, donations, free training, etc. from formula manufacturers.
10. Mothers shall be given sufficient education in group classes, individual counseling and/or home visits so that they can adopt optimum breast-feeding practices.

iii) Advantages of breast feeding

There are beneficial effects of breastfeeding on long-term neurodevelopment (IQ) in preterm infants.

Mothers who breastfeed experience both short- and long-term health benefits.

- Long term advantages (with cumulative lactation of all pregnancies > 12-23 months):
    - Reduction of hypertension, hyperlipidemia, cardiovascular disease, and diabetes in the mother.
    - Reduced risk of ovarian and breast cancer.

The American Academy of Pediatrics recommends vitamin D supplementation (400 IU/day starting soon after birth), and, when needed, fluoride after 6 months for breastfed infants.

Advantages of Breast feeding

Exactly the nutrients that baby needs

Easy digestion and efficiently used

Protects against infections and allergies

Costs less

Helps mom and baby to bond

Helps baby's development

Can help delay a new pregnancy

Protects the mother's health

Helps uterus return to previous size,
reduce bleeding, & prevent anemia

Breastfeeding also reduces the risk of ovarian
cancer and possibly breast cancer in mother

High carbohydrate content, essential amino acids (cystine & taurine)
and fatty acids (linoleic acid) are important for infant's brain growth

Disadvantages of Bottle feeding

Bottle feeding can can diarrhea

Cleaning and sterilizing bottles is difficult

Animal milk can become easily contaminated

Bottle feeding consumes more time, fuel and money

Air swallowing is more common with bottle feeding

Composition of animal milk is not suited for babies

Cow's milk or formula may be over-diluted and therefore causes malnutrition

Bottle feeding may cause nipple confusion

Supplementation feeding will decrease breast-milk supply

Supplemental feeding of water is unnecessary and dangerous

iv) Common Breastfeeding Problems

Breast tenderness, engorgement, and cracked nipples are the most common problems encountered by breastfeeding mothers.

a) Insufficient milk syndrome

- A cyring baby, or restless baby during feed, breasts feel empty, mother unsure of her ability to feed or not confident about her milk supply constitutes the symptoms of this disorder.
- It occurs mostly due to anxiety, exhaustion, psychosocial factors, delayed initiation, infrequent feeding, and mother's lack of confidence about her milk supply.
    - Reassurance and discuss with the mother the indicators of sufficient milk intake, proper positioning, optimal breast feeding practices, increase fluid and dietary intake:
        - A well-hydrated infant voids six to eight times a day. Each voiding should soak, not merely moisten, a diaper, and urine should be colorless.

Indicators of sufficient milk intake
Urination ≥ 6 times/day
Weight gain ½ - 1 kg/month
Satisfied baby after feed

        - By 5 to 7 days, loose yellow stools should be passed at least four times/day.
        - Rate of weight gain provides the most objective indicator of adequate milk intake. Total weight loss after birth should not exceed 7%, and birth weight should be regained by 10 days.
    - If infant is temporarily separated from mother, it is important for mothers to regularly express breast-milk to sustain lactation.

b) Nipple confusion

If bottle-feeding is practiced, *child gets distressed when put to the breast*. Discontinuation of use of pacifiers and bottle-feeding is recommended.

c) Sore and Cracked nipples

Nipple tenderness requires attention to proper latch-on and positioning of the infant. Causes include:

- Incorrect positioning at the breast
- Use of tight clothing or excessive use of antiseptics to clean breast.
- Candidal/fungal infection of nipples

Management include:

- Correction of positioning decreases pain, avoid use of soaps and breast creams.
- Supportive measures include nursing for shorter periods, beginning feedings on the less sore side, apply a drop of breast milk to affected part after each feed & air dry, and applying lanolin cream after each nursing session.
- Temporary pumping, which is well tolerated, may be needed.
- Treat suspected fungal infection with:
    - Either gentian violet 0.5% to mother's nipples for 5 days and 0.25% gentian

violet to baby's mouth daily for 5 days or until 3 days after the lesions have healed,

- Or, apply Nystatin cream 100,000 IU/g for 7 days after the lesion has healed. Apply 1 ml nystatin suspension 100,00 IU to the child's mouth 4 times/day by dropper after breastfeeds for 7 days, or as long as the mother is treated.

d) Breast engorgement

A painful, edematous, tight and shiny breast, which may turn red. The mother may have fever.

- Delay in initiation of breast feeding
- Poor attachment to the breast
- Infrequent breast feeding
- Restriction of length of feed and incomplete emptying.

Engorgement, **one of the most common causes of lactation failure**, should receive prompt attention because milk supply can decrease quickly if the breasts are not adequately emptied. Applying warm or cold compresses to the breasts before nursing and hand expression or pumping of some milk can provide relief to the mother and make the areola easier to grasp by the infant.

If infant is temporarily separated from mother, it is important for mother to regularly express breast-milk to prevent this complication.

e) Mastitis/Abscess

If a lactating woman **reports fever, chills, and malaise, mastitis should be considered**.

- It occurs due to obstruction in lactiferous duct(s). Clinically, breast is lump and tender, with or without fever.
- Breastfeeding usually should not be stopped because the maternal mastitis commonly has no adverse effects on the breastfed infant. Treatment includes frequent and complete emptying of the breast and antibiotics.
- Untreated mastitis may progress to a breast abscess in which case incision and drainage, antibiotics, and regular emptying of the breast may be required.

f) Breast-feeding jaundice

Poor feeding or delay in initiation of breast feeding can lead to this.

Feeding frequency during the first 3 days of life of breastfed infants is inversely related to the level of bilirubin; frequent feedings stimulate meconium passage and excretion of bilirubin in the stool. Infants who have insufficient milk intake and poor weight gain in the first week of life may have an increase in unconjugated bilirubin secondary to an exaggerated enterohepatic circulation of bilirubin. This is known as breastfeeding jaundice.

Management is centered on improving maternal milk production (dietary measures) and breastfeeding more frequently without supplementary fluids. Water supplements are of no value here.

g) Breast-milk jaundice

It is a diagnosis of exclusion. Occurs by 5-10 days of age, may persist for upto a month. Hemolysis, infection, biliary atresia, and metabolic diseases should be ruled out. It is due to a substance in breast milk, that enhances intestinal absorption of bilirubin, in which case, all children of the mother develop this late onset form of jaundice. Baby is otherwise thriving and healthy.

v) Contraindications to breast-feeding

- Mother can breast feed after therapy is initiated in cases of active tuberculosis, syphilis, or varicella.
- *Women with active tuberculosis can breast feed their infants if the latter are given isoniazid (INH) 10mg/kg/day for 6 weeks.* The mother is treated with anti-TB drugs simultaneously for 6-9 months. At the end of 6 weeks, the infant receives BCG vaccine and is closely monitored. In countries where INH-resistant BCG vaccine is available, infants can be vaccinated at birth.
- If a woman has herpetic lesions on her breast, nursing and contact with the infant on that breast should be avoided. Women with genital herpes can breastfeed, however, hand-washing hygiene should be stressed.
- Vaccination at birth with recombinant HBV vaccine prevents disease (~highly effective) in neonates born to women who are Hepatits B carriers, & breastfeeding is continued.

Medical contraindications for breastfeeding include:

- Certain pediatric metabolic disorders e.g. galactosemia,
- Infants with phenylketonuria.

Table. Maternal Contraindications and Recommendations for Breastfeeding

Maternal contraindications	Recommendations for mother
Maternal active tuberculosis	Can breastfeed if infant receives INH for 6 weeks, mother receives ATT for 6-9 months simultaneously.
Varicella	Should not breastfeed; expressed milk may be given.
H1N1 influenza	Should not breastfeed; expressed milk may be given.
Herpes simplex infection of the breast	Should not breastfeed; expressed milk may be given.
Human immunodeficiency virus (HIV)	In industrialized countries mothers are not recommended to breastfeed. In developing countries women are recommended to combine breastfeeding with antiretroviral therapy (ART) for 6 months.
Alcohol	Limit ingestion to less than 0.5 mg/kg alcohol body weights due to association with motor development.
Radiopharmaceutical agents	*Express milk before exposure to feed infant.* Radioactivity may be present in milk from 2 to 14 days. Express milk and discard during therapies.
Use of phencyclidine (PCP), cocaine, or amphetamines	Recommended to stop use of drugs as it can affect infant neurobehavioral development.
Chemotherapy & immunosuppressives	Substitute formula.

a) Maternal Drug Use

Few therapeutic drugs are absolutely contraindicated; these include radioactive compounds, antimetabolites, lithium, and certain antithyroid drugs. Maternal use of illicit or recreational drugs is a contraindication to breastfeeding.

b) Working mothers

Optionally, mothers can 3-month maternity leave after birth of baby or use expressed milk for feeding with a cup and spoon.

- Frozen breast milk can be stored for upto **3 months.**
- Refrigerated breast milk is good for upto **48 hours.**

(IV) Replacement Feeding

A wet-nurse is always preferable to formula feeding. The replacement feeding should be given with micronutrient supplementation (e.g. iron etc.), if prepared at home. Caloric density of formulas is 20 kcal/oz similar to that of human milk. Formula milk is prepared as: Sugar:Water:Milk::1:5:10.

Table. Ratio to dilute formula milk until infant is 6 months of age:1:5:10			
Sugar	**Water**	**Milk**	**Total**
4 g	20 ml	40 ml	60 ml
6 g	30 ml	60 ml	90 ml
8 g	40 ml	80 ml	120 ml
10 g	50 ml	100 ml	150 ml

Goat milk is deficient is folates, and should be supplemented.

Table. Formula feeding practices		
Age	**Amount**	**Frequency**
<1 month	60 ml	8 times/day
1-2 months	90 ml	7 times/day
2-4 months	120 ml	6 times/day

- Cow's milk–based formulas are the vast majority of commercial formulas.
- Soy-based and hypoallergenic formulas formulas, which sometimes have added iron, may be used for newborns who may be allergic to cow's milk.
- Specialized formulas are designed for premature, low birth weight babies. The carbohydrate is generally lactose.

Table. Composition of Breast Milk and Infant Formulas		
Component	**Breast Milk**	**Standard Formula**
Osmolality	253 mOsm/L	230 mOsm/L
Carbohydrate	7.2 per dL	6.9–7.2 per dL
Fat	4.0 per dL	3.6 per dL
Protein	1.1 per dL	↑
Sodium	8.0 mg/L	6.5–8.3 mg/L
Calcium	290 mg/L	↑
Phosphorus	140 mg/L	↑
Renal solute load	75 mOsm/L	↑
IgA, IgM and IgG	Present	-
Lactoferrin	Present	-
Lysozyme	Present	0
Free fatty acids	Present	Added to some formulas
Linoleic acid	Present	Added to some formulas

(V) Complementary Foods

Complementary feeding of semisolid foods is recommended by WHO by 6 months of age. By this age, an exclusively breastfed infant requires additional sources of several nutrients, including protein, iron, and zinc etc.

Signs suggesting readiness for complimentary feeding
1. At least 4 months of age 2. Hungry soon after, despite frequent feeding 3. Not gaining weight adequately

i) Food groups

A complimentary diet should include a share from these four major food groups:

Food group	Food	Functions	Key nutrients
Staple	Chapatti, rice	Energy, growth, protection	Protein, iron, calories
Protein	Legumes, eggs, milk-animal protein breast milk	Growth, protection	Protein, iron, folic acid, calories, calcium
Vitamins and minerals	Fruits, vegetables	Protection, growth	Vitamins A and C, iron, folic acid
Energy rich	Fats, oats, sugar	Energy	Calories

ii) Other recommendations

- It it helpful if single-grain cereals are used for weaning (rice, oatmeal, barley) for identifying food allergies and intolerance.
- An infant should never be put to sleep with a bottle or cup filled with milk, formula, or juice because this can result in ***Early Childhood Caries (ECC).***
- All foods with the potential to obstruct the young infant's main airway should be avoided in general until 4 years of age or older. **Because of the risk of infant botulism, honey should not be given before 1 year of age.**
- Diet should provide approx. 100-110 cal/kg for the expected weight for each age. It should also provide 1-1.5 g/kg of protein. As the child grows total caloric requirement increases but decreases per unit of weight, e.g. at 1 year of age, it is 110 cal/kg/day decreasing to 90 cal/kg/day at 4 years of age.
- From 1-2 years of age, a child requires 3 meals + 2 snacks daily. After 2 years, cow's milk should be given 2 times/day. 8 oz. (1 glass) at a time

(VI) Feeding during illness

As a general rule, during any illness, a child should receive two extra meals than are usually recommended for that age and vitamin A containing green leafy vegetables should be included in diet.

(VII) Diet as the infant grows

i) Milk

- The consumption of cow's milk is ideally not introduced until about 1 year of age when it is better tolerated.
- Where available internationally, Low-fat (2%) or whole milk is recommended until 2 years or age,

- Where available internationally, Fat-free or 1% milk is recommended after 2 years of age.
- Excessive milk intake (more than 24 oz/day) should be avoided in toddlers because larger intakes may reduce the intake of a good variety of nutritionally important solid foods and also result in iron deficiency anemia.

ii) Iron Intake

Iron deficiency is the most common nutritional deficiency. Toddlers age group is most at risk for iron deficiency anemia and provision of a balanced diet is important.

- Iron fortified cereal is good source for iron during weaning. Ground meat is a good source for an older infant.
- For preterm- or low birth weigh, oral iron supplemental drops daily can be started from 1 month of age till 12 months.

Up to 6 Months of Age

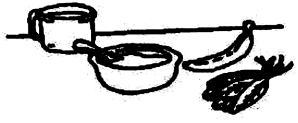
- Breast feed as often as the child wants, day and night, at least 8 times in 24 hours.
- Breast feed at least for 10 minutes on each breast every time
- Do not give other foods water.
- Do not use bottles or pacifiers

6 Months up to 12 Months

Breastfeed as often as the child wants.

Give adequate servings of:
Khichri*, Rice (Bhatt)* with seasonal vegetables (Carrot, Spinach, Potatoes etc.), or Minced Meat. Rice Kheer, Suji ka Halwa or Kheer*, Dalia*, Vermicelli's*, Choori*, Mashed Potato or vegetables*, Egg, Banana, Seasonal Fruit and any foods listed for 4 to 6 month child.
(upto 9 months food should be mashed)

- 3 times per day if breastfed;
- 5 times per day if not breastfed.
- Each serving should be equivalent to 1/2-3/4 or a cup.



12 Months up to 2 Years

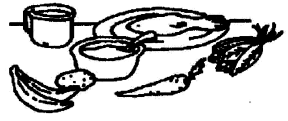
- Breastfeed as often as the child wants.
- Give adequate servings of:
  Roti, Parattha, Khichri or Rice, Curry, Minced Meat, Chicken, Egg, Seasonal Vegetables, Choori, Vermicelli's, and/or any foods listed for 6-12 months child
- Give food at least 3 times per day

AND

- Give also snacks 2 times per day between meals such as seasonal fruit (Banana, Apple, Mango, Orange etc.) Biscuit, Rusk, Chips, Pakora or Samosa, Lassi, Yoghurt, Bread with Egg, Halwa etc.

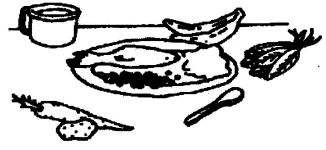
OR

Family foods 5 times per day.



2 Years and Older

- Give family foods at 3 meals each day. Also, twice daily, give nutritious food between meals, such as:
- Seasonal fruit (Banana, Apple, Mango, Orange etc.) Biscuit, Rusk, Chips, Pakora, Samosa, Lassi, Yoghurt, Bread with Eggs, Halwa etc.



Wash your hands before preparing the child's food and use clean cooking utensils.

** A good daily diet should be adequate in quantity and include an energy-rich food (for example, thick cereal with added oil / Ghee / Butter); meat, fish, eggs, or pulses; and fruits and vegetables.*

CHAPTER 10 PEDIATRIC UNDERNUTRITION

Pediatric undernutrition is usually the result of inadequate food supply, access, or utilization; poor access to health and sanitation; and/or inappropriate feeding.

The greatest risk of undernutrition is in utero through age 2.

The risk factors for malnutrition are:

Social	Medical
Mother - ill - working - incompetent	Low birth weight
	Twins
	Mixed feeds or bottle feeding
	Delayed feeding of solids
Paternal - ill - unemployed	Chronic/recurrent diarrhea
	Recurrent respiratory infections
	Measles, TB, whooping cough
Parental loss	Recurrent otitis media, pnemonia
> 2 children < 5 years age	Incomplete vaccinations
Inadequate child care for working mothers	Others (congenital anomalies e.g. cleft lip)
Drug addiction in family	
Previous infant/child death	

(I) Z-score

A Z-score indicates how many standard deviations away a value is from the mean.

Some classifications use Z-scores of anthropometric measurements to define various grades of malnutrition.

Table. Definitions of Malnutrition

CLASSIFICATION	DEFINITION	GRADING	
Gomez	Weight below % median WFA	Mild (grade 1)	75%–90% WFA
		Moderate (grade 2)	60%–74% WFA
		Severe (grade 3)	< 60% WFA
Wellcome (no edema)	Weight below % median WFA	60-80% expected	Underweight
		< 60% of expected	Kwashiorkor
Wellcome (edema)	Weight below % median WFA + edema	60-80% expected	Marasmus
		< 60% of expected	Marasmic Kwashi-orkor
Waterlow	z -scores (SD) below median WFH	Mild	80%–90% WFH
		Moderate	70%–80% WFH
		Severe	< 70% WFH
WHO (wasting)	z -scores (SD) below median WFH	Moderate	– 3 ≤ z-score <–2
		Severe	z -score <–3
WHO (stunting)	z -scores (SD) below median HFA	Moderate	– 3 ≤ z -score <–2
		Severe	z -score <–3

Acronyms: BMI, Body mass index; HFA, height for age; MUAC, mid-upper arm circumference; NCHS, National Center for Health Statistics USA; SD, standard deviation; WFA, weight for age; WFH, weight for height; WHO, World Health Organization.

Protein-calorie malnutrition (PCM) is a spectrum of conditions caused by varying levels of protein and calorie deficiencies.

Primary PEM is caused by social or economic factors that result in a lack of food.

Secondary PEM occurs in children with various conditions associated with combinations of;

- Increased caloric requirements (infection, trauma, cancer),
- Increased caloric loss (malabsorption),
- Reduced caloric intake (anorexia, cancer, oral intake restriction, social factors).

Protein and calorie malnutrition may be associated with other nutrient deficiencies, which may be evident on physical examination.

	Classification	
	Moderate malnutrition	**Severe malnutrition (type)**[b]
Symmetrical oedema	No	Yes (oedematous malnutrition)[c]
Weight-for-height	–3 ⩽ SD-score <–2[d] (70–79%)[e]	SD-score <–3 (<70%) (severe wasting)[f]
Height-for-age	–3 ⩽ SD-score <–2 (85–89%)	SD-score <–3 (<85%) (severe stunting)

[a] For further information about anthropometric indicators, see reference *1*.
[b] The diagnoses are not mutually exclusive.
[c] This includes kwashiorkor and marasmic kwashiorkor in older classi cations. However, to avoid confusion with the clinical syndrome of kwashiorkor, which includes other features, the term "oedematous malnutrition" is preferred.
[d] Below the median NCHS/WHO reference; the SD-score is de ned 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.

$$\text{SD-score} = \frac{(\text{observed value}) - (\text{median reference value})}{\text{standard deviation of reference population}}$$

[e] Percentage of the median NCHS/WHO reference (see footnote in Appendix 1).
[f] This corresponds to marasmus (without oedema) in the Wellcome clinical classi cation (*2, 3*), and to grade III malnutrition in the Gomez system (*4*). However, to avoid confusion, the term "severe wasting" is preferred.

Table. Physical Signs of Nutritional Deficiency Disorders

SYSTEM	SIGNS	DUE TO DEFICIENCY OF
GPE	Reduced weight for height	Calories
Skin and hair	Pallor	Anemias (iron, folate, B12)
	Edema	Protein, thiamine
	Dermatitis	Riboflavin, essential fatty acids, biotin
	Photosensitivity dermatitis	Niacin
	Acrodermatitis	Zinc
	Follicular hyperkeratosis (sandpaper-like)	Vitamin A
	Depigmented skin	Calories, protein
	Alopecia	Zinc, biotin, protein
	Depigmented pluckable hair	Protein > calories
Eye/vision	Adaptation to dark	Vitamins A, E, zinc
	Color discrimination	Vitamin A
	Bitot spots, xerophthalmia, keratomalacia	Vitamin A
	Conjunctival pallor	Nutritional anemias

	Fundal microaneurysms	Vitamin C
Face, mouth, neck	Moon facies	Kwashiorkor
	Old-man facies	Marasmus
	Angular stomatitis	Riboflavin, iron
	Cheilosis	Vitamins B6, niacin, riboflavin
	Bleeding gums	Vitamins C
	Atrophic papillae	Riboflavin, iron, niacin, folate, B12
	Smooth tongue	Iron
	Red tongue (glossitis)	Vit B6, B12, niacin, riboflavin, folate
	Parotid swelling	Protein
	Caries	Fluoride
	Goiter	Iodine
Cardiovascular	Heart failure	Thiamine, selenium
Genital	Hypogonadism	Zinc
Skeletal	Costochondral beading	Vitamins D, C
	Subperiosteal hemorrhage	Vitamin C, copper
	Cranial bossing	Vitamin D
	Epiphyseal enlargement	Vitamin D (rickets)
	Craniotabes	Vitamin D, calcium
	Tender bones	Vitamin C
	Transverse nail line	Protein
Neurologic	Neuropathy	Thiamine, vitamins E, B6, B12
	Ophthalmoplegia	Thiamine
	Tetany	Vitamin D, Calcium
	Ataxia	Vitamin B 12

i) Failure to Thrive

It describes a circumstance in which a child fails to gain weight appropriately or, in more severe cases, experiences failure in linear growth or head circumference.

Signs and symptoms of mild & moderate PCM
Growth curve starts to falter
Irritable
Disturbed sleep pattern
Decreased sleep pattern
Decreased appetite
Early hair changes like dry, brittle and sparse hair
Anemia
Mouth ulcers, cheliosis
Decreased tone in muscles; flabby arms and thighs
Rib cage prominent
Increased frequency of infections

ii) Marasmus

Marasmus results from the body's physiologic response to inadequate calories and nutrients.

- Marasmic children may be apathetic, weak or irritable when touched.

- Bradycardia and hypothermia signify severe and life-threatening malnutrition.
- Edema is absent. The skin is dry and thin, and the hair may be thin, sparse, and easily pulled out.
- Inadequate weaning practices and diarrhea are common associations in developing countries.
- Stunting (impaired linear growth) occurs due to a combination of malnutrition, especially micronutrients, and recurrent infections.

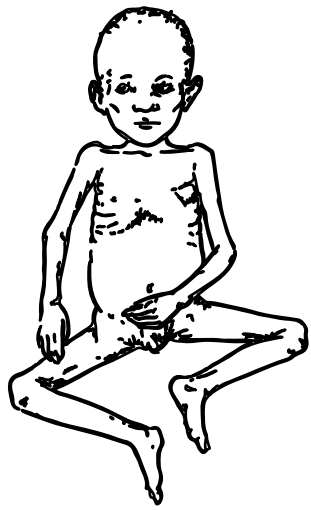
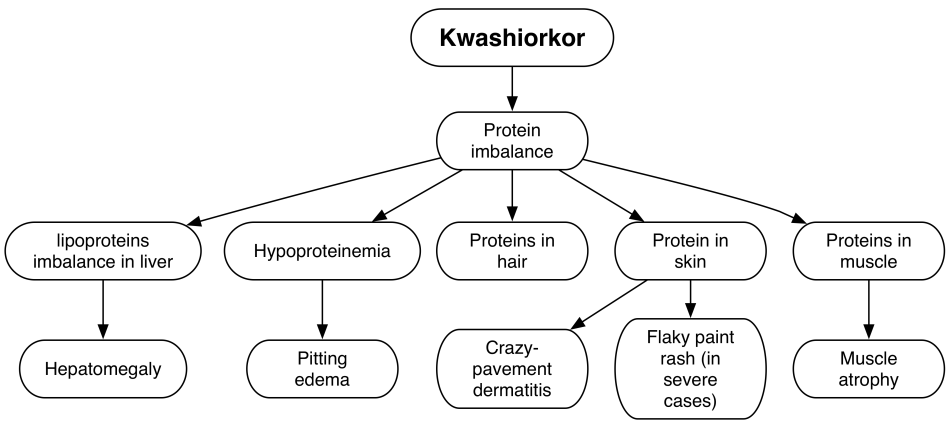


Figure. Child with marasmus

Marasmus
Appearance: lethargic or irritable
Loss of subcutaneous fat resulting in loose axillary and inguinal skin folds
Loss of buccal pad of fat
Large prominent eyes
Prominent rib cage

iii) Kwashiorkor



- Kwashiorkor results from inadequate protein intake in the presence of fair to good caloric intake.

- The hypoalbuminemic state results in pitting edema that ascends upwards with increasing severity.

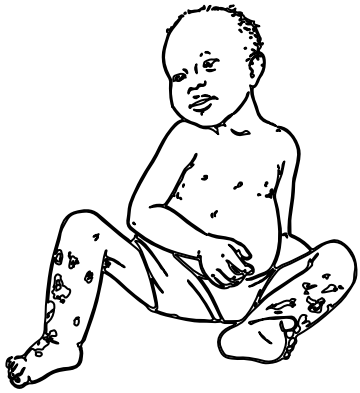


Figure. Edema in severe acute malnutrition

- Acute infection, and specific amino acid or micronutrient imbalances are likely to contribute to the etiology.
- *Apathy and disinterest in eating are typical of kwashiorkor.*
- Body weight is near normal for age due to edema; hence is a poor parameter of nutritional status in this case.
- Atrophy of muscle mass. But unlike marasmus, there is a relative maintenance of subcutaneous adipose tissue.
- The hair is sparse dull brown, red, or yellow-white.
- **Flag Sign**: Nutritional repletion restores hair color, leaving a band of hair with altered pigmentation followed by a band with normal pigmentation making hair look somewhat like flags.
- Skin changes: vary from hyperpigmented hyperkeratosis to an erythematous macular rash on the trunk and extremities (**crazy pavement dermatitis**).
- Enlarged parotid glands and facial edema result in moon facies.
- Abdomen is distended (*pot belly*), and hepatomegaly is common.
- **Flaky paint rash**: In the most severe form of kwashiorkor, a superficial desquamation occurs over pressure surfaces ("flaky paint" rash).

Kwashiorkor
Apathy
Edema
Hyperpigmentation
Wet, oozing skin
Hair changes: dry and coarse, depigmented, loss of curliness and pluckable
Enlarged liver due to fatty infiltration

iv) Mixed Marasmus-Kwashiorkor

These children often have concurrent **wasting and edema** in addition to **stunting**. These children exhibit features of dermatitis, neurologic abnormalities, and fatty liver.

(II) Investigations

Test	Result and significance
Tests that may be useful	
Blood glucose	Glucose concentration <54 mg/dl (3 mmol/l) is indicative of hypoglycaemia
Examination of blood smear by microscopy	Presence of malaria parasites is indicative of infection
Haemoglobin or packed-cell volume	Haemoglobin <40 g/l or packed-cell volume <12% is indicative of very severe anaemia
Examination and culture of urine specimen	Presence of bacteria on microscopy (or >10 leukocytes per high-power eld) is indicative of infection
Examination of faeces by microscopy	Presence of blood is indicative of dysentery Presence of *Giardia* cysts or trophozoites is indicative of infection
Chest X-ray	Pneumonia causes less shadowing of the lungs in malnourished children than in well-nourished children Vascular engorgement is indicative of heart failure Bones may show rickets or fractures of the ribs
Skin test for tuberculosis	Often negative in children with tuberculosis or those previously vaccinated with BCG vaccine
Tests that are of little or no value	
Serum proteins	Not useful in management, but may guide prognosis
Test for human immunode ciency virus (HIV)	Should not be done routinely; if done, should be accompanied by counselling of the child's parents and result should be con dential
Electrolytes	Rarely helpful and may lead to inappropriate therapy

(III) Treatment of Malnutrition

The basal metabolic rate and immediate nutrient needs decrease in cases of malnutrition. This improves when nutrients are provided.

Activity	Initial treatment:		Rehabilitation:	Follow-up:
	days 1–2	days 3–7	weeks 2–6	weeks 7–26
Treat or prevent: hypoglycaemia hypothermia dehydration	⟶			
Correct electrolyte imbalance	⟶	⟶	⟶	
Treat infection	⟶	⟶		
Correct micronutrient de ciencies	⟵ without iron	⟶	with iron ⟶	
Begin feeding	⟶	⟶		
Increase feeding to recover lost weight ("catch-up growth")		⟶	⟶	⟶
Stimulate emotional and sensorial development	⟶	⟶	⟶	⟶
Prepare for discharge		⟶	⟶	

i) Initial treatment

Life-threatening problems are identified and treated, specific deficiencies are corrected, metabolic abnormalities are reversed and feeding is begun. Sensory stimulation and emotional support is important.

- To treat or prevent hypoglycaemia and hypothermia;
- To treat or prevent dehydration and restore electrolyte balance;
- To treat incipient or developed septic shock, if present;
- To start to feed the child;
- To treat infection;
- To identify and treat any other problems, including vitamin deficiency, severe anaemia and heart failure.

a) Hypoglycemia

- Blood glucose <54mg/dl or <3mmol/l, is an **important cause of death during the first 2 days of treatment**. To prevent hypoglycemia, the child should be fed every 2 or 3 hours, day and night.
- Sweating and pallor do not usually occur in malnourished children with hypoglycaemia. Often, the only sign before death is drowsiness.
- If hypoglycemia is suspected, treatment is given immediately without confirmation.
    - If the patient is conscious/able to drink, give 50 ml of 10% glucose or sucrose, or give F-75 diet by mouth, which ever is available most quickly.
    - If the child is losing consciousness, or has convulsions, give 5ml/kg of body weight of sterile 10% glucose intravenously (IV), followed by 50ml of 10% glucose or sucrose by nasogastric (NG) tube. *If IV glucose cannot be given immediately, give the NG dose first.* When the child regains consciousness, immediately begin giving F-75 diet or glucose in water (60g/l). Continue frequent oral or NG tube feeding with F-75 diet to prevent a recurrence.
    - All malnourished children with suspected hypoglycaemia should also be treated with broad-spectrum antimicrobials for serious systemic infection.

b) Hypothermia

- If the rectal temperature is < 35.5°C (95.9°F) or underarm is < 35.0°C (95.0°F), the child should be warmed. Either use the "**kangaroo technique**" by placing the child on the mother's bare chest or abdomen (skin-to-skin) and covering both of them.
- Monitor rectal temperature every 30 minutes to prevent over-warming if child is placed under an incandescent lamp.

c) Dehydration

- Dehydration progresses from "some" (5-10% weight loss) to "severe" (>10% weight loss), whereas septic shock progresses from "incipient" to "developed", as blood flow to the vital organs decreases.
- *Mental state, mouth/tongue/tears and skin elasticity may be misleading in a child with malnutrition and should not be relied upon.*
- Children with PCM are deficient in potassium and have abnormally high sodium, the oral rehydration salts (ORS) solution should contain less sodium and more potassium than the standard WHO-recommended solution.

- By diluting one packet of the standard WHO-recommended ORS in 2 litres of water, instead of 1 litre, and adding 50g of sucrose (25g/l) and 40ml (20ml/l) of mineral mix solution, a **RE**hydration **SO**lution for **MAL**nourished children (**ReSoMal**) can be made. Magnesium, zinc and copper should also be given to correct deficiencies of these minerals. Between 70 and 100ml of ReSoMal/kg is usually enough to restore normal hydration. Give this amount over 12 hours, starting with 5ml/kg every 30 minutes for the first 2 hours orally or by NG tube, and then 5–10ml/kg per hour.

Table. Composition of mineral mix	
Substance	**Amount**
Potassium chloride	89.5 g
Tripotassium citrate	32.4 g
Magnesium chloride (MgCl2 · 6H2O)	30.5 g
Zinc acetate	3.3 g
Copper sulfate	0.56 g
Sodium selenate	10 mg
Potassium iodide	5 mg
Water to make	1000 ml

The body of the malnourished child may have compensated for micronutrient deficiencies with lower metabolic and growth rates, and **refeeding may unmask these deficiencies**.

Refeeding Syndrome
Fluid retention, Hypophosphatemia, Hypomagnesemia, Hypokalemia.

- Nutritional rehabilitation should be initiated and advanced slowly.
- Oral rehydration is recommended over intravenous fluid to avoid excessive fluid and solute load and resultant heart or renal failure.

d) Dietary treatment

Begin feeding these children with a diet that is high in carbohydrate.

- F-75 and F-100, are used for severely malnourished children. F-75 (75 kcal/100ml) is used during the initial phase of treatment, while F-100 (100kcal/100ml) is used during the rehabilitation phase, after the appetite has returned. A mineral mix (containing potassium, magnesium and other essential minerals) must be added to diet.
- Alternatively, locally prepared high-density diet-1 (HDD-1) can be used which provide 150 kcal/100ml.

e) Antibiotics

- Children with no apparent signs of infection or complications should be given cotrimoxazole orally twice daily for 5 days.
- Children with complications (septic shock, hypoglycaemia, hypothermia, skin infections, respiratory or urinary tract infections, or who appear lethargic or sickly) should be given:
    - Ampicillin, IM or IV for 2 days, followed by amoxicillin orally for 5 days, and
    - Gentamicin, IM or IV once daily for 7 days.

f) Treating complications

- There is high risk of developing blindness due to vitamin A deficiency. Hence, a large dose of vitamin A should be given routinely to all malnourished children on day 1 (unless a dose has been given during the past month).
- If there are any clinical signs of vitamin A deficiency, a large dose should be given on the first 2 days, followed by a third dose at least 2 weeks later as:

Age	Dose on days 1, 2, 14
< 6 months	50,000 IU
6 – 12 months	100,000 IU
> 12 months	200,000 IU

- If the haemoglobin < 40 g/l or the PCV is < 12%, the child has **very severe anaemia**, which can cause heart failure. Children with very severe anaemia need a blood transfusion. Give 10ml/kg of packed red cells or whole blood slowly over 3 hours.
- Heart failure is usually a complication of over hydration or very severe anemia. Stop all oral and IV fluids; give furosemide IV, and digitalis should be avoided until the diagnosis is unequivocal.

ii) Rehabilitation

- In this phase:
    - Intensive feeding is given to recover most of the lost weight,
    - Emotional and physical stimulation are increased,
    - Mother is trained to continue care at home, and
    - Preparations are made for discharge of the child.
- When nutritional rehabilitation is initiated, calories can be safely started at 20% above the child's recent intake. If no estimate of the caloric intake is available, 50% to 75% of the normal energy requirement is safe.
- When nutritional rehabilitation has begun, caloric intake can be increased 10% to 20% per day, monitoring for electrolyte imbalances, poor cardiac function, edema, or feeding intolerance. If any of these occurs, further caloric increases are not made until the child's status stabilizes.
- Caloric intake is increased until appropriate regrowth or catch-up growth is initiated. Catch-up growth refers to gaining weight at greater than 50th percentile for age and may require 150% or more of the recommended calories for an age-matched, well-nourished child.
- **Rule of thumb** for infants and children up to 3 years of age is to provide 100 to 120 kcal/kg (based on ideal weight for height).
- Protein needs also are increased as anabolism begins and are provided in proportion to the caloric intake.
- Vitamin and mineral intake in excess of the daily-recommended intake is provided to account for the increased requirements.
- Iron supplements are not recommended during the acute rehabilitation phase. *Additional iron may interfere with intestinal absorption of other nutritional molecules and pose an oxidative stress;*
- In most cases, cow's milk–based formulas are tolerated and provide an appropriate mix of nutrients. If feeding intolerance occurs, use lactose-free or supplemental formulas.

iii) Follow-up

Follow up to prevent relapse and assure the continued physical, mental and emotional development of child.

(IV) Complications of Malnutrition

Malnourished children are more susceptible to:

- Infection, especially sepsis, pneumonia, and gastroenteritis.
- Hypoglycemia (may also be a sign of sepsis)
- Hypothermia
- Bradycardia and poor cardiac output, which is exacerbated by acute fluid or solute loads.
- Micronutrient deficiencies also can complicate malnutrition. Vitamin A and zinc deficiencies are common in the developing world and are an important cause of altered immune response and increased morbidity and mortality.
- Depending on the age at onset and the duration of the malnutrition, malnourished children may have permanent growth stunting (from malnutrition in utero, infancy, or adolescence) and delayed development (from malnutrition in infancy or adolescence).
- Environmental (social) deprivation may interact with the effects of the malnutrition to impair further development and cognitive function.

CHAPTER 11 VITAMIN & MINERAL DEFICIENCIES

Micronutrients include vitamins and trace elements.

Table. Etiology of Vitamin and Nutrient Deficiency States	
Etiology	**Deficiency**
Diet	
Vegans (strict)	Vitamins B12, D, iron
Breastfed infant	Vitamins K, D
Cow's milk–fed infant	Iron
Parenteral alimentation	Essential fatty acids, trace elements
Alcoholism	Calories, vitamin B1, B6, folate
Acrodermatitis enteropathica	Zinc
Medical problems	
Malabsorption syndromes	Vitamins A, D, E, K, zinc, essential fatty acids
Cholestasis	
Medications	
Sulfonamides	Folate
Phenytoin, phenobarbital	Vitamins D, K, folate
Antibiotics	Vitamin K
Isoniazid	Vitamin B 6
Antacids	Iron, phosphate, calcium
Penicillamine	Vitamin B 6
Intrinsic factor deficiency	Vitamin B 12

(I) Water-Soluble Vitamins

Water-soluble vitamins are not stored in the body except for vitamin B12; intake therefore alters tissue levels.

i) B Vitamins

The B vitamins thiamine, riboflavin, and niacin are routinely added to enriched grain products; isolated deficiencies in normal hosts are rare.

a) Niacin

About 70% of the total niacin equivalents in human milk are derived from tryptophan conversion. Niacin is stable in foods and withstands heating and prolonged storage.

Pellagra, or niacin deficiency disease, is characterized classically with the 4 D's in addition to photosensitivity: **D**ermatitis, **D**iarrhea and **D**ementia, and **D**eath.

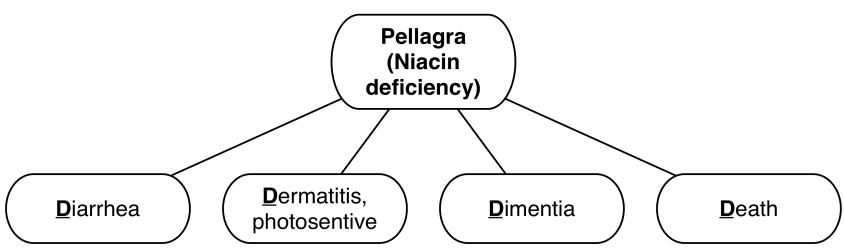


Table. Water Soluble Vitamins				
Vitamin	**Purpose**	**Deficiency**	**Comments**	**Source**
Thiamine (B1)	Coenzyme in decarboxylation (e.g., pyruvate → acetyl-CoA)	Beriberi	Inborn errors of lactate metabolism; boiling milk destroys B 1	Liver, meat, milk, cereals, nuts, legumes
Riboflavin (B2)	Coenzyme as FAD in oxidation-reduction reactions	Anorexia, mucositis, anemia, cheilosis, nasolabial seborrhea	Photosensitizer	Milk, cheese, liver, meat, eggs, whole grains, green leafy vegetables
Niacin (B3)	Coenzyme as NAD in oxidation-reduction reactions	Pellagra: photosensitivity, dermatitis, dementia, diarrhea, death	Tryptophan is a precursor	Meat, fish, liver, whole grains, green leafy vegetables
Pyridoxine (B6)	Cofactor in amino acid metabolism	Seizures, hyperacusis, microcytic anemia, nasolabial seborrhea, neuropathy	Deficiency secondary to drugs: Isoniazid, Penicillamine	Meat, liver, whole grains, peanuts, soybeans
Biotin	Cofactor in carboxylase reactions of amino acids	Alopecia, dermatitis, hypotonia, death	Bowel resection, biotinidase deficiency, ingestion of raw eggs	Yeast, meats; made by intestinal flora
B12	Coenzyme for 5-methyl tetrahydrofolate formation; DNA synthesis	Megaloblastic anemia, peripheral neuropathy, posterior lateral spinal column disease, vitiligo	Vegans; fish tapeworm; short gut syndrome; transcobalamin or intrinsic factor deficiencies	Meat, fish, cheese, eggs
Folate	DNA synthesis	Megaloblastic anemia; neural tube defects	**Goat milk is deficient**; drug antagonists; heat inactivates	Liver, greens, vegetables, cereals, cheese
Ascorbic acid (C)	Reducing agent; collagen metabolism	Scurvy: irritability, purpura, bleeding gums, periosteal hemorrhage, aching bones	May improve tyrosine metabolism in preterm infants	Citrus fruits, green vegetables; **cooking destroys it**

b) Thiamine

- Infantile beriberi occurs between 1 and 4 months of age in:
    - Breastfed infants whose mothers have a thiamine deficiency (alcoholism),
    - Infants with protein-calorie malnutrition,

- Infants receiving unsupplemented hyperalimentation fluid, and
- Infants receiving boiled milk (thiamine is lost during milk pasteurization and sterilization)

- Acute wet beriberi with cardiac symptoms and signs predominates in infantile beriberi. Apathy, vomiting, restlessness, and pallor progress to dyspnea, cyanosis, and death from heart failure.
- Infants with beriberi have a characteristic **aphonic cry**; *no sound is heard when the child appears to be crying.* Other signs include peripheral neuropathy and paresthesias.

ii) Vitamin C

Ascorbic acid accelerates hydroxylation reactions, i.e. hydroxylation of proline in the formation of collagen. A deficiency of ascorbic acid results in the clinical manifestations of scurvy:

- Infantile scurvy is manifested by irritability, bone tenderness with swelling, and **pseudoparalysis of the legs**.
- Subperiosteal hemorrhage, bleeding gums and petechiae, hyperkeratosis of hair follicles, and a succession of mental changes characterize the progression of the illness.
- Anemia secondary to bleeding is also seen in chronic scurvy.
- The disease may occur if infants are fed unsupplemented cow's milk in the first year of life or if the diet is devoid of fruits and vegetables.

Features	Rickets	Scurvy
Etiology	Vitamin D deficiency	Vitamin C deficiency
Clinical features	Bowed legs, wrist and knee broadening, growth failure	Gum bleeding, pseudoparalysis
Symptoms	Painless	Painful
Rosary	Rachitic rosary, Rounded	Scorbutic rosary, Angulated
Defect	Defective mineralization of bone	Defective collagen formation
Radiological features	- Thinned out cortex, - Fraying of zone of calcification. - Widening of growth plate - Splaying (widening) and cupping of metaphysis - Bowing of diaphysis - White line of healing in healing phase of rickets	- Pencilled cortex - White line of Frankel - Zone of Trummerfield - Wimberger's sign - Subperiosteal hemorrhages - White line of Frankel - Ground glass osteopenia
Bones	Easily bendable	Easily breakable

- Radiological changes in survy:
  - Small epiphysis with thin pencilled cortex (**Wimberger's sign**)
  - Zone of provisional calcification becomes dense (**White line of frankel**)
  - Radiolucent zone beneath zone of provisional calcification (**Zone of Trummerfield**)
  - Marginal metaphyseal fractures (**Pelcan's spurs**)
- There may be subperiosteal hemorrhages and hematomas. Daily requirement is 2-35 mg daily. It is present in high concentrations in adrenal glands and lenses.

iii) Vitamin B6

The pyridoxal and pyridoxamine forms of the vitamin are destroyed by heat; heat treatment can be responsible for vitamin B6 deficiency—seizures in infants receiving improperly processed formulas. Goat's milk is deficient in **vitamin B6 in addition to folates**.

Children receiving isoniazid or penicillamine may require additional vitamin B6 because the drug binds to the vitamin. *Vitamin B6 is unusual as a water-soluble vitamin in that very large doses (≥500 mg/day) have been associated with a sensory neuropathy.*

iv) Folic acid, cobalamin and megaloblastic anemia

a) Folic acid

- Folate deficiency, characterized by:
    - Glossitis
    - Macrocytic anemia, and
    - Hypersegmented neutrophils,
- Causes:
    - Low dietary intake,
    - Malabsorption, or
    - Vitamin-drug interactions, e.g.
        - Anticonvulsants (phenytoin)
        - Antimetabolites (methotrexate)
- Deficiency can develop within a few weeks of birth because infants:
    - Require 10 times as much folate as adults relative to body weight, and
    - Have scant stores of folate in the newborn period.
- *Folate is particularly heat labile. Heat-sterilizing home-prepared formula can decrease the folate content by half.*
- Evaporated milk and goat's milk are low in folate.
- Patients with chronic hemolysis (sickle cell anemia, thalassemia) require extra folate.
- First occurrence and recurrence of neural tube defects are reduced significantly by maternal supplementation during embryogenesis.
- Because closure of the neural tube occurs before usual recognition of pregnancy, all women of reproductive age are recommended to have a folate intake of at least 400 µg/day as prophylaxis.

b) Vitamin B12 (Cobalamin)

- Its large stores in the liver also are unusual for a water-soluble vitamin. Efficient enterohepatic circulation normally protects from deficiency for months to years.
- Dietary sources of the vitamin are animal products only. Strict vegetarians should take a vitamin B 12 supplement.
- Vitamin B 12 deficiency in children is rare.
- Early diagnosis and treatment of this disorder in childhood are important because of the danger of irreversible neurologic damage.

- Depression of serum vitamin B12 and the appearance of hypersegmented neutrophils and macrocytosis (indistinguishable from folate deficiency)—early manifestations
- Vitamin B12 deficiency also causes neurologic manifestations— depression, peripheral neuropathy, posterior spinal column signs, dementia, and eventual coma. The neurologic signs do not occur in folate deficiency, but administration of folate may mask hematologic signs of vitamin B12 deficiency, while the neurologic manifestations progress.
- Patients with vitamin B12 deficiency also have increased urine levels of methylmalonic acid (MMA).

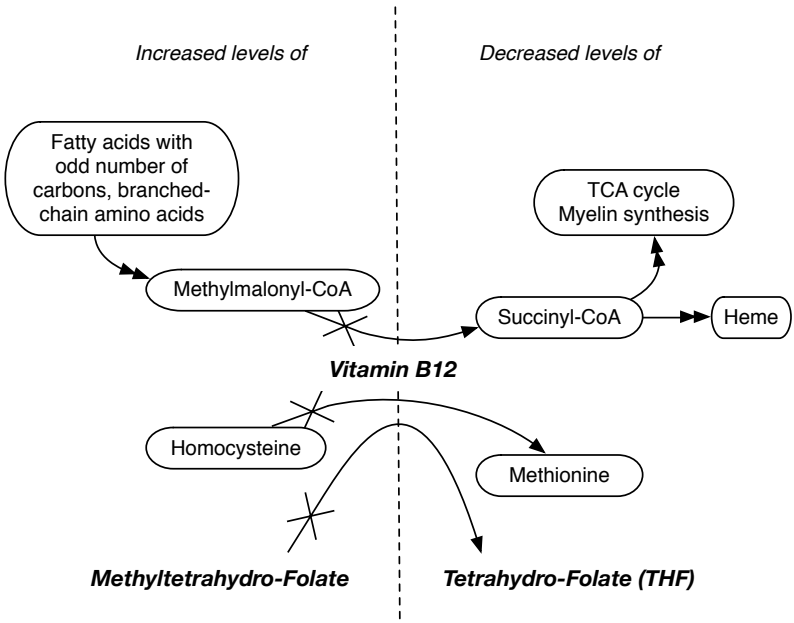


Figure. Biochemical relationship between folic acid, B12 and their effects.

(II) Fat-Soluble Vitamins

Fat-soluble vitamins generally have stores in the body, and dietary deficiencies generally develop more slowly than for water-soluble vitamins but occur more commonly due to complexity of fat absorption and its association with various diseases.

Table. Fat soluble Vitamins

Vitamin	Funtions	Deficiency	Comments	Source
A	Epithelial cell integrity; vision	Night blindness, xerophthalmia, Bitot spots, follicular hyperkeratosis; immune defects	Common with protein-calorie malnutrition; malabsorption	Liver, milk, eggs, green and yellow vegetables, fruits
D	Maintain serum calcium, phosphorus levels	Rickets: reduced bone mineralization		Fortified milk, cheese, liver; sunlight
E	Antioxidant	Hemolysis in preterm infants; areflexia, ataxia		Seeds, vegetables, germ oils, grains
K	Post-translation carboxylation of clotting factors II, VII, IX, X and proteins C, S	Prolonged prothrombin time; hemorrhage; elevated Protein Induced in Vitamin K Absence (**PIVKA**)	Malabsorption; breastfed newborns	Liver, green vegetables; made by intestinal flora

i) Vitamin A

Retinol influences the growth and differentiation of epithelia. In the eye, retinol is metabolized to form photosensitive rhodopsin.

Diseases of the kidney diminish excretion of retinol-binding protein, whereas liver parenchymal disease or malnutrition lowers the synthesis of retinol-binding protein.

The clinical manifestations of vitamin A deficiency in humans appear as a group of ocular signs termed ***xerophthalmia***.

The first sign of deficiency in children is **impaired dark adaptaion**, followed by night blindness (Stage XN), which is followed by xerosis of the conjunctiva (Stage X1A) and cornea (Stage X2). ***Stages upto XIB are reversible if Vitamin A is administered***.

Table. Classification of xerophthalmia

XN	Night blindness	
X1	X1A	Contunctival xerosis
	X1B	Bitot spots
X2	Corneal xerosis	
X3	X3A	Corneal ulceration/keratomalacia < 1/3 of corneal surface
	X3B	Corneal ulceration/keratomalacia ≥ 1/3 of corneal surface
XF	Xerophthalmic fundus	
XS	Scarring	

Untreated, xerophthalmia can result in ulceration, necrosis, keratomalacia (softening of cornea), and a permanent corneal scar.

Clinical and subclinical vitamin A deficiencies are associated with:

- Immunodeficiency;
- Increased risk of infection, **especially measles**, and
- Increased risk of mortality

Xerophthalmia and vitamin A deficiency should be urgently treated.

Age	Prophylactic treatment	Therapeutic treatment
< 6 months	50,000 IU orally	50,000 IU on day 1, 2, 14 orally
6 months to 1 year	100,000 IU orally	100,000 IU orally on day 1, 2, 14
> 1 year	200,000 IU orally	200,000 IU on day 1, 2, 14 orally

- Chloramphenicol or tetracycline eye drops for 4-10 days if there is pus, inflammation and corneal clouding and ulceration.
- Atropine eye drops for 3-5 days for clouding and ulceration.
- Saline soaked eye pads.

Hypervitaminosis A also has serious sequelae, including headaches, pseudotumor cerebri, hepatotoxicity, and teratogenicity.

ii) Vitamin E

- Vitamin E deficiency occurs in children with fat malabsorption secondary to liver disease, untreated celiac disease, cystic fibrosis, and abetalipoproteinemia.
- In these children, without vitamin E supplementation, a syndrome of progressive sensory and motor neuropathy develops; the first sign of deficiency is loss of deep tendon reflexes.
- Deficient preterm infants at 1 to 2 months of age have hemolytic anemia characterized by an elevated reticulocyte count, an **increased sensitivity of the erythrocytes to hemolysis in hydrogen peroxide**, peripheral edema, and thrombocytosis.

iii) Vitamin D

Vitamin D deficiency appears as rickets in children and as osteomalacia in postpubertal adolescents. Breastfed infants, especially those with dark-pigmented skin, are at risk for vitamin D deficiency.

a) Causes

- Inadequate direct sun exposure
- Inadequate vitamin D intake
- Drugs (phenobarbital, phenytoin)
- Malabsorption,

b) Rickets

The pathophysiology of rickets results from defective bone growth, especially at the epiphyseal cartilage matrix, which fails to mineralize.

The clinical manifestations of rickets are most common during the first 2 years of life and may become evident only after several months of a vitamin D–deficient diet:

- Rachitic metaphysis: The uncalcified osteoid results in a wide, irregular zone of poorly supported tissue. This soft, rather than hardened, zone produces lateral bulging or flaring of the ends of bones.
- Craniotabes is caused by thinning of the outer table of the skull, which when compressed feels like a Ping-Pong ball to the touch.
- Rachitic rosary: Enlargement of the costochondral junction.
- Thickening of the wrists and ankles may be palpable.
- The anterior fontanelle is enlarged, and its closure may be delayed.
- In advanced rickets, scoliosis and exaggerated lordosis may be present.
- Bowlegs or knock-knees may be evident in older infants, and
- Greenstick fractures may be observed in long bones.

The best measure of vitamin D status is the level of 25-(OH)-D. Others:

- The serum calcium usually is normal but may be low (tetany may occur if < 7.5 mg/dL),
- Serum phosphorus level usually is reduced,
- Serum alkaline phosphatase activity is elevated.

Characteristic radiographic changes:

- Thinned out cortex,
- Fraying of zone of calcification.
- Widening of growth plate
- Splaying (widening) and cupping of metaphysis
- Bowing of diaphysis

Table. Stoss therapy (German; "Stoss"- push, blow)	
Age	**Therapy**
< 2 years of age	Inj. Vit D3 (300,000 IU I/M)
> 2 years of age	Inj. Vit D3 (600,000 IU I/M)
Repeat Xray wrist after 4 weeks, if findings persist, repeat Stoss therapy. Consider other causes of rickets	

Breastfed infants born of mothers with adequate vitamin D stores usually maintain adequate serum vitamin D levels for at least 2 months, but rickets may develop subsequently if these infants are not exposed to the sun or do notreceive supplementary vitamin D.

Toxic effects of excessive chronic vitamin D may include hypercalcemia, muscle weakness, polyuria, and nephrocalcinosis.

iv) Vitamin K

- Vitamin K1 (phylloquinone)- plant form
- Vitamin K2 (menaquinone)- synthesized by intestinal bacteria
- Plasma factors II (prothrombin), VII, IX, X, Protein C and S in the cascade of blood coagulation factors depend on vitamin K for synthesis and activation.
- Phylloquinone is absorbed from the intestine and transported by chylomicrons.

- Vitamin K deficiency has been seen in: (often these problems are combined with the use of antibiotics that affect intestinal flora)
    - Impaired fat absorption caused by obstructive jaundice,
    - Pancreatic insufficiency,
    - Celiac disease, etc.

Hemorrhagic disease of the newborn, a disease more common among breastfed infants, occurs in the first few weeks of life and can be prevented by prophylactic intramuscular vitamin K (0.5 to 1 mg) on the first day of life (recommended).

(III) Minerals

The major minerals are those that require intakes of more than 100 mg/day and contribute at least 0.1% of total body weight.

Table. Characteristics of Trace Mineral Deficiencies

Mineral	Function	Manifestations of deficiency	Comments	Sources
Iron	Heme-containing macromolecules (e.g., hemoglobin, myoglobin etc)	Anemia, koilonychia, reduced muscle and mental performance	History of pica, cow's milk, gastrointestinal bleeding	Meat, liver, grains, legumes
Copper	Redox reactions (e.g., cytochrome oxidase)	Hypochromic anemia, neutropenia, osteoporosis, hypotonia, hypoproteinemia	Inborn error, Menkes kinky hair syndrome	Liver, nuts, grains, legumes, chocolate
Zinc	Metalloenzymes (e.g., alkaline phosphatase, carbonic anhydrase, DNA polymerase); wound healing	Acrodermatitis enteropathica: poor growth, acro-orificial rash, alopecia, delayed sexual development, hypogeusia, infection	Protein-calorie malnutrition; weaning; malabsorption syndromes	Meat, grains, legumes
Selenium	Antioxidant; glutathione peroxidase	Keshan cardiomyopathy in China	Endemic areas; long-term TPN without Se	Meat, vegetables
Fluoride	Strengthening of dental enamel	Caries	Narrow therapeutic index, *fluorosis may cause staining of the teeth*	Seafood, fortified water
Iodine	Thyroxine, triiodothyronine production	Simple endemic goiter. Myxedematous cretinism: congenital hypothyroidism. Neurologic cretinism: mental retardation, deafness, spasticity, normal thyroxine level at birth.	Endemic in New Guinea, the Congo; endemic in Great Lakes area before use of iodized salt	Seafood, iodized salt

TPN, Total parenteral nutrition.

i) Iron and iron deficiency anemia

Iron is used in the synthesis of hemoglobin, myoglobin, and enzyme iron. There are two categories of iron in food:

- Heme iron, present in hemoglobin and myoglobin, which is supplied by meat and efficiently absorbed.
- Nonheme iron salts, *represent the major form of iron intake consumed by infants*. Enhancers influence the absorption of nonheme iron, such as: ascorbic acid, meat, fish, and poultry.

After about 4 months of age, iron reserves become marginal in a term infant, and there is progressive risk for anemia as the iron requirements increase (preterms affected earlier):

- Inadequate intake
- Hookworm infestation
- Meckel's diverticulum
- Peptic ulcer disease, etc.

The diagnosis of iron deficiency anemia is established when there is:

- Microcytic hypochromic anemia,
- ↓ serum ferritin levels,
- ↓ serum iron levels,
- ↓ transferrin saturation,
- ↑ total iron-binding capacity.

Treatment of iron deficiency anemia includes changes in the diet to provide adequate iron and the administration of 2 to 6 mg iron/kg/24 hr (as ferrous sulfate) divided twice or three times daily. Reticulocytosis is noted within 3 to 7 days of starting treatment.

Oral treatment should be continued for 5 months. *Parenteal iron therapy carries risk of anaphylaxis.*

Prevention involves the provision of following steps:

- Premature infants fed human milk may develop iron deficiency anemia earlier unless they receive iron supplements.
- Formula-fed preterm infants should receive iron-fortified formula.
- Deworming older children where worm infestations are endemic.

ii) Zinc

- Zinc is the **second most abundant trace mineral** and is important in protein metabolism and synthesis, in nucleic acid metabolism, and in stabilization of cell membranes.
- Dietary zinc is absorbed (20% to 40%) in the duodenum and proximal small intestine. The best dietary sources of zinc are animal products, including human milk, from which it is readily absorbed.
- Whole grains and legumes also contain moderate amounts of zinc, but phytic acid inhibits absorption from these sources. *Poor bioavailability secondary to phytic acid is more likely than low intake in the widespread occurrence of zinc deficiency.*
- GI tract is the major route of excretion of zinc. In the presence of ongoing losses, such as in chronic diarrhea, requirements can drastically increase.

- Acute, acquired severe zinc deficiency occurs premature infants fed human milk without fortification.
- Clinical manifestations:
    - Mild zinc deficiency: anorexia, growth faltering, and immune impairment.
    - Moderately severe manifestations: Delayed sexual maturation, rough skin, and hepatosplenomegaly.
    - Severe deficiency: acral and periorificial erythematous, scaling dermatitis rash; growth and immune impairment; diarrhea; mood changes; alopecia; night blindness; and photophobia.

a) Acrodermatitis enteropathica

- It is an autosomal recessive disorder that begins within 2 to 4 weeks after infants have been weaned from breast milk. It is characterized by an acute perioral and perianal dermatitis, alopecia, and failure to thrive.
- The disease is caused by severe zinc deficiency from a specific defect of intestinal zinc absorption.
- Plasma zinc levels are markedly reduced, and serum alkaline phosphatase activity is low.
- Treatment is with oral zinc supplements 150mg/day. Zinc paste can be applied locally to skin lesions.

CHAPTER 12 POISONING

The most common agents ingested by young children include cosmetics, personal care products, analgesics, and cleaning solutions.

Fatal childhood poisonings are commonly caused by analgesics, antihistamines, sedatives, and fumes/gases/vapors.

(I) Clinical Features

Any child who presents with unexplained symptoms including altered mental status, seizure, cardiovascular compromise, or metabolic abnormality should be considered to have ingested a poison until proven otherwise.

Determination of all substances that the child was exposed to, type of medication, amount of medication, and time of exposure is crucial in directing interventions.

Certain complexes of symptoms and signs are relatively specific to a given class of drugs (toxidrome).

Table. Toxidromes (signs & symptoms relatively specific for a class of drugs)	
Agent	**Manifestations**
Acetaminophen	Nausea, vomiting, pallor, delayed jaundice–hepatic failure (72–96 hours)
Amphetamine, cocaine, and sympathomimetics	Tachycardia, hypertension, hyperthermia, psychosis and paranoia, seizures, mydriasis, diaphoresis, piloerection, aggressive behavior
Anticholinergics	Mania, delirium, fever, red dry skin, dry mouth, tachycardia, mydriasis, urinary retention
Carbon monoxide	Headache, dizziness, coma, other systems affected
Cyanide	Coma, convulsions, hyperpnea, bitter almond odor
Ethylene glycol (antifreeze)	Metabolic acidosis, hyperosmolarity, hypocalcemia, oxalate crystalluria
Iron	Vomiting (bloody), diarrhea, hypotension, hepatic failure, leukocytosis, hyperglycemia, late intestinal stricture
Narcotics	Coma, respiratory depression, hypotension, pinpoint pupils, bradycardia
Cholinergics (organophosphates, nicotine)	Miosis, salivation, urination, diaphoresis, lacrimation, bronchospasm (bronchorrhea), muscle weakness and fasciculations, emesis, defecation, coma, confusion, pulmonary edema, bradycardia
Salicylates	Tachypnea, fever, lethargy, coma, vomiting, diaphoresis, alkalosis (early), acidosis (late)
Cyclic antidepressants	Coma, convulsions, mydriasis, hyperreflexia, arrhythmia (prolonged Q-T interval), cardiac arrest, shock

(II) Investigations

- Specific toxin-drug assays;
- Arterial blood gases
- Serum osmolarity and electrolytes

- Blood glucose
- Calculation of the anion or osmolar gap.
- 12-lead electrocardiogram

Quantitative toxicology assays are important for some agents than others.

(III) Treatment

The four foci of treatment for poisonings are:

- Supportive care,
- Decontamination,
- Enhanced elimination, and
- Specific antidotes.

i) ABC approach and supportive care

Supportive care is the mainstay of treatment in most cases.

Maintaining the airway, establishing effective breathing, and supporting the circulation is always the priority.

If the level of consciousness is depressed, and a toxic substance is suspected, glucose (1 g/kg intravenously), 100% oxygen, and *naloxone* should be administered.

ii) Gastrointestinal Decontamination

The intent of gastrointestinal decontamination is to prevent the absorption of a potentially toxic ingested substance and, in theory, to prevent the poisoning.

Recommendations from the American Academy of Clinical Toxicology (AACT) and the European Association of Poison Centres and Clinical Toxicologists (EAPCCT)
Syrup of ipecac should not be administered routinely to poisoned patients because of potential complications and lack of evidence that it improves outcome.
Gastric lavage should not be used routinely, if ever, in the management of poisoned patients because of lack of efficacy and potential complications.
Single-dose activated charcoal decreases drug absorption when used within 1 hour of ingestion; but has no effect on outcome, hence it should be used selectively. Charcoal is ineffective against caustic or corrosive agents, hydrocarbons, heavy metals (arsenic, lead, mercury, iron, lithium), glycols, and water-insoluble compounds.
The administration of a cathartic (sorbitol or magnesium citrate) alone has no role in the management of the poisoned patient. The AACT does not recommend the use of a cathartic in combination with activated charcoal.
Whole-bowel irrigation using polyethylene glycol as a nonabsorbable cathartic may be effective for toxic ingestion of sustained-release or enteric-coated drugs. There is theoretical benefit in its use for potentially toxic ingestions of iron, lead, zinc, or packets of illicit drugs.

iii) Enhanced Elimination

Multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Alkalinization of urine may be helpful for salicylate or methotrexate ingestion. Dialysis may be used for substances that have a low volume of distribution, low molecular weight, low protein binding, and high degree of water solubility, such as methanol, ethylene glycol, salicylates, theo-

phylline, bromide, and lithium.

iv) Specific Antidotes

Table. Specific Antidotes	
Poison	**Antidote**
Acetaminophen	N -Acetylcysteine
Benzodiazepine	Flumazenil
β-Blockers	Glucagon
Carbon monoxide	Oxygen
Tricyclic antidepressants	Sodium bicarbonate
Iron	Deferoxamine
Lead	Edetate calcium disodium (EDTA)
	Succimer (2,3-dimercaptosuccinic acid ([DMSA])
Nitrites/ Methemoglobinemia	Methylene blue
Opiates	Naloxone
Organophosphates	Atropine
	Pralidoxime (2 PAM; Protopam)

(IV) Prevention

Properly educating parents regarding safe storage of medications and household toxins is necessary for preventing ingestions.

CHAPTER 13 PATTERNS OF INHERITANCE

(I) Types of Genetic Disorders

1. Single-gene mutations, accounting for 6% of children with congenital anomalies
2. Chromosomal disorders, accounting for approximately 7.5%
3. Multifactorially inherited conditions, accounting for 20%
4. Disorders that show an unusual pattern of inheritance, accounting for 2% to 3%
5. Conditions caused by exposure to teratogens, accounting for 6%

(II) Basic terminology

i) Point mutation

Point mutation is a change in a single DNA base. It is the **most common** type of mutation.

ii) Missense mutation

A point mutation that changes a codon and the resulting amino acid that goes into the protein is referred to as a **missense mutation**.

iii) Nonsense mutation

A point mutation that changes the codon to a "stop" codon so that transcription stops prematurely is called a **nonsense mutation.**

iv) Frameshift mutation

A frameshift mutation often stems from the loss or addition of one or more DNA bases; this causes a shift in how the DNA is transcribed and generally leads to premature stop codons.

v) Penetrance

Some individuals who are carriers of a mutation known to cause an AD disorder may not show clinical signs of the disorder, whereas other such individuals manifest symptoms. This is known as penetrance.

If all individuals who carry a mutation for an AD disorder show signs of that disorder, the gene is said to have *complete penetrance*. Many AD disorders show decreased penetrance.

vi) Expression

AD disorders show variability in symptoms expressed in different individuals carrying the same mutated gene. Some individuals have only mild clinical symptoms, whereas others have more severe disease. This phenomenon is referred to as **variable expressivity.**

vii) Mutational hotspot

An extremely active site for mutations is known as Mutational hotspot. e.g. base pair site 1138 of FGFR-3 gene causing Achondroplasia.

viii) Pleiotropy

Mutation in a single gene causing abnormalities in multiple organ systems is known as Pleiotropy, e.g. FBN1 gene mutation in Marfan's syndrome involve three systems: cardiac, ophthalmologic, and skeletal.

ix) Skewed X inactivation

Early in female embryonic development, one X chromosome is randomly inactivated in each cell. Sometimes heterozygous (carrier) females show some manifestations of an X-linked recessive disorder. This occurs due to skewed (skewed=neither perpendicular, nor parallel/asymmetrical) X chromosome inactivation during embryonic development. e.g: colorblindness, Duchenne Muscular Dystrophy (DMD), Hemophilia A.

x) Heteroplasmy

If more than one population of mitochondria are present in the oocyte, then this phenomenon called heteroplasmy.

When this fertilized egg divides, mitochondria with heteroplasmy will be distributed randomly. The presence of symptoms in the offspring, and their severity, depends on the ratio of mutant to wild-type mtDNA present in a particular tissue. e.g. in families with **MELAS**, a range of symptoms are seen in first-degree relatives, including progressive ophthalmoplegia, hearing loss, cardiomyopathy, and diabetes mellitus.

xi) Genomic imprinting

Imprinting is an epigenetic phenomenon, a nonheritable change in the DNA that causes an alteration in gene expression based on parental origin of the gene.

Example: Prader-Willi Syndrome is caused by deficiency of the protein product of the gene SNRPN (small nuclear ribonucleoprotein). Although present on both maternally and paternally derived chromosome 15, SNRPN is expressed only in the paternally derived chromosome. **Expression is blocked in the maternal chromosome** because the bases of the open reading frame are *hypermethylated* (inactivated); this physical change in the DNA prevents gene expression. PWS results whenever a paternal chromosome 15 is missing, either through deletion or through UPD.

(III) Pedigree Drawing

- It is a pictorial representation of a family history.
- Males are represented by squares and females by circles.
- Matings are connected with a solid line between each partner's symbols. **Unmarried couples are often connected by a dashed line.**
- Ages or birthdays may be written next to or underneath each symbol.
- The proband (the patient who is the initial contact) is *indicated with an arrow*.
- Affected individuals are indicated by shading, or some other technique, which should be explained in a key.
- Carriers for a disorder (e.g., sickle cell disease) usually are indicated by a dot in the center of their symbol.

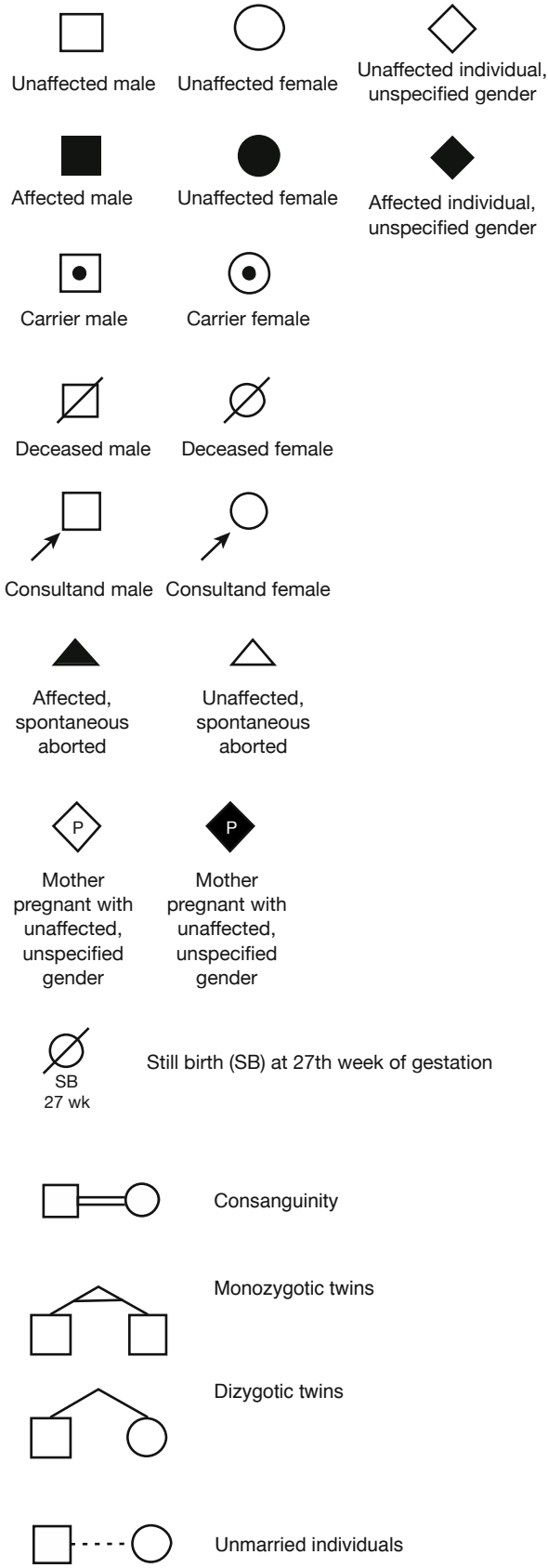


Figure. Pedigree symbols and relationships.

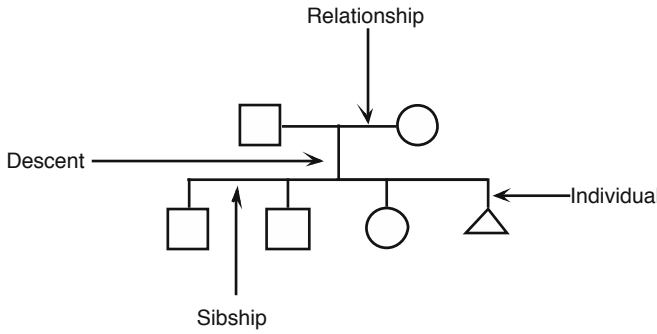


Figure. Assembling the pedigree chart.

i) Autosomal Dominant Disorders (AD)

In AD disorders, an affected parent has a 50% chance of passing the mutated gene to each child.

Common examples:

- Achondroplasia,
- Osteogenesis Imperfecta,
- Huntington's Chorea,
- Marfan's syndrome,
- Polycystic Kidney disase,
- Familial polyposis coli,
- Neurofibromatosis type 1,
- Familial hypercholestrolemia,
- Congenital Spherocytosis.

Rules of Autosomal Dominant Inheritance
Trait appears in every generation
Each child of an affected parent has a one in two (50%) chance of being affected
Males and females are equally affected
Male-to-male transmission occurs
Traits generally involve mutations in genes coding for regulatory/structural proteins (collagen)

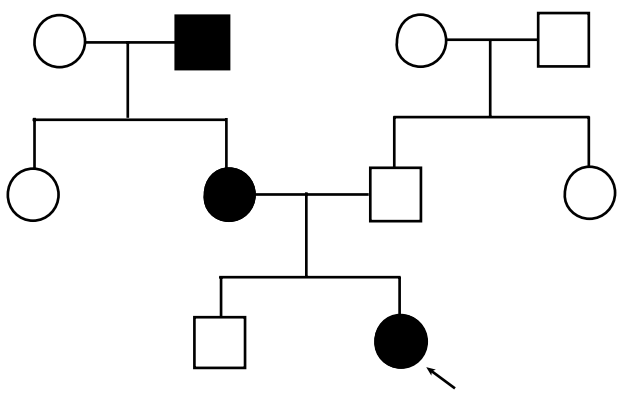


Figure. Pattern of autosomal dominant inheritance.

Table. Autosomal Dominant Diseases	
DISEASE	**COMMENTS**
Achondroplasia	Mutations in fibroblast growth factor receptor-3 (FGFR-3) on chromosome 4. 40% of cases are new mutations.
Neurofibromatosis 1	About 50% of cases result from new mutations in the gene for neurofibromin, a **tumor suppressor gene** located at Chromosome 17. Variable expression.
Neurofibromatosis 2 (NF2, bilateral acoustic neuromas, Merlin)	The NF2 gene is a **tumor suppressor gene** located at 22. The protein is called "*Merlin*"
Huntington disease (HD)	Trinucleotide (CAG) repeat expansion in the "Huntington" protein gene on chromosome 4. *Genetic Anticipation* phenomenon is seen with successive generations.
Myotonic dystrophy (DM, Steinert disease)	Trinucleotide (CTG) repeat expansion in the DM kinase gene at chromosome 19. *Genetic Anticipation* phenomenon is seen with successive generations.
Marfan syndrome (FBN-1)	The syndrome is caused by mutations in the fibrillin-1 (FBN-1) gene on chromosome 15. Variable expression.
Hereditary Angioneurotic Edema (HANE) (C-1 esterase inhibitor that regulates C1 component of complement)	Located on chromosome 11. The phenotype of episodic and variable subcutaneous and submucosal swelling and pain is caused by diminished or altered esterase inhibitor protein.

a) Achondroplasia

It is the most common skeletal dysplasia in humans.

Caused by a defect in cartilage-derived bone.

Clinical features:

- Short stature,
- Macrocephaly,
- Flat midface with a prominent forehead, and
- Rhizomelic shortening of the limbs.
- Dental malocclusion,
- Obstructive apnea, and
- Hearing loss due to middle ear dysfunction are common in later childhood.
- People with ACH have normal life spans and normal intelligence.

The diagnosis of ACH is made on the basis of clinical findings; characteristic x-ray abnormalities confirm the diagnosis.

Molecular testing is available but is usually reserved for special cases. Prenatal diagnosis is possible by molecular testing, using fetal cells obtained through amniocentesis or CVS.

b) Neurofibromatosis Type 1

Although the penetrance of NF1 is 100%, the expression is highly variable. Many affected individuals are never diagnosed due to very mild features.

c) Marfan Syndrome (MFS)

- Skeletal findings:
    - Tall, thin body habitus (dolichostenomelia),
    - Joint laxity,
    - Scoliosis,
    - Pes planus,
    - Spider-like fingers and toes (arachnodactyly),
    - Abnormalities of the sternum (pectus excavatum or carinatum),
- Eye findings:
    - High myopia, which can lead to vitreoretinal degeneration;
    - An abnormal suspensory ligament of the lens, which can lead to ectopia lentis (dislocation of the lens);
    - Cataracts.
- Cardiac findings:
    - Progressive dilatation of the aortic root.
    - Aortic insufficiency followed by aortic dissection is a common complication.
- Facial Features:
    - Enophthalmos,
    - Downslanting palpebral fissures,
    - Malar hypoplasia,
    - Retrognathia.

Other clinical features of MFS include dural ectasia, abnormal pulmonary septation, and striae.

Many of the symptoms of MFS are caused not by the defect in the fibrillin protein itself but rather by **excess in transforming growth factor-beta (TGF - β),** *a protein usually bound by fibrillin*. **Losartan, an angiotensin II receptor antagonist that also lowers levels of TGF - β, may prevent aneurysms in patients with MFS.**

ii) Autosomal Recessive Disorders (AR)

Disorders that are inherited in an AR manner manifest only when both copies of a gene pair located on a **non-sex chromosome** have a mutation.

If both members of a couple are carriers (or heterozygotes) for this mutation, each of their offspring has a 25% chance of being affected.

Rules of Autosomal Recessive Inheritance
Trait appears in siblings, not in their parents or their offspring
On average, 25% of siblings of the proband are affected (at the time of conception, each sibling has a 25% chance of being affected)
A normal sibling of an affected individual has a two thirds chance of being a carrier (heterozygote)
Males and females are likely to be affected equally
Rare traits are likely to be associated with parental consanguinity
Traits generally involve mutations in genes that code for enzymes (e.g., phenylalanine hydroxylase–deficient in PKU) and are associated with serious illness and shortened life span

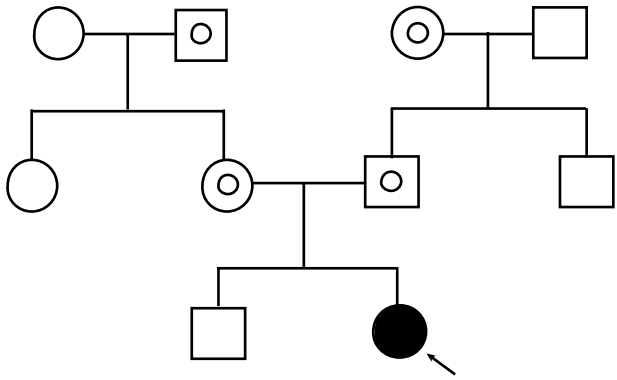


Figure. Pattern of autosomal recessive inheritance

Table. Autosomal Recessive Diseases	
DISEASE	**COMMENTS**
Congenital Adrenal Hyperplasia (21-hydroxylase deficiency)	A deficiency causes virilization in females. The gene is located at Chromosome 6 within the HLA complex.
Phenylketonuria (PKU, phenylalanine hydroxylase deficiency)	There are hundreds of disease-causing mutations in the PAH gene located on chromosome 12. Women with elevated phenylalanine have infants with damage to the central nervous system because high phenylalanine is neurotoxic and teratogenic
Cystic fibrosis (CF)	The gene CF transmembrane conductance regulator (CFTR) is on chromosome 7.
Friedreich ataxia (FA, frataxin)	Frataxin is a mitochondrial protein involved with ***iron metabolism and respiration.*** It is a trinucleotide (GAA) repeat disorder located on chromosome 9. ***FA does not show anticipation***
Gaucher disease, all types (glucocerebrosidase deficiency deficiency)	The gene is located on chromosome 1. Some mutations lead to neuropathic disease while others are milder in expression.
Sickle cell disease (hemoglobin beta chain 6th glu→val mutation)	A single base change results in an amino acid substitution of valine for glutamic acid at position 6 of the beta chain of hemoglobin, with resulting hemolytic anemia. The gene is on chromosome 11. *Penicillin prophylaxis reduces death from pneumococcal infections in affected infants*

a) Cystic Fibrosis

- Cystic fibrosis (CF) is an *autosomal recessive* pattern genetic disorder that affects multiple organ systems; most notable are the lungs and GI tract.
- It is caused by mutation of one single gene, known as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene on chromosome 7, which encodes an ion channel important for chloride and bicarbonate transport across epithelia.
- The most common mutation in CFTR is a deletion of phenylalanine at position 508 (called delta F508, or ΔF508), which accounts for about two-thirds of the mutations found in CF patients.
- The severity of disease is extremely variable from patient to patient
- This variation is multifactorial, related to differences in compliance to medical regimens, environmental exposures, and effect of other genes that modify the CF phenotype.

Clinical features

The hallmark of the disease is the production of thick, tenacious secretions, particularly in the respiratory and GI systems.

This is related to imbalance of ion and water transport across these epithelial structures due to CFTR mutations.

The earliest presentation of CF is meconium ileus, which can be identified shortly after birth as abdominal distension and lack of passage of meconium in the first days of life.

This is the presenting symptom in approximately 15–20% of children with CF. In children without meconium ileus; the most common presenting signs include those of exocrine pancreatic insufficiency (failure to thrive, persistent diarrhea, chronic abdominal pain) and airway inflammation (prolonged cough, recurrent wheezing).

Diagnosis

- Sweat Chloride Test—most commonly used diagnostic test. Sweat chloride levels > 60 mEq/L. However, in infants, levels above 30 mEq/L are considered abnormal.
    - If the sweat chloride test is nondiagnostic, or positive, the next step is often genetic testing to identify specific mutations in the CFTR gene.
- Blood spot for elevated immune reactive trypsinogen (IRT)— screening test
- Genetic testing identify mutation is of prognostic value.
- According to the CF Foundation, a diagnosis of CF can be made if the patient has suggestive signs and symptoms, *or* a positive family history, *or* a positive newborn screen, *and* evidence of CFTR gene or protein abnormality, i.e., abnormal sweat chloride test, abnormal nasal potential difference, or two CF disease-causing mutations in *trans*.

Clinical features

- Pancreatic Disease/CFRD
    - Exocrine pancreatic insufficiency is ***often the earliest presentation of cystic fibrosis***.
    - Patients will usually develop pancreatic insufficiency and chronic malabsoption within the first year of life.
    - Symptoms and signs include chronic abdominal pain and cramping, abdominal distension, diarrhea, steatorrhea, and failure to thrive.
    - Laboratory studies may reveal deficiencies in fat-soluble vitamins.
    - Exocrine pancreatic insufficiency in CF is a result of production of thick secretions and obstruction of the pancreatic ducts and acini leading to their destruction.
    - The diagnosis of CF should be considered in *idiopathic recurrent pancreatitis, even in the absence of other manifestations of the disease.*
- Patients with CF are also at high risk to develop endocrine pancreatic insufficiency, i.e., CF-related diabetes (CFRD). It occurs due to insulin deficiency, *not insulin resistance*.
- Lung Disease
    - Onset of respiratory symptoms varies from patient to patient, but can be present early in infantile age.
    - Thick, tenacious mucus accumulates in the large, medium, and small airways:
    - Chronic wet cough,
    - Prolonged cough after respiratory illnesses,

- Wheezing,
- Dyspnea on exertion,
- Chest tightness
- Hemoptysis can also occur
- Systemic signs or symptoms such as fever, weight loss, fatigue, and anorexia may be seen in exacerbations.
- Respiratory failure is the most common cause of mortality in CF.
- ***Chronic recurrent infections and fibrosis leads to bronchiectasis and obstructive lung disease.***

- Other Clinical Manifestations of CF
  - Sinus disease: Recurrent sinusitis and inflammation can lead to nasal polyps.
  - Intestinal obstruction due to thick, adherent mucus and fecal material, similar in mechanism to meconium ileus in the newborn, called **distal intestinal obstruction syndrome (DIOS).**
  - Chronic biliary obstruction leading to the development of cirrhosis of the liver can also occur.
  - Fertility prblems
    - Majority of males with CF is **infertile (**azoospermic**).**
    - Women with CF can have thick cervical mucus that prevents pregnancy, but this can be overcome by the use of artificial insemination or in vitro fertilization.

Treatment

- Treatment and Management of GI Disease
  - High-calorie, high-protein diet— to maintain normal growth.
  - Pancreatic enzyme replacement therapy with oral preparations of pancreatic enzymes.

- Treatment and Management of Lung Disease
  - Mechanically assisting clearance of the mucus by means of:
    - Manual chest percussion or mechanical external chest wall oscillation
    - Oscillating positive expiratory pressure (PEP),
    - Using devices such as intrapulmonary percussive ventilation (IPV) or a flutter valve.
  - In addition to mechanically aiding mucus clearance, there are also therapies that help by making mucus less thick and more easily cleared:
    - Dornase alfa— breaks down the extracellular DNA,
    - Inhaled hypertonic saline reduces airway mucus viscocity.
    - Inhaled bronchodilators
  - Anti-inflammatory Medications
    - High-dose ibuprofen
    - Corticosteroids are not routinely used for CF lung disease due to side effects with long-term use.

- Azithromycin for its antimicrobial and immunomodulatory effects

- Antibiotics
  - Staphylococcus aureus and Pseudomonas aeruginosa are predominant organisms.
  - Aminoglycosides, cephalosporins, carbapenems, and extended-spectrum beta-lactams are antibiotics commonly used.
  - IV antibiotics— acute pulmonary exacerbations
  - It is standard to treat acute exacerbations for 2–3 weeks at a time.
  - Aerosolized antibiotic formulations of tobramycin and aztreonam— can be used in maintenance therapy (not for acute exacerbations).
- Lung Transplant— provide a prolongation and improved quality of life, it is not a cure for CF. The management of post-transplant patients is beyond the scope of this publication.

- Vitamin Supplementation
  - The malabsorption of fat leads to malabsorption of fat-soluble vitamins A, D, E, and K.
  - These deficiencies can be seen by laboratory measurement before the onset of clinical signs and symptoms, and so *high suspicion and surveillance is recommended as part of routine CF care*.

Outcomes and Prognosis

The median life expectancy is shortened significant, but continues to improve with better management nowadays.

iii) X-Linked Recessive Inheritance

Most disorders involving the X chromosome are recessive.

Rules of X-Linked Recessive Inheritance
Incidence of the trait is higher in males than in females
Trait is passed from carrier females, who may show mild expression of the gene, to half of their sons, who are more severely affected
Each son of a carrier female has a one in two (50%) chance of being affected
Trait is transmitted from affected males to all of their daughters (carriers); it is never transmitted father to son
Because the trait can be passed through multiple carrier females, it may skip generations

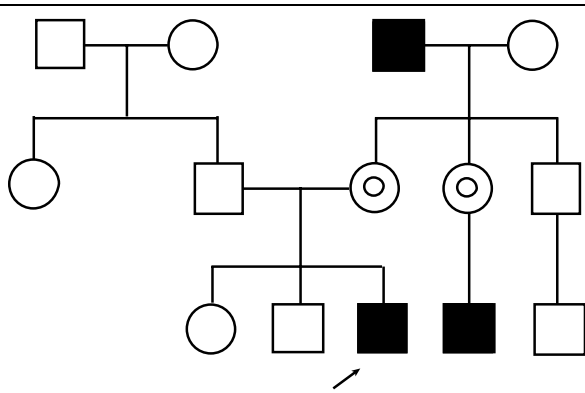


Figure. Pattern of X-linked recessive inheritance

Table. X-Linked *Recessive* Diseases	
Disease	**Comments**
Fragile X syndrome (FRAXA)	A trinucleotide (CGG) repeat disorder that is associated with localized methylation (inactivation) of distal genes.
Duchenne muscular dystrophy (DMD, pseudohypertrophic progressive MD)	Large gene and mutations and deletions may occur anywhere. The gene product is called **dystrophin** is absent in DMD but abnormal in Becker MD
Hemophilia A (factor VIII deficiency, classic hemophilia)	Factor VIII is essential for normal blood clotting. Phenotype depends on severity of genotype mutations and residual factor VIII activity
Rett syndrome (autism, dementia, ataxia, and loss of purposeful hand use);	These diseases are a subset of autism. There is a loss of regulation (repression) for other genes, lethal in males. **MECP2 (methyl-CpG- binding protein 2) gene is involved.**
Color blindness	Deutan color blindness and protan color blindness.
Glucose-6-phosphate dehydrogenase deficiency (G6PD)	Oxidative stress causes hemolysis. Variants can confer partial resistance to severe malaria

iv) X-Linked Dominant Inheritance

Both males and females are affected by this group of disorders, but females have less severe symptoms due to X-chromosome inactivation.

Many X-linked dominant disorders are lethal in males. Affected mothers can have affected or normal daughters but **only normal sons**. ***Affected sons die in utero***. Examples:

a) X-linked vitamin D–resistant rickets (hypophosphatemic rickets)

A disorder in which the kidney's ability to reabsorb phosphate is impaired. Phosphate levels and resulting rickets are not as severe in females as in males.

b) Incontinentia pigmenti

In this disorder, a characteristic *swirling skin pattern* of hyperpigmentation that develops after a perinatal skin rash with blistering.

Affected females also have variable involvement of the CNS, hair, teeth, nails and eyes.

c) Rett syndrome

It is caused by mutations in the MECP2 gene, females are normal at birth, but later in the first year of life develop microcephaly and **developmental regression** and plateau.

About 50% of patients develop seizures. Girls often are diagnosed with autism and, by 2 years of age, adopt a handwashing posture (results in loss of all purposeful hand movements).

v) Other Types of Genetic Disorders

a) Multifactorial Disorders (Polygenic inheritance)

These result from the interplay of genetic and environmental factors.

- These disorders **do not** follow simple mendelian modes of inheritance; rather, affected individuals tend to cluster in families.
- The disorders occur more often in first and second-degree relatives than would be expected by chance.

- They are more likely to be concordant (although not 100%) in monozygotic twins than in dizygotic twins.
- Examples:
    - Congenital malformations, including cleft lip and palate and spina bifida,
    - Asthma,
    - Atherosclerosis,
    - Diabetes,
    - Cancer, etc.

Hypertrophic Pyloric Stenosis

- Occurring in about 1 in 300 children,
- Male:Female::5:1 ratio.
- If the thickness of the pyloric muscle in a population is plotted on a statical graph, a bell-shaped curve may be seen. The position on the bell-shaped curve of an individual is determined by many factors, including the expression of multiple, unknown genes. HPS may result when an individual's genetic and environmental influences cause him or her to fall to an extreme position on this curve, past a certain point, which is called a threshold. In HPS, this threshold is farther to the left for males than it is for females.

Neural Tube Defects

Multiple genetic and nongenetic factors dictate the speed with which the neural tube closes, as follows:

1. Ethnicity.
2. Environmental component.
3. Seasonality: more likely during late fall and early winter.
4. Nutrition: Periconceptual folic acid has significantly lowers the risk.
5. Genetic component.

b) Disorders with Unusual Patterns of Inheritance

Mitochondrial Inheritance

- Human cells contain non-nuclear DNA; a single chromosome is present in each mitochondrion, and mutations within this DNA are associated with a group of diseases.
- Mitochondrial DNA (mtDNA), is circular, replicates independently of nuclear DNA and is involved in energy production.
- ***mtDNA is maternally derived. A woman with a mutation in mtDNA passes this mutation to all of her children.***
- In heteroplasmy, ***the severity of disease varies, depending on the percentage of mitochondria bearing the mutation that are present.*** If an abundance of mutant mitochondria exists in tissue that has high-energy requirements (brain, muscle, and liver), clinical symptoms occur. If fewer mutant mitochondria are present, lesser clinical symptoms may be seen.
- MELAS (**M**itochondrial **E**ncephalomyopathy with **L**actic **A**cidosis and **S**troke-like episodes) is a mitochondrial disorder. Episodic vomiting, seizures, and recurrent cerebral insults that resemble strokes between 5 and 10 years of age.

Uniparental Disomy

Evaluation of a child with uniparental disomy (UPD) reveals a **normal karyotype** but the indi-

vidual inherits two copies of one parent's chromosome and no copy from the other parent.

Most common mechanism is from a ***spontaneous rescue mechanism***. At the time of conception, through nondisjunction, the fertilized egg is trisomic for a particular chromosome, with two copies of one parent's chromosome and one copy of the other parent's chromosome. Often, there is a spontaneously loss one of three copies of the affected chromosome. If the single chromosome from one parent is lost, the patient has UPD.

Prader-Willi and Angelman Syndromes

Prader-Willi syndrome (PWS), is characterized by

- Hypotonia of prenatal onset;
- Postnatal growth delay;
- A characteristic appearance, including
    - Almond-shaped eyes
    - Small hands and feet;
- Developmental disability;
- Hypogonadotropic hypogonadism; and
- Obesity after infancy.

Newborns cannot consume enough calories to maintain their weight due to hypotonia.

During the first year of life, muscle tone improves and children develop a voracious appetite.

Angelman syndrome (AS) is a condition with:

- Moderate to severe mental retardation,
- Absence of speech,
- Ataxic movements of the arms and legs,
- A characteristic facial appearance, and
- Seizure disorder characterized by inappropriate laughter.

Both PWS and AS can occur as a result of deletion or UPD (less common) in **15q11**.

If the deletion occurs in paternal chromosome 15, the affected individual has PWS, whereas AS results from a deletion occurring only in the maternal chromosome 15.

Expansion of a Trinucleotide Repeat

Human DNA appears as repeat sequences, two or three bases repeated over and over again. Expansion of such trinucleotide repeats can cause diseases, e.g.

Trinucleotide repeat disorders	Trinucleotide repeat basepairs
Fragile X syndrome	CGG
Huntington's disease	CAG
Myotonic dystrophy	CTG
Friedreich ataxia	GAA

Although an increase in the number of the three repeated bases is at the heart of each disorder, the molecular mechanism differs.

Fragile X Syndrome

It is the **most common cause of inherited intellectual disability in males**.

Features include:

- Characteristic facial findings (large head; prominent forehead, jaw, and ears),
- Large testicular volume (macroorchidism),
- Mild connective tissue disorder, including lax joints
- A characteristic neurobehavioral profile, including intellectual disability (ranging from mild to profound) and autism spectrum disorders.

FRAX results from a failure to express FMRP, the protein product of the FMR1 gene. "Fragile X Mental Retardation Protein" (FMRP) shuttles mRNA between the nucleus and cytoplasm in the central nervous system and other areas (incl. testis) during early embryonic development.

The trinucleotide repeats **tend to expand during DNA replication** due to slippage.

(IV) Teratogenic Agents

Chemical, physical, or biologic agents that have the potential to damage embryonic tissue and result in congenital malformations are known as Teratogens. These include:

- Drugs (prescription and nonprescription);
- Intrauterine infections (rubella);
- Maternal diseases, such as diabetes mellitus; and
- Environmental substances, such as alcohol and heavy metals.

i) Drugs

Fetal alcohol spectrum disorder occurs due to comsumption of alcohol during pregnancy. Lesser consumption during all or part of the gestation will lead to milder symptoms. To cause the full-blown fetal alcohol syndrome, pregnant women must drink alcohol throughout the pregnancy.

Warfarin, retinoic acid, and phenytoin are additional teratogenic agents.

ii) Maternal Infections

Few major potentially teratogenic infections in utero include rubella, cytomegalovirus, toxoplasma, herpes simples, varicella among others.

iii) Maternal Disease

Maternal diabetes mellitus and maternal phenylketonuria can result in congenital anomalies in the fetus. Strict control of these disorders before and during pregnancy protects the developing child.

iv) Radiation

- There is an increased risk of microcephaly, mental retardation, and skeletal malformations.
- It is estimated that approximately **25 rad** of exposure causes these effects.
- The dose from routine radiologic diagnostic examinations is in the millirad range.

CHAPTER 14 GENETIC ASSESSMENT

Individuals referred to a geneticist because of suspicion of a genetic disorder are called **probands**; individuals who come for genetic counseling are **consultands**.

(I) Prenatal Counseling

i) Familial Factors

Consanguinity does not increase the likelihood of offspring having any particular single genetic disorder, **but it may increase the chance that a child will be born with a rare autosomal recessive (AR) condition**, as the mutated gene segregates through that family. *The risk of first cousins producing a child with an AR disorder is 1 in 64.*

People of Ashkenazi Jewish background may choose to be screened for heterozygosity for a panel of AR disorders, including Tay-Sachs disease, Niemann-Pick disease, Bloom syndrome, Canavan disease, Gaucher syndrome, cystic fibrosis, Fanconi anemia, and familial dysautonomia.

People of African-American ancestry may choose to be screened for sickle cell anemia.

ii) Screening

- High levels of AFP associated with
    - Neural tube defects (NTDs), and
    - Disruption of fetal integument e.g. omphalocele or gastroschisis,
- Low levels of AFP were found to be associated with fetal aneuploidy.

Low maternal serum AFP detects 50% of fetuses with autosomal trisomies:

- Down syndrome,
- Trisomy 18,
- Trisomy 13.

Three other proteins— were added to the maternal serum screening to create **the quad screen** with sensitivity 80%.

- Unconjugated estriol (uE3),
- Inhibin A, and
- Human chorionic gonadotropin (HCG)

The quad screen is done in the *second trimester*.

During the first trimester, measurement of a fluid collection of the posterior neck of the developing fetus is termed ***nuchal translucency test***. An increase in the nuchal translucency is a marker for chromosomal anomalies as well as genetic and structural abnormalities in the fetus. This association provided a noninvasive first trimester marker.

Testing for abnormalities with two additional first trimester analytes, **free β-HCG and PAPP-A** (pregnancy associated plasma protein) has enhanced first trimester screening to a detection rate of almost 90%.

A combination of first and second trimester screening together with the women's age produces an individualized risk factor.

Both of these first and second trimester screening tests are just screens to identify increased

risk. If this risk is high, or if there is concern about fetal anomalies from family history, ultrasound, or serum screening, then a more definitive test, either chorionic villus sampling (CVS) or amniocentesis, is offered as further testing (but with risk of pregnancy loss due to procedure).

Fetal cells are usually tested for chromosomal abnormalities by cytogenetic techniques, but the use of *chromosomal microarray* is becoming more common. Biochemical testing for a known family history of an inherited metabolic disorder can also be done on the fetal cells, as well as molecular screening for familial mutations for known disorders

It is common for pregnant women to have a screening sonogram at 18 weeks' gestation. An **anomaly scan** is done to look for congenital anomalies. Brain, heart, kidneys, lungs, and spine are examined.

iii) Maternal Factors

The following conditions may necessitate genetic counselling.

- Acute illnesses such as varicella, Lyme disease, and cytomegalovirus.
- Maternal smoking,
- Alcohol use, and
- Maternal exposure to radiation or chemicals.

(II) Postnatal—Newborn and Infant

Consultation with a geneticist for a newborn or infant may be prompted by many different findings, including

- Presence of a malformation,
- Abnormal results on a routine newborn screening test,
- Abnormalities in growth (e.g., failure to gain weight, increase in length, or abnormal head growth),
- Developmental delay,
- Blindness or deafness, and
- Family history of a genetic disorder or chromosomal abnormality or (as a result of prenatal testing) the presence of a genetic disorder or chromosomal abnormality in the infant.

(III) Adolescent and Adult

Adolescents and adults may be seen by a geneticist for evaluation of a genetic disorder that has late onset.

- Huntington disease
- Adult-onset spinal muscular atrophy, present later in life.
- Hereditary blindness (retinal degenerative diseases)
- Deafness (Usher syndrome, neurofibromatosis type 2) may not show significant symptoms until adolescence or early adulthood.

Genetic consultation also may be prompted for a known family history of a hereditary cancer syndrome (breast, thyroid, colon, and ovarian cancers).

A known family history or personal history of a genetic disorder or chromosomal abnormality

might prompt testing in anticipation of pregnancy planning.

(IV) General Approach

i) Family History

- A pedigree is drawn based on family history helps determine if there is an autosomal dominant, AR, X-linked, or sporadic disorder.
- When a child is affected with the new onset of an AD disorder, it is necessary to closely examine the parents to check for the presence of manifestations.
    - If the parents are unaffected, the child's condition is most likely the result of a new mutation; the risk of recurrence is extremely low (*although not 0, because of the possibility of gonadal mosaicism in one of the parents*).
    - When one parent is affected (even mildly so due to varying penetrance), the recurrence risk rises to 50%.
- A history of more than two spontaneous abortions increases the risk that one of the parents has a balanced translocation and the spontaneous abortions are due to chromosomal abnormalities in the fetus.

ii) Pregnancy

Follow-up is needed if an amniocentesis or CVS reveals abnormal results. A fetal ultrasound may detect a malformation that needs follow-up when the infant is born.

iii) Medical History

- Children with neuromuscular disorders may have a normal period followed by increasing weakness or ataxia.
- Children with lysosomal storage diseases, such as the mucopolysaccharidoses, **often have recurrent ear infections and can develop sleep apnea.**

iv) Development

The onset of the disability may not always be present from the newborn period. Many inborn errors of metabolism, including *storage disorders*, cause developmental manifestations after a period of normal development.

v) Physical Examination

A careful and thorough physical examination is necessary for all patients with signs, symptoms, or suspicion of genetic disease.

(V) Laboratory Evaluation

i) Chromosome Analysis

Lymphocytes obtained from blood are the usual source but bone marrow aspiration, skin biopsy (fibroblasts), or, prenatally, from amniotic fluid or chorionic villi also can be used. Cells are placed in culture medium and stimulated to grow, their division is arrested in **either metaphase or prophase**, slides are made, the chromosomes are stained with Giemsa or other dyes, and the chromosomes are analyzed.

- In metaphase, chromosomes are short, squat, and easy to count. Metaphase analysis should be ordered in children whose features suggest a known aneuploidy syndrome, such as a trisomy or monosomy.
- Chromosomes analyzed in prophase are long, thin, and drawn out; analysis gives far more details than are seen in metaphase preparations. ***Prophase analysis is ordered in individuals with multiple congenital anomalies without an obvious disorder***.

ii) Fluorescent In Situ Hybridization

FISH allows the identification of the presence or absence of a specific region of DNA.

- A complementary DNA probe specific for the region in question is generated, and a fluorescent marker is attached.
- The probe is incubated with cells from the subject and viewed under a microscope.
- The bound probe fluoresces, allowing the number of copies of the DNA segment in question to be counted.

This technique is useful in **Prader-Willi syndrome and Angelman syndrome**, in which a deletion in a segment of **15q11** occurs, and in **velocardiofacial (DiGeorge) syndrome**, which is associated with a deletion of **22q11**.

Spectral karyotyping is a method similar to FISH but uses different probes, being more helpful in identifying ***translocations***.

iii) Microarray Comparative Genomic Hybridization

- Microarray comparative genomic hybridization (array CGH) has supplanted prophase analysis in cases in which a subtle chromosomal deletion or duplication (copy number variant) is suspected.
- In array CGH, DNA from the individual being studied and a normal control is labeled with fluorescent markers and hybridized to thousands of FISH-like probes for sequences spread around the genome.
- The probes are derived from known genes and noncoding regions. By analyzing the ratio of intensity of the fluorescent marker at each site, it is possible to determine whether the individual in question has any difference in copy number compared with the control DNA.

iv) Direct DNA Analysis

Using polymerase chain reaction, the specific gene in question can be amplified and analyzed.

The website www.genetests.org lists disorders in which direct DNA analysis is available and identifies laboratories performing such testing.

CHAPTER 15 CHROMOSOMAL DISORDERS

Fifty percent of spontaneous abortuses have chromosomal abnormalities, the most common being 45,X (TS); it is *estimated that 99% of 45,X fetuses are spontaneously aborted.*

In newborns and older children, features that suggest the presence of a chromosome anomaly include low birth weight (small for gestational age), failure to thrive, developmental delay, and the presence of three or more congenital malformations.

(I) Definitions

i) Robertsonian Translocation

A Robertsonian translocation, which occurs when the long arms (q) of two acrocentric chromosomes fuse at the centromeres, and the short arms (p), containing copies of ribosomal RNA, are lost.

ii) Mosaicism

If an individuals with two genetically different populations of cells, it is called Mosaicism. For example, ~1-2% cases with Down's syndrome have mosaicism, i.e. one population of cells with trisomy 21 and one with a normal chromosome complement.

Mosaicism can result from

- A nondisjunctional event that occurs after fertilization and after a few cell divisions,
- From trisomic rescue.

(II) Abnormalities in Number (Aneuploidy)

Aneuploidy is a change in the number of chromosomes that results from nondisjunction. A cell may have one (monosomy) or three (trisomy) copies of a particular chromosome.

i) Trisomies

a) Down's Syndrome

- DS is the most common abnormality of chromosomal number.
- Most cases (92.5%) are due to nondisjunction; mostly occurring during maternal meiosis-I phase.
- As a result of nondisjunction, there are three copies of chromosome 21 (trisomy 21); using standard cytogenetic nomenclature, trisomy 21 is designated 47,XX,+21 or 47,XY,+21.
- In 4.5% of cases, the extra chromosome is part of a **robertsonian translocation,** which occurs when the long arms (q) of two acrocentric chromosomes fuse at the centromeres, and the short arms (p), containing copies of ribosomal RNA, are lost.
- The parents of DS infants with translocations should have a karyotype to exclude a balanced translocation.

Children with DS are most likely diagnosed in the newborn period. These infants tend to have normal birth weight and length, but are **hypotonic**. The characteristic facial appearance features are shown in figure:

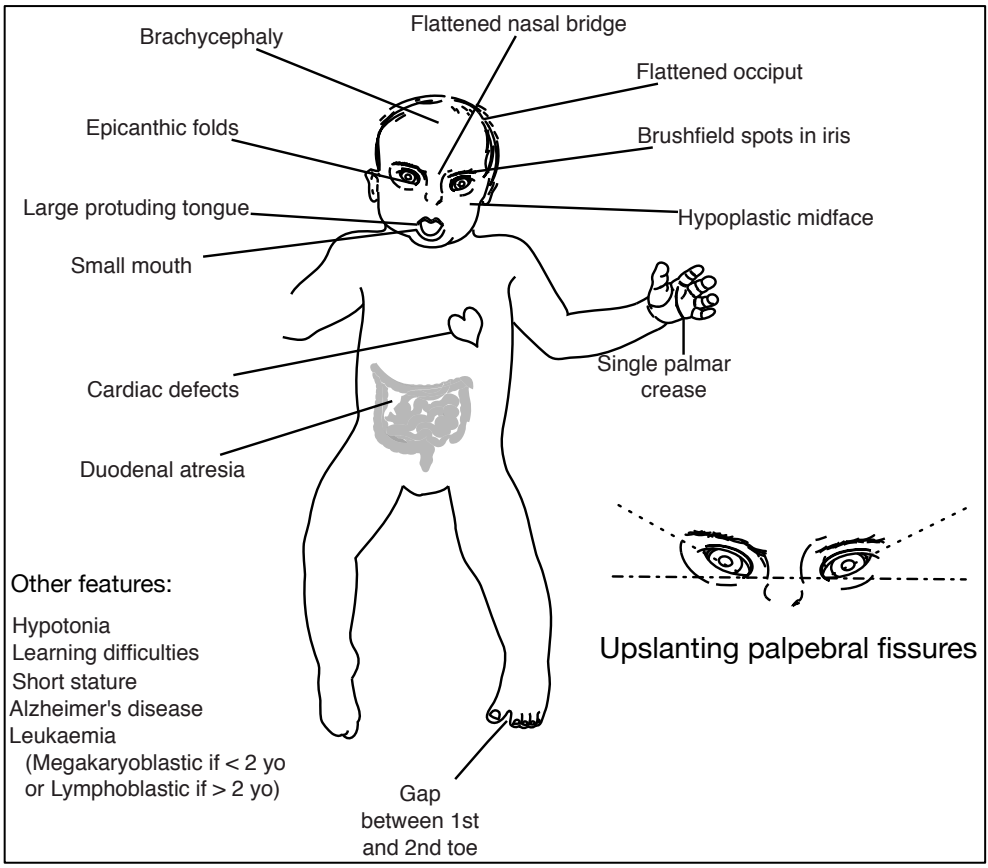


Figure. Some features of Down's syndrome.

Infants also have short broad hands, often with a **single transverse palmar crease**, and a **wide gap between the first and second toes**. The severe hypotonia may cause feeding problems and decreased activity.

- Approximately 50% cases have congenital heart disease , including atrioventricular canal, ventriculoseptal or atrioseptal defects, and valvular disease.
- Approximately 10% of newborns with DS have gastrointestinal tract anomalies . The three most common defects are duodenal atresia, annular pancreas, and imperforate anus.
- 4% to 18% of infants with DS are found to have congenital hypothyroidism, which is identified as part of the newborn screening program. Acquired hypothyroidism can also occur and thyroid function testing is carried out periodically during the child's life.

Polycythemia at birth (hematocrit levels >70%) is common and may require treatment. Some infants with DS show a **leukemoid reaction**, with markedly elevated white blood cell counts. Although this resembles congenital leukemia, it is a self-limited condition, resolving on its own over the first month of life.

- Increased risk of leukemia:
    - In children with DS < 2 years of age, the type is generally **acute megakaryoblastic leukemia;**
    - In individuals > 3 years of age, the types of leukemia are similar to those of other children, with **acute lymphoblastic leukemia** (ALL) being the predominant type.
- Those affected develop Alzheimer-like features after 35 years of age.

- The recurrence risk for parents who have had a child with DS depends on the child's cytogenetic findings.
    - *If the child has a robertsonian translocation, chromosomal analysis of both parents must be performed.*
    - **Risk is higher if mother is the carrier of the translocation.**

Table. Clinical Findings in Trisomies 21, 18, and 13.

Features	Trisomy 21	Trisomy 18	Trisomy 13
Incidence	1 in 200	1 in 3000	1 in 5000
General	Mental retardation, short stature	Severe developmental delays, Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1yr	Severe developmental delays, Renal abnormalities. Nuclear projections in neutrophils. Only 5% live >6 mo
Head & face	Protruding tongue, epicanthic folds, protuding tongue, small mouth, flat nasal bridge, flattened occiput, hypoplastic midface	Small and premature appearance, Tight palpebral fissures, Narrow nose and hypoplastic nasal alae, Narrow bifrontal diameter, Prominent occiput, Micrognathia, Cleft lip or palate	Scalp defects (e.g., cutis aplasia) Microphthalmia, Corneal abnormalities. Cleft lip and palate (60%–80%) Microcephaly, Sloping forehead, Holoprosencephaly (arrhinencephaly), Capillary hemangiomas Deafness
Eyes	Epicanthic folds, Brushfield's spots	Short narrow, palpebral fissures, corneal opacity.	Hypotelorism, iris coloboma, retinal dysplasia
Chest	40% septal defects, endocardial cushion defect	Congenital heart disease (e.g., VSD, PDA, and ASD) **in 80%.** Short sternum, small nipples	Congenital heart disease (e.g., VSD, PDA, and ASD) **in 80%.** Thin posterior ribs (missing ribs)
Extremities	Clinodactyly of 5th finger, single palmar crease, wide gap b/w 1st and 2nd toe.	Flexion deformity, Limited hip abduction, Clinodactyly and overlapping fingers; index over third, fifth over fourth Rocker-bottom feet, hypoplastic nails	Overlapping of fingers and toes (clinodactyly). Polydactyly, Hypoplastic nails, hyperconvex nails.
Other	Anal/duodenal atreasia, increased leukemia & Alzheimer's risk.	Esophageal atresia, horse-shoe kidney, spina bifida, umblical inguinal hernia.	Exomphalos, Polycystic kidney
Survival	Long	90% die within 1st year	80% die in 1st year

ASD, Atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

b) Trisomy 18

Trisomy 18 (47,XX,+18 or 47,XY,+18) is the second most common autosomal trisomy.

More than 95% of conceptuses with trisomy 18 are spontaneously aborted in the first trimester. Less than 10% of affected infants survive until their first birthday.

Clinical features include:

- Hypertonia,
- Prominent occiput,
- Micrognathia,
- Low-set and malformed ears,
- Short sternum,
- Rocker-bottom feet,
- Hypoplastic nails, and
- Characteristic clenching of fists—the second and fifth digits overlap the third and fourth digits.

c) Trisomy 13

The third of the common trisomies, trisomy 13 (47,XX,+13 or 47,XY,+13). It is usually fatal in the first year of life.

Infants with trisomy 13 have numerous malformations. These infants are small for gestational age and can have:

- Microcephaly
- Midline facial defects such as
    - Cyclopia (single orbit),
    - Cebocephaly (single nostril), and
    - Cleft lip and palate are common, as are
    - Midline central nervous system anomalies, such as alobar holoprosencephaly.
- The forehead is generally sloping, ears are often small and malformed, and microphthalmia or anophthalmia may occur.
- Postaxial polydactyly of the hands is common, as is clubfeet or rocker-bottom feet.
- Hypospadias and cryptorchidism are common in boys, hypoplasia of the labia minora in girls.
- Congenital heart disease.
- Punched-out scalp lesion over the occiput called **aplasia cutis congenital** (highly specific for Trisomy 13);

Aplasia cutis congenital in conjunction with polydactyly and facial findings are *essentially pathognomonic for the diagnosis of trisomy 13*.

d) Klinefelter Syndrome

- **KS is the most common genetic cause of hypogonadism and infertility in men**. It is caused by the presence of an extra X chromosome (47,XXY), which can arise from a nondisjunction in either the sperm or the egg.
- Before puberty, boys with KS are phenotypically indistinguishable from the rest of the

population and the diagnosis is often made when the boy is 15 or 16 years of age.

- Clinical features include:
    - Tall, with long limbs.
    - Gynecomastia during adolescence or adulthood
    - Failure to develop secondary sexual characteristics, i.e.
        - Facial hair
        - Deepening of voice
        - Libido
    - Osteopenia and osteoporosis can develop during adulthood.
- Because of these findings, testosterone supplementation is indicated.
- Failure of growth and maturation of the testes leads to testosterone deficiency and failure to produce viable sperm.
- Through the use of isolation of viable sperm through testicular biopsy, coupled with in vitro fertilization and intracytoplasmic sperm injection, it is possible for men with KS to father children of a normal chromosome complement.

ii) Monosomies

a) Turner Syndrome (TS)

TS is the only condition in which a monosomic conceptus survives to term; however, 99% of embryos with 45,X are spontaneously aborted.

Affected women tend to have normal intelligence and life expectancy.

Turner's syndrome typically has:

- Short stature
- A characteristic facial appearance with low-set, mildly malformed ears,
- Triangular face,
- Flattened nasal bridge, and
- Epicanthal folds.
- Webbing of the neck, with or without **cystic hygroma**,
- A shield-like chest with widened internipple distance, and
- Puffiness of the hands and feet.

Internal malformations include:

- Congenital heart defect
    - Coarctation of the aorta (most common)
    - Bicuspid aortic valve;
    - Poststenotic aortic dilation with aneurysm
- Renal anomalies
- Horseshoe kidney,
- Acquired hypothyroidism.
- Gonadal dysgenesis (streak gonads)

Gonadal dysgenesis leads to estrogen deficiency, which causes failure to develop secondary sexual characteristics and results in amenorrhea.

Estrogen replacement is required to complete secondary sexual development but infertility cannot be corrected.

Assisted reproductive technology using donor ova has allowed women with TS to bear children.

Turner syndrome is not associated with advanced maternal age. It is believed that the 45,X karyotype results from a loss of either an X or a Y chromosome after conception; that is, *it is a postconceptual* ***mitotic*** *(rather than meiotic) nondisjunctional event.*

Features	Klinefelter's (47, XXY)	Turner's (45, XO)
Incidence	1 in 1000	1 in 2500
Associations	Increasing maternal age	Increasing maternal age
Phenotype	Tall, with long limbs, gynecomastia, underdeveloped 2° sexual characteristics, sparse facial hair	Short stature, webbed neck, shield chest, increased carrying angle of elbows, puffy hands and feet, hyperconvex nails.
Gonads	Hypoplastic testis, with Leydig cell Hyperplasia, Sertoli cell hypoplasia, Azoospermia.	Streak ovaries with deficient follicles, gonadal dysgenesis.
Reproductive function	Infertile	Amenorrhea and infertile
Congenital abnormality	No increased incidence	Coarctation of aorta
I.Q.	10-20 points below normal	Mildly deficient to normal

(III) Chromosomal Deletions

i) Cri du Chat Syndrome

A deletion in the short arm of chromosome 5 is responsible for cri du chat syndrome, with its characteristic catlike cry during early infancy, the **result of tracheal hypoplasia**.

Other clinical features include low birth weight and postnatal failure to thrive, hypotonia, developmental disability, microcephaly, and craniofacial dysmorphism, including ocular hypertelorism, epicanthal folds, downward obliquity of the palpebral fissures, and low-set malformed ears.

Larger deletions are associated with more severe expression. Most cases arise de novo.

ii) Aniridia Wilms Tumor Association

WAGR syndrome (**W**ilms tumor, **A**niridia, **G**enitourinary anomalies, and mental **R**etardation) is caused bya de novo deletion of 11p13.

Genitourinary abnormalities include cryptorchidism and hypospadias. Patients often have short stature, and half may have microcephaly. *Wilms tumor develops in 50% of patients* with aniridia, genitourinary abnormalities, and mental retardation.

iii) Chromosome 22q11 Deletion Syndromes

Also known as: Velocardiofacial syndrome and DiGeorge syndrome. Most commonly arises de novo, but can be Autosomal dominant.

DiGEORGE MALFORMATION SEQUENCE

Damage to the third and fourth pharyngeal pouches, embryonic structures that form parts of the cranial portion of the developing embryo, leads to abnormalities in the developing face, thymus gland, parathyroid glands, and the conotruncal region of the heart.

- Common features include
    - Clefting of the palate with velopharyngeal insufficiency,
    - Conotruncal cardiac defects (including truncus arteriosus, ventriculoseptal defect, tetralogy of Fallot, and right-sided aortic arch), and
    - A characteristic facial appearance, including:
        - A prominent nose
        - A broad nasal root.
- Speech and language difficulties are common, as is mild intellectual impairment
- About 70% have immunodeficiencies, largely related to **T-cell dysfunction**. Psychiatric disturbances, including schizophrenia and bipolar disorder may also be seen.

The deletion that occurs in chromosome 22q11 is **usually too small to be seen by standard chromosome analysis**; either ***fluorescent in situ hybridization or chromosomal microarray is needed to identify the deletion***.

A gene called TBX1 is within the deleted sequence. It is believed that deletion of one copy of TBX1 is responsible for many of the features of the various 22q11 deletion syndromes.

CHAPTER 16 DYSMORPHOLOGY

Dysmorphology is the specialty focusing on recognition of patterns of congenital malformations, and dysmorphic features that characterize a particular syndrome. Dysmorphology syndromes have a unifying, identifiable etiology.

This etiology may be:

- Presence of a mutation in a single gene, e.g. Rett syndrome
- By the deletion or duplication of chromosomal material, e.g. Prader-willi syndrome,
- By exposure to a teratogenic substance during embryonic development.

(I) Definitions

i) Deformations

Deformations arise as a result of environmental forces acting on normal structures. They occur later in pregnancy or after delivery. e.g. **plagiocephaly** (rhomboid shaped head). Deformations often resolve with minimal intervention, while malformations often require surgical and medical management.

ii) Malformation

A malformation sequence is the end result of a malformation that has secondary effects on later developmental events.

For example: Pierre Robin sequence comprises a triad of anomalies (micrognathia, U-shaped cleft palate, and obstructive apnea), which results from a single malformation, the failure of the jaw to grow at a critical time during gestation.

Unlike deformations, malformations often require surgical and medical management.

iii) Association

An association differs from a syndrome in that no single underlying etiology explains the recognizable pattern of anomalies that occur together commonly and not by chance. The VACTERL association (**V**ertebral anomalies, **A**nal atresia, **C**ardiac defects, **T**racheo**E**sophageal fistula, **R**enal anomalies, and **L**imb anomalies) is an example of a group of malformations that occur more commonly together than might be expected by chance.

No single unifying etiology explains this condition, so it is considered an association.

Table. Terms used in dysmorphology
Terms related to the face and head
Canthus: The lateral or medial angle of eye formed by the junction of the upper & lower lids
Columella: The fleshy tissue of the nose that separates the nostrils
Glabella: Bony midline prominence of the brows
Nasal alae: The lateral flaring of the nostrils
Nasolabial fold: Groove that extends from the margin of the nasal alae to the lateral aspects of the lips
Hypertelorism: Increased distance between the pupils of the two eyes
Philtrum: The vertical groove in the midline of the face between the nose and the upper lip
Synophrys: Eyebrows that meet in the midline
Telecanthus: A wide space between the medial canthi

Terms related to the extremities

Amelia—missing limb (melia means 'limb')

Brachydactyly: Condition of having short digits

Clinodactyly: A digit is crooked and curves toward or away from adjacent digits

Polydactyly: The condition of having six or more digits on an extremity

Syndactyly: The condition of having two or more digits at fused regardless of extend of fusion.

(II) History and Physical Examination

i) Pregnancy History

The history of the pregnancy and birth can reveal multiple risk factors that are associated with dysmorphology.

Small for gestational age infants may have a chromosome anomaly or may have been exposed to a teratogen.

Large for gestational age infants may be infants of diabetic mothers or have an overgrowth syndrome, such as Beckwith-Wiedemann syndrome.

As a woman gets older there is increased risk of nondisjunction leading to trisomies. **Advanced paternal age may be associated with the risk of a new mutation leading to an autosomal dominant trait.**

ii) Family History

A pedigree comprising *at least three generations* should be constructed, searching for similar or dissimilar abnormalities in first- and second-degree relatives. A history of pregnancy or neonatal losses should be documented.

iii) Physical Examination

When examining children with dysmorphic features, the following approach should be used.

a) Growth

Anthropometric measures should be taken and plotted on appropriate growth curves.

- Small size or growth restriction may be secondary to a chromosomal abnormality, skeletal dysplasia, or exposure to toxic or teratogenic agents.
- Larger than expected size suggests an overgrowth syndrome (Sotos or Beckwith-Wiedemann syndrome) or, in the newborn period, might suggest a diabetic mother.

***The clinician should note if the child is proportionate**:*

- Limbs that are too short for the head and trunk imply the presence of a short-limbed bone dysplasia, such as achondroplasia.
- A trunk and head that are too short for the extremities suggest a disorder affecting the vertebrae, such as spondyloepiphyseal dysplasia.

b) Craniofacial

- The size and shape of head is noted
- Careful assessment of the distance between the eyes (inner canthal distance) and the

pupils (interpupillary distance) may confirm the impression of:

- Hypotelorism (eyes that are too close together), which suggests a defect in midline brain formation, or
- Hypertelorism (eyes that are too far apart).

- The length of the palpebral fissure should be noted and may help define *whether the opening for the eye is short, as is found with fetal alcohol syndrome*, or excessively long, as in Kabuki makeup syndrome (short stature, mental retardation, long palpebral fissures with eversion of lateral portion of lower lid).
- The palpebral fissures may be slanting:
  - Upward (Down syndrome), or
  - Downward (Treacher Collins syndrome).
- Nasal bridge, which can be:
  - Flattened (Down syndrome, fetal alcohol syndrome, etc), or
  - Prominent as in velocardiofacial syndrome.
- The ears should be checked for size, shape, position (*low-set ears are below a line drawn from the outer canthus to the occiput*), and orientation.
- The mandibular region is the area from the lower portion of the ears bounded out to the chin by the mandible. In most newborns, the chin is often slightly retruded (that is, slightly behind the vertical line extending from the forehead to the philtrum).
  - If this retrusion is pronounced, the child may have the Pierre Robin malformation sequence.

iv) Neck

Examination of the neck may reveal webbing, a common feature in Turner syndrome and Noonan syndrome.

v) Trunk

The chest may be examined for symmetry and shape:

- Shield-like chest in Turner's syndrome and Noonan syndrome
- Pectus deformity is common in Marfan syndrome.

vi) Extremities

- Multiple contractures also are found with *arthrogryposis multiplex congenital.*
- Radioulnar synostosis, an inability to pronate or supinate the elbow, occurs in fetal alcohol spectrum disorder and in some X chromosome aneuploidy syndromes.
- Examination of hands may reveal:
  - Polydactyly (the presence of extra digits) usually occurs as an isolated autosomal dominant trait but also can be seen in *trisomy 13.*
  - Oligodactyly (a deficiency in the number of digits) is seen in:
    - Fanconi syndrome (anemia, leukopenia, thrombocytopenia, and associated heart, renal, and limb anomalies—usually radial aplasia and thumb malformation or aplasia)
    - Secondary to intrauterine amputation, which may occur with amni-

otic band disruption sequence.

- Syndactyly (a joining of two or more digits) is common to many syndromes, including Smith-Lemli-Opitz syndrome
- Palmar crease patterns may show:
    - A transverse palmar crease, indicative of hypotonia during early fetal life, is seen in approximately 50% of children with Down syndrome *(and 10% of individuals in the general population)*.
    - A characteristic palmar crease pattern is also seen in fetal alcohol spectrum disorder.

vii) Genitalia

Hypospadias is common as an isolated defect.

If there is an associated cryptorchidism with hypospadias, then possibility of a syndrome should be suspected.

(III) Laboratory Evaluation

- Radiologic imaging:
    - Ultrasound evaluations of the head and abdomen to look for anomalies in the brain, kidney, bladder, liver, and spleen.
    - Skeletal radiographs should be performed if there is concern about a possible skeletal dysplasia.
    - Magnetic resonance imaging may be indicated in children with neurologic abnormalities or a spinal defect. The presence of craniosynostosis may indicate a computed tomography scan of the head.
- ECG and Echocardiogram if pathologic heart murmur.
- Chromosome analysis
- Microarray comparative genomic hybridization
- Direct DNA analysis can be performed to identify specific mutations.
- For those patients for whom testing does not yield a diagnosis, whole-exome sequencing or whole-genome sequencing is emerging as good test.

i) Diagnosis

Clinical geneticists have attempted to resolve the difficulty in diagnosing by developing scoring systems, cross-referenced tables of anomalies that help in the development of a differential diagnosis, and computerized diagnostic programs.

An accurate diagnosis is important for:

- It offers an explanation to the family why their child was born with congenital anomalies and allays parental guilt.
- It allows anticipation of medical problems associated with a particular syndrome and appropriate screening.
- It permits genetic counseling to be done to identify the risk to future children and permits prenatal testing to be done for the disorders for which it is available.

CHAPTER 17 METABOLIC ASSESSMENT

- Genetic metabolic disorders result from the deficiency of an enzyme, its cofactors, or biochemical transporters that lead to the deficiency of a required metabolite, the buildup of a toxic compound, or a combination of both processes
- Inborn Errors of Metabolism (IEMs) are frequent causes of sepsis-like presentations, mental retardation, seizures, and neurologic impairment and death.
- With the exception of phenylketonuria (PKU), and medium chain acyl-CoA dehydrogenase (MCAD) deficiency are relatively common.
- Delay in diagnosis may result in end organ damage including progressive neurologic injury or death.

Table. Some hypoglycemia causing metabolic disorders

Disorder	Deficiency of	Accumulation of	Result
Medium-chain fatty acid oxidation defects	Fat for energy		Use of glucose with consequent hypoglycemia
Long-chain fatty acid oxidation defects	Fat for energy	Long-chain fats	Use of glucose with consequent hypoglycemia; mitochondrial dysfunction in liver, heart, etc., leading to organ dysfunction
Glycogen storage disease	Glucose to prevent fasting hypoglycemia	Glycogen resulting in storage in liver, muscle, heart	Risk of hypoglycemic brain injury and storage tissue dysfunction
Ketone utilization disorders	Fat for energy	Ketones	Risk of hypoglycemic brain injury; profound metabolic acidosis and reversible neurologic dysfunction
Galactosemia		Galactose	Elevated galactose leads to severe hepatic dysfunction, neurologic injury, and impaired immune response

Table. Some cellular compartment metabolic disorders

Disorder	Deficiency/accumulation	Result
Mitochondrial disease	Deficiency of ATP (energy) in affected tissues	Failure of affected tissues to carry out normal functions, e.g., muscle weakness, failure of relaxation of blood vessel muscles
Lysosomal storage disorders	Tissue-specific accumulation of compound not metabolized by lysosome	Cell type–specific damage and dysfunction as a result of lysosomal failure and reaction to waste product buildup

(I) Symptoms and screening investigations

The hypoglycemic and intoxicating (encephalopathy) metabolic disorders should be considered in all neonates presenting with

- Lethargy,
- Poor tone,
- Poor feeding,
- Hypothermia,
- Irritability, or
- Seizures.

Inborn errors of metabolism often present:

- A few hours to weeks after birth, often mimicking late-onset sepsis, or
- Intermittent illness separated by periods of being well (in those that survive neonatal period without recognized symptoms).
- Metabolic stress associated with fasting or fever may unmask an inborn error of metabolism during infancy or in older children.
- Introduction of new foods:
    - Fructose or sucrose in the diet may lead to decompensation in hereditary fructose intolerance.
    - Increased protein intake may unmask disorders of ammonia detoxification, in older children

Inaddition to baseline investigations, such cases should be evaluated by:

- Plasma ammonia,
- Blood glucose, and
- Anion gap.

Significant ketosis in the neonate is unusual and suggests an ***organic acid disorder****.*

Similarly specific metabolic disorders predispose to cardiomyopathy, myopathy, hepatopathy, developmental delay, sepsis and developmental regression; appropriate evaluation should be tailored to the clinical presentation.

(II) Types of Clinical Presentation of Inborn Errors

i) Presentation with dysmorphic findings

Congenital malformations or dysmorphic features are not intuitively thought of as symptoms and signs of inborn errors.

Conditions that cause congenital malformations include

- Carbohydrate-deficient glycoprotein syndrome,
- Disorders of cholesterol biosynthesis (Smith-Lemli-Opitz syndrome),
- Disorders of copper transport (Menkes syndrome, occipital horn syndrome),
- Maternal phenylketonuria syndrome,

- Glutaric aciduria II (also known as multiple acyl-coenzyme A [CoA] dehydrogenase deficiency), and
- Several storage diseases.

ii) Energy Deficiency

Disorders involving the energy producting pathways (i.e. carbohydrate metabolism, oxidative phosphorylation, or fatty acid oxidation) may manifest:

- Hypoglycemia,
- Myopathy,
- Cardiomyopathy;
- CNS dysfunction, including mental retardation and seizures;
- Renal tubular acidosis.

a) Ketosis

A mild form of hypoglycemic ketonuric metabolic acidosis can occur normally in the course of a virual illness. In such cases, administration of carbohydrate restores balance.

b) Ketotic hypoglycemia

- Ketotic hypoglycemia is a common condition in which tolerance for fasting is impaired.
- Symptomatic hypoglycemia with seizures or coma occurs when the child encounters a catabolic stress.
- The stress may be significant (viral infection with vomiting) or minor (a prolongation by several hours of the normal overnight fast).
- Ketotic hypoglycemia first appears in the second year of life and occurs in otherwise healthy children.
- It is treated by frequent snacks and the provision of glucose during periods of stress. The pathophysiology is poorly understood.
- Although ketonuria is a normal response to prolonged (not overnight) fasting in older infants and children. A severe form occurring in neonates suggests an organic acid disorder.
- **A high anion gap metabolic acidosis with or without ketosis suggests a metabolic disorder.**
- Although ketone production may be reduced in some fatty acid oxidation disorders, the presence of ketonuria does not exclude this group of disorders.

c) Severe ketosis

It may be the result of disorders of ketone utilization such as:

- Ketothiolase deficiency,
- SCOT (succinyl-CoA:3 ketoacid CoA transferase) deficiency.

In these conditions, which frequently present in the context of fasting, infection with fever, or decreased intake secondary to vomiting and diarrhea, hypoglycemia may be profound.

As ketone bodies accumulate, cyclic vomiting may ensue.

Table. Etiologies of infantile metabolic acidosis due to IEMs.	
Disorder	**Comment**
Methylmalonic acidemia (MMA)	Hyperammonemia, ketosis, neutropenia, thrombocytopenia
Propionic acidemia	Similar to MMA
Isovaleric acidemia	Similar to MMA; odor of sweaty feet
Pyruvate dehydrogenase deficiency	Lactic acidosis, hyperammonemia
Pyruvate carboxylase deficiency	Lactic acidosis, hypoglycemia, and ketosis
Respiratory chain (mitochondrial) disorders	Lactic acidosis, ketosis occasionally seen
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	Moderate acidosis, hypoglycemia, decreased ketosis, possible hyperammonemia
Other fatty acid oxidation defects	Similar to MCAD, with potential hepatic and cardiac disease
Galactosemia	Renal tubular acidosis, Escherichia coli neonatal sepsis, hypoglycemia
3-Hydroxy-3-methyl-glutaryl-CoA lyase deficiency	Severe lactic acidosis, hyperammonemia, hypoglycemia
Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria 2)	Metabolic acidosis, hypoglycemia, lethal renal malformations

iii) Toxic Presentation

The toxic presentation often presents as an **encephalopathy**.

Fever, infection, fasting, or other catabolic stresses may precipitate the symptom complex.

A metabolic acidosis, vomiting, lethargy, and other neurologic findings may be present.

Diagnostic testing is most effective when metabolites are present in highest concentration in blood and urine at presentation.

Abnormal metabolism of amino acids, organic acids, ammonia, or carbohydrates may be at fault.

a) Hyperammonemia

The severity of hyperammonemia may provide a clue to the etiology:

Severe Neonatal Hyperammonemia

- Levels of blood ammonia are >10 times normal in the neonatal period (>1000 µmol/L).
- Infants with genetic defects in urea synthesis, transient neonatal hyperammonemia, and impaired synthesis of urea and glutamine secondary to genetic disorders of organic acid metabolism can have
- Poor feeding, hypotonia, apnea, hypothermia, and vomiting rapidly give way to coma and occasionally to intractable seizures.
- Death occurs in hours to days if the condition remains untreated.

Moderate Neonatal Hyperammonemia

- Moderate neonatal hyperammonemia (range, 200 to 400 µmol/L) is associated with depression of the central nervous system, poor feeding, and vomiting.
- Seizures are not characteristic. Respiratory alkalosis may occur.

Hyperammonemia in Later Infancy and Childhood

- Infants who are affected by defects in the urea cycle may continue to do well while receiving the low-protein intake of breast milk, developing clinical hyperammonemia when dietary protein is increased or when catabolic stress occurs.
- During a crisis, the plasma ammonia level is usually 200 to 500 µmol/L. If a crisis occurs during an epidemic of influenza, the child mistakenly may be thought to have Reye syndrome.
- Older children may have neuropsychiatric or behavioral abnormalities.

Table. Some encephalopathy causing metabolic disorders

Disorder	Deficiency of required:	Accumulation of toxic:	Result
Urea cycle defects		Ammonia	Central nervous system dysfunction, probably mediated through glutamine
Propionic, methymalonic, or other organic acidemias		Organic acids	Systemic or local impairment of mitochondrial function; impaired neurotransmission; impairment of urea cycle
Phenylketonuria	Tyrosine	Phenylalanine	Impairment of tryptophan metabolism leading to serotonin deficiency; defective neurotransmission and white matter damage
Maple syrup urine disease		Leucine	Leucine toxicity leading to cerebral edema

iv) Specific Organ Presentations

Toxic accumulation of metabolites due to block can occur in a variety of organ or system. Symptoms relate to organ-specific or system-specific toxicity and injury, e.g:

- Nervous system (seizures, coma, ataxia),
- Liver (hepatocellular damage),
- Eye (cataracts, dislocated lenses),
- Renal (tubular dysfunction, cysts),
- Heart (cardiomyopathy, pericardial effusion).

Table. Inborn Errors of Metabolism Presenting with Hepatomegaly or Hepatic Dysfunction in Infants

HEPATOMEGALY	HEPATIC FAILURE	JAUNDICE
Glycogen Storage Disease type I	Citrin deficiency Galactosemia	Citrin deficiency Galactosemia
Glycogen Storage Disease type III	Hereditary fructose intolerance	Hereditary fructose intolerance
Mucopolysaccharidosis I and II	Tyrosinemia type 1 (fumarylacetoacetate hydrolase deficiency)	Infantile tyrosinemia (fumarylacetoacetate hydrolase deficiency)
Gaucher and Niemann-Pick diseases	GSD IV (slowly evolving)	Crigler-Najjar disease Rotor, Dubin-Johnson syndromes

(III) Clinical and Lab Investigations

Careful attention should be given to:

- *Loss of developmental milestones* ***(regression)***,
- Cardiac findings: Cardiomyopathy/cardiac failure,
- Neurologic findings: Seizures, Abnormal tone,
- Developmental assessment,
- Visual symptoms,
- Poor developmental progress, global developmental delay,
- Cystic renal malformation, and
- Renal tubular dysfunction.

Table. Initial Diagnostic Evaluation for a Suspected Inborn Error of Metabolism

BLOOD AND PLASMA	URINE
Arterial blood gas with anion gap	Glucose
Glucose Ammonia,	pH
Liver fuction tests	Ketones
Complete blood count with differentials	Reducing substances
Lactate	Organic acids
Pyruvate	Acylglycines
Organic acids	Orotic acid
Amino acids	
Acylcarnitines	
Carnitine	

Normal testing in the well state does not rule out a metabolic disorder. Disorders that may show abnormal test results only during an acute presentation include:

- Urea cycle disorders,
- Ketone utilization disorders,
- Milder forms of fatty acid oxidation defects,
- Intermittent maple syrup urine disease,

(IV) Genetic Aspects of Inborn Errors

i) Mechanisms of Inheritance

- Most inborn errors of metabolism are autosomal recessive.
- X-linked conditions manifest earlier in males.
- In general, carriers of recessive or X-linked (females) diseases are asymptomatic. However, in ornithine transcarbamylase deficiency, females can be symptomatic if they have a low proportion of normal cells in the liver.
- Most disorders of mitochondrial function occur due mutations in autosomal genes.
- Mutations in the mitochondrial DNA also lead to mitochondrial disease, the severity of which depends on the *heteroplasmy* phenomenon.

ii) Genetic testing

Due to the correlation between certain mutations and clinical outcome, genetic testing offers important information for at-risk family members. Identification by Neonatal Screening

iii) Neonatal screening

In most states, infants are tested at 24 to 48 hours. A positive test must be evaluated. Specific follow-up testing and treatment of an affected child depends on the disorder.

Consistent with most screening tests, a significant proportion of infants who have a positive neonatal screening test do not have a metabolic disorder.

Tandem **mass spectrometry** can be used to screen for a core panel of 29 disorders.

Table. Some disorders identifiable by newborn screening programs.
Phenylketonuria (PKU), Tyrosinemia
Maple syrup urine disease (MSUD)
Propionic acidemia
Methylmalonic acidemias
Isovaleric acidemia
Defects of beta oxidation
Galactosemia
Urea cycle defects

iv) Confirmatory and specialized Testing

The neonatal screening tests and cut-off values are designed to be high sensitive. But this has a drawback of higher rate of false positive results. This is why confirmatory testing is necessary.

Table. Specialized Metabolic Testing		
Test	**Substances measured:**	**Helpful in identifying:**
Plasma amino acid profile	Amino acids	PKU, urea cycle defects, tyrosinemias, MSUD, homocystinuria
Plasma total homocysteine	Protein-bound and free homocysteine	Homocystinuria, some forms of methylmalonic acidemia
Urine amino acid profile	Amino acids	Disorders of amino acid renal transport
Plasma acylcarnitine profile	Acylcarnitine derivatives of organic and fatty acid catabolism	Organic acid disorders, fatty acid oxidation disorders
Urine acylglycine profile	Acylglycine derivatives of organic and fatty acid catabolism	Organic acid disorders, fatty acid oxidation disorders
Plasma carnitines	Free, total, and acylated carnitine	Primary and secondary carnitine deficiency— organic acid and fatty acid disorders
Urine organic acid profile	Organic acids	Organic acid, mitochondrial and fatty acid disorders
Urine or blood succinylacetone	Succinylacetone	Tyrosinemia I
Urine oligosaccharide chromatography	Glycosaminoglycans, mucopolysaccharides	Lysosomal storage disorders
MSUD, Maple syrup urine disease; PKU, phenylketonuria.		

Amino acids in the deficient pathway of the organic acid disorders may be abnormal, but often they are normal or may not be diagnostic.

- Amino acid analysis is performed in plasma, urine, and cerebrospinal fluid.
    - The plasma amino acid profile is **most useful** in identifying disorders of amino acid catabolism.
    - The urine amino acid profile is not the test of choice for diagnosing disorders of amino acid or organic acid metabolism.
    - The *urine amino acid profile is helpful in diagnosing primary disorders of renal tubular function*, such as Lowe syndrome and **cystinuria**, as well as secondary disorders of renal tubular function (e.g. cystinosis and Fanconi syndrome).
- Markers of disordered fatty acid oxidation are measured in urine and plasma.
    - Excessive intermediates of fatty acid oxidation and organic acid catabolism are conjugated with glycine and carnitine. The urine acylglycine profile and the plasma acylcarnitine profile reflect this accumulation.
    - In organic acid disorders and fatty acid oxidation disorders, measurement of plasma carnitine may reveal a secondary deficiency of carnitine and abnormal distribution of free and acylated carnitine.
- The plasma free fatty acid profile is helpful in diagnosis of disorders of fatty acid oxidation.
    - Excess 3-OH-butyrate suggests a disorder of ketone metabolism; absence of ketones or decreased amounts of 3-OH-butyrate suggests a fatty acid oxidation disorder.
    - Disorders of organic acid metabolism, such as propionic acidemia and methylmalonic acidemia, have **typical urine organic acid profiles**.
- Disorders of purine and pyrimidine metabolism are suggested by the presence of an abnormal **urinary** profile of purines, pyrimidines and intermediates in their metabolism.
- Storage disorders show abnormalities in **urine** mucopolysaccharides (glycosaminoglycans, glycoproteins), sialic acid, heparan sulfate, dermatan sulfate, or chondroitin sulfate.
- Specific enzymology depends on the disorder; tissue can be either white blood cells or cultured skin fibroblasts, depending on assay.
- In many disorders, an abnormal metabolic profile is consistently present during illness and when the child is well. In some cases, it is only diagnostic during an episode of illness.

(V) Overview of Treatment

The basic principles for treatment of inborn errors of metabolism are:

- Removal of toxic compounds is the **first goal of therapy** in disorders causing toxic encephalopathy. This can be achieved by:
    - Hemodialysis,
    - Hemovenovenous filtration,
    - Administration of alternate pathway agents.
- Another strategy is to enhance deficient enzyme activity through administration of enzyme *cofactors* (e.g., pyridoxine in homocystinuria, tetrahydrobiopterin in PKU).

- Providing missing products is helpful (e.g., tyrosine in the treatment of phenylketonuria).
- A major principle is to decrease flux through the deficient pathway by restricting precursors in the diet.
- Examples include the restriction of protein in disorders of ammonia detoxification and of **amino acid precursors** in the organic acid disorders.

CHAPTER 18 CARBOHYDRATE DISORDERS

(I) Glycogen Storage Diseases

- Glycogen, the storage form of glucose, is found most abundantly in the liver (where it regulates blood glucose levels) and in muscles (where it facilitates *anaerobic* energy).
- Related diseases include those that:
    - Predominantly affect the liver and have a direct influence on blood glucose (types I, VI)
    - Predominantly involve *muscles and affect the ability to do anaerobic work* (types V and VII)
    - Affect the liver and muscles and directly influence blood glucose and muscle metabolism (type III)
    - Diseases that affect various tissues but have no direct effect on blood glucose or on the ability to do anaerobic work (types II and IV)
- Many glycogen storage diseases are characterized by hypoglycemia and hepatomegaly.
- The accumulation of glycogen is stimulated by insulin.
- Glycogenolysis occurs through a cascade initiated by *epinephrine or glucagon*.
- *In the liver and kidneys, glucose-6-phosphatase hydrolyses glucose 6-phosphate to produce glucose, but this enzyme is not present in muscles.*

i) Diagnosis

- The diagnosis of type I or type III glycogen storage disease is suggested by an elevated uric acid, lactate, and triglycerides in blood.
- Muscle biopsy
- Liver biopsy
- DNA mutation testing

ii) Treamtent

Treatment of hepatic glycogen storage disease is aimed at maintaining satisfactory blood glucose levels or supplying alternative energy sources to muscle.

- In glucose-6-phosphatase deficiency (type I), the treatment usually requires nocturnal intragastric feedings of glucose during the first 1 or 2 years of life. Thereafter, snacks or nocturnal intragastric feedings of uncooked cornstarch may be satisfactory. There may be an increased incidence of hepatic tumors (sometimes malignant) in adolescence and adult life.
- Enzyme replacement early in life is effective in Pompe disease (type II), which involves cardiac and skeletal muscle.

Table. Glycogen Storage Diseases (all are autosomal recessive)				
	Defect in	**Organs affected**	**Clinical syndrome**	**Prognosis**
Type 1: von Gierke	Glucose-6-phosphatase	Liver, kidney, GI tract, platelets	Hypoglycemia, lactic acidosis, ketosis, hepatomegaly, hypotonia, slow growth, diarrhea, bleeding disorder, gout, hypertriglyceridemia, xanthomas	Early death from hypoglycemia, lactic acidosis; do well with early diagnosis and strict adherence to dietary therapy; hepatomas may occur in late childhood
Type II: Pompe	Lysosomal α-glucosidase	All; Striated muscle, nerve cells	Symmetrical profound muscle weakness, cardiomegaly, heart failure, shortened P-R interval	Death in the first year of life is usual; milder variants exist; ***therapy with recombinant human α-glucosidase***
Type III: Cori	Debranching enzyme	Liver, muscles	Early in course hypoglycemia, ketonuria, hepatomegaly that resolves with age; may show muscle fatigue.	Very good for hepatic disorder; if myopathy present, it tends to be like that of type I and V
Type IV: Andersen	Branching enzyme	Liver, other tissues	Hepatic cirrhosis starting at several months of age, early liver failure.	Death from hepatic failure in first decade typically
Type V: McArdle	Muscle phosphorylase	Muscle	Muscle fatigue beginning in adolescence	Good, with sedentary lifestyle
Type VI: Hers	Liver phosphorylase	Liver	Mild hypoglycemia with hepatomegaly, ketonuria	Good
Type VII: Tarui	Muscle phosphofructokinase	Muscle	Clinical findings similar to type V	Similar to that of type V
Type VIII	Phosphorylase kinase	Liver	Clinical findings similar to type III, without myopathy	Good

(II) Galactose metabolic disorders

i) Galactosemia

Galactosemia is an **autosomal recessive disease** caused by deficiency of galactose-1-phosphate uridyltransferase.

Clinical manifestations are most striking in a neonate who, when fed milk show:

- Signs of liver failure (hyperbilirubinemia, disorders of coagulation, hypoglycemia),
- Signs of renal tubular function (acidosis, glycosuria, aminoaciduria),
- And cataracts.

Affected infants are at increased risk for death and severe neonatal **Escherichia coli sepsis**.

Major effects on liver and kidney function and the development of cataracts are limited to the first few years of life.

a) Investigations

- Laboratory manifestations of galactosemia depend on dietary galactose intake.
- When galactose is ingested (as lactose), levels of plasma galactose and erythrocyte galactose 1-phosphate are elevated. Hypoglycemia is frequent, and albuminuria is present.
- Galactose frequently is present in the urine and can be detected by a positive reaction for reducing substances without a reaction with glucose oxidase on urine strip tests.
- The absence of urinary reducing substances cannot be relied on to exclude the diagnosis.
- The diagnosis is made if there is significantly decreased **erythrocyte** galactose-1-phosphate uridyltransferase activity.
- DNA testing for the mutations in galactose-1-phosphate uridyltransferase confirms the diagnosis and may be useful in predicting prognosis.
- Renal tubular dysfunction may be evidenced by a normal–anion-gap hyperchloremic metabolic acidosis.

b) Treatment

Elimination of dietary galactose results in rapid improvement.

ii) Galactokinase deficiency

- Galactokinase deficiency, an autosomal recessive disorder, also leads to the accumulation of galactose in body fluids, which results in the formation of galactitol (dulcitol) through the action of **aldose reductase**. Galactitol, acting as an osmotic agent, can be responsible for:
- Cataract formation, and
- Increased intracranial pressure (rarely).
- These are the only clinical manifestations.
- Individuals homozygous for galactokinase deficiency usually develop cataracts after the neonatal period, whereas heterozygous individuals may be at risk for cataracts as adults.

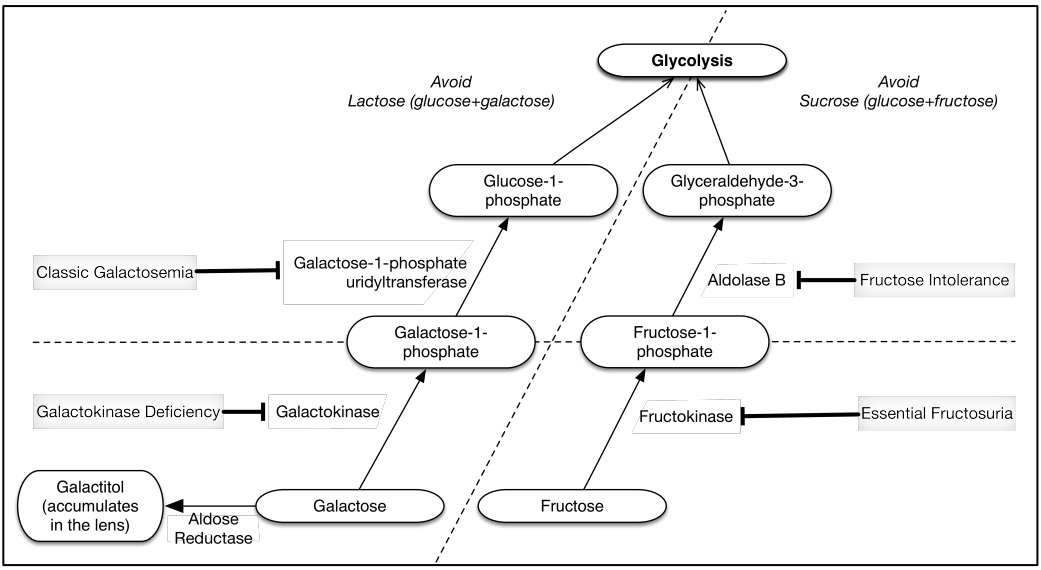


Figure. Galactose and fructose metabolic disorders schematic.

(III) Fructose metabolic disorders

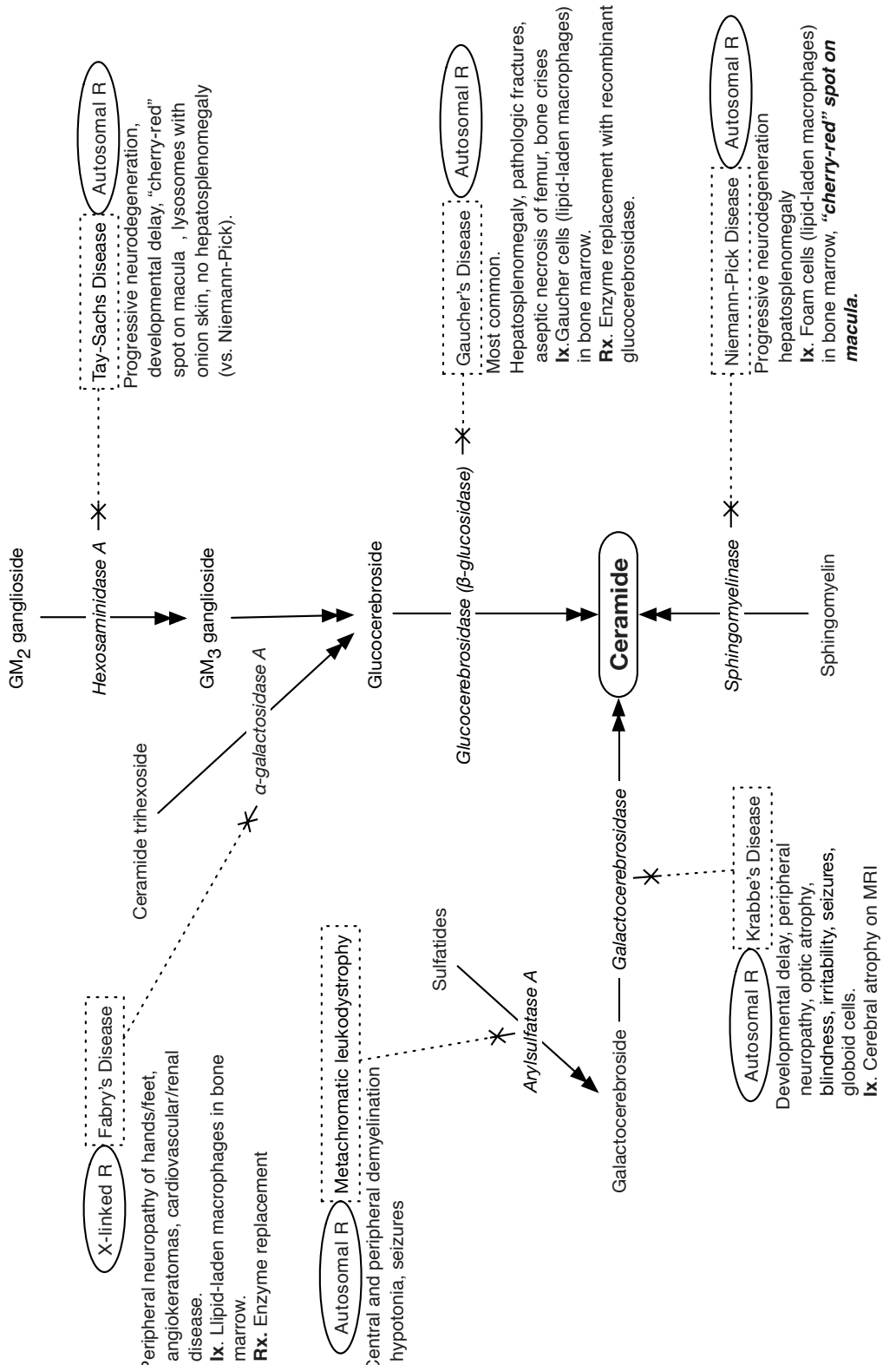
Hereditary fructose intolerance, in many ways, is analogous to galactosemia.

When fructose is ingested, deficiency of fructose-1-phosphate aldolase leads to the intracellular accumulation of fructose 1-phosphate with resultant emesis, hypoglycemia, and severe liver and kidney disease.

Elimination of fructose and sucrose from the diet prevents clinical disease. Fructosuria is caused by fructokinase deficiency, but its deficiency is not associated with clinical consequences.

CHAPTER 19 LYSOSOMAL STORAGE DISEASES

(I) Sphingolipidoses



(II) Mucopolysaccharidoses (MPS)

i) MPS type I (Hurler syndrome)

It is due to deficiency of α-L-iduronidase. **Autosomal recessive.**

a) Clinical features

Patients are normal at birth but subsequently present with:

- Coarse facies,
- **Corneal clouding,**
- Neurodegeneration,
- Hernias,
- Dysostosis multiplex, and
- Hepatosplenomegaly.

b) Investigations

- Abnormal glycosaminoglycans in urine helps make diagnosis

c) Management

- Bone marrow transplantation is recommended for the severe infantile form.
- Enzyme replacement provides does not affect CNS manifestations.

ii) MPS type II (Hunter syndrome)

An **X-linked recessive disease** caused by iduronate-2-sulfatase deficiency.

a) Clinical features

- Coarse facial features,
- **No corneal opacities**,
- Macrocephaly,
- Mild dwarfism,
- Hepatosplenomegaly,
- Dysostosis multiplex,
- Mental retardation.

b) Investigations

Diagnosed is usually made by detection dermatan and heparan sulfate excretion in urine.

c) Management

Enzyme replacement therapy does not affect CNS manifestations.

iii) MPS type III (Sanfilippo syndrome):

A heparan N-sulfatase deficiency.

a) Clinical features

Presenting symptoms may include marked overactivity, destructive tendencies, and other behavioral aberrations, such as sleep disturbances in a child 4–6 years of age.

Also presents with visceromegaly, mild corneal clouding, and claw hands.

b) Investigations

Heparan sulfate excretion in urine.

iv) MPS type IV (Morquio syndrome):

- An N-acetylgalactosamine-6-sulfatase deficiency.
- Corneal clouding is observed. Normal intelligence
- Chondroitin 6-sulfate and keratan sulfate excretion in urine make diagnosis

v) MPS type VI (Maroteaux-Lamy disease):

- An N-acetylgalactosamine-4-sulfatase deficiency.
- Corneal clouding is observed. Normal intelligence
- Cardiomyopathy, hepatosplenomegaly.
- Dermatan sulfate excretion in urine.
- Enzyme replacement therapy and bone marrow transplantation are options

CHAPTER 20 AMINO ACID DISORDERS

(I) Disorders of Amino Acid Metabolism

- Disorders of amino acid metabolism are the result of the inability to catabolize specific amino acids derived from protein.

i) Phenylketonuria

- Classic PKU is the result from a defect in the hydroxylation of phenylalanine to form tyrosine.
- The activity of phenylalanine hydroxylase in the liver is absent or greatly reduced.
- Affected infants are normal at birth, but if untreated, **severe mental retardation** (IQ 30) develops in the first year of life.

a) Investigations

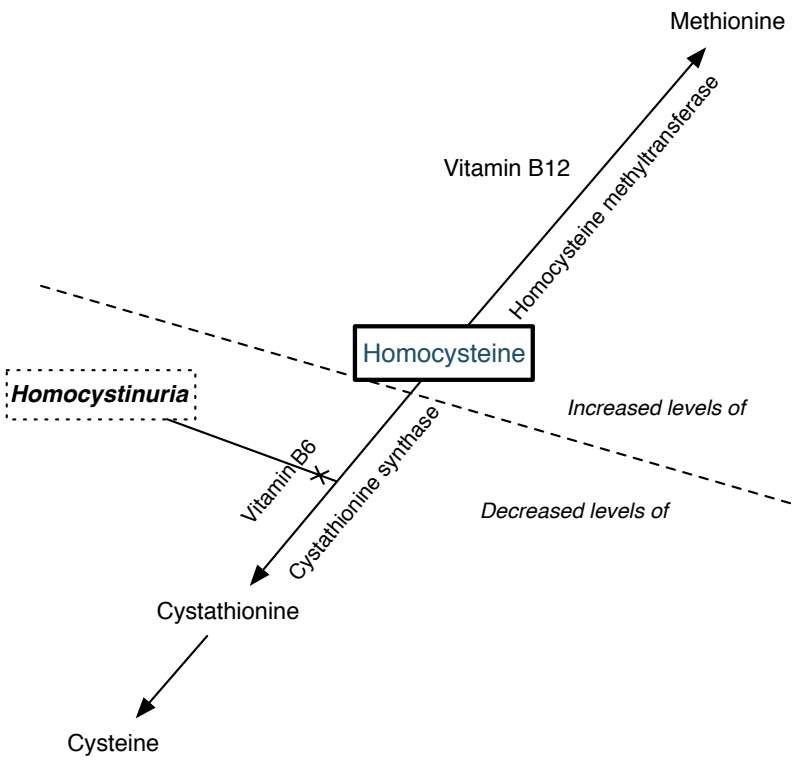
- A positive newborn screening test must be followed up by performing quantitative plasma amino acid analysis.
- A plasma phenylalanine value of greater than 360 μM (6 mg/dL) is consistent with the diagnosis, and should be evaluated and treated.
- Untreated, *classic PKU* is characterized by blood phenylalanine concentrations higher than 600 μM.
- A significant percentage of premature infants and a few full-term infants have transient elevations in phenylalanine.
- Short-term follow-up usually identifies these infants promptly.
- A small percentage of infants diagnosed with PKU (≤2% in the United States) have a defect in the synthesis or metabolism of tetrahydrobiopterin, the cofactor for phenylalanine hydroxylase and for other enzymes involved in the intermediary metabolism of aromatic amino acids.
- Such disorders in biopterin metabolism are diagnosed by measuring dihydrobiopterin reductase in erythrocytes and by analyzing biopterin metabolites in urine. This testing should be carried out in all hyperphenylalaninemic infants.

b) Treatment

- Treatment is guided by plasma phenylalanine values and keep them in therapeutic range of 120 to 360 mM using a diet specifically restricted in phenylalanine but otherwise nutritionally complete.
- If the elevated level has been sustained, the dysfunction may not be reversible. Outcome of treatment in classic PKU is excellent.
    - Most infants with classic PKU who are treated within the first 10 days of life achieve normal intelligence.
- Tetrahydrobiopterin modified preparation may be in some cases.
- Counselling for prevention of “maternal PKU syndrome”.
- Maternal hyperphenylalaninemia requires rigorous management before conception and throughout pregnancy to prevent fetal brain damage, congenital heart disease, and microcephaly.

ii) Homocystinuria

- Homocystinuria, autosomal recessive, involves connective tissue, brain, and the vascular system, is caused by a deficiency of ***cystathionine β-synthase***.
- Homocysteine is an important intermediate in the normal metabolism of the sulfur amino acids.
- When cystathionine β-synthase is deficient, homocysteine accumulates in the blood and appears in the urine. There is enhanced reconversion of homocysteine to methionine increasing its concentration in blood.
- The neonatal screening test most commonly used measures methionine.



a) Clinical Features

Many of the phenotypic features of Homocystinuria are shared with **Marfan's syndrome**. Some characterisitic features of Homocystinuria include:

- Dislocated ocular lenses,
- Long, slender extremities,
- Malar flushing,
- Livedo reticularis.
- Arachnodactyly,
- Scoliosis,
- Pectus excavatum or carinatum,
- Mental retardation
- Major arterial or venous thromboses can occur.

b) Investigations

- Plasma amino acid profile shows hypermethioninemia.
- Measurement of cystathionine β-synthase is not clinically available, but numerous mutations in the gene are known and can be tested.
- Elevated total homocysteine in the blood confirms diagnosis.

c) Treatment

- There are two clinical forms of homocystinuria
- In one form, activity of the deficient enzyme can be enhanced by the administration of large doses of pyridoxine (100 to 1000 mg/day) while the other form is pyridoxine-unresponsive.
- Other measure that may have value in certain cases include:
    - Methionine-restricted diet
    - Cystine supplementation
    - Folate supplementation
    - Supplemental betaine (trimethylglycine)
- The prognosis is good for infants whose plasma homocysteine concentration is controlled.

iii) Maple Syrup Urine Disease

Maple syrup urine disease (MSUD), autosomal recessive disease, is also called ***branched chain ketoaciduria***. A deficiency of the decarboxylase initiates the degradation of the ketoacid analogs of the three branched chain amino acids—leucine, isoleucine, and valine.

Maple syrup urine disease (MSUD)	
Block in degradation pathway of branched chain amino acids	Leucine
	Isoleucine
	Valine

a) Clinical features

Clinical manifestations of the classic form typically begin within 1 to 4 weeks of birth. Hallmark of the disease include:

- Profound depression of the CNS, associated with alternating hypotonia and hypertonia (**extensor spasms**),
- **Opisthotonos**, and
- Seizures.
- The urine has the odor of maple syrup.

b) Investigations

There may be:

- Metabolic acidosis, with elevation of the undetermined anions; the acidosis is caused, in part, by plasma branched chain organic acids and, in part, by the usual ketone bodies, β-hydroxybutyrate and acetoacetate.
- Branched-chain ketoacids in urine (but not β-hydroxybutyrate or acetoacetate) react

immediately with 2,4-dinitrophenylhydrazine to form a copious, white precipitate.

- Large increases in plasma leucine, isoleucine, and valine concentrations and identification of alloisoleucine in the plasma in excess— definitive diagnosis.
- The urinary organic acid profile is usually abnormal and shows the ketoacid derivatives of the branched chain amino acids.

c) Treatment

- Provision of adequate calories and protein, with restriction of leucine, is crucial for acute and chronic management.
- Hemodialysis, hemofiltration, or peritoneal dialysis—lifesaving
- Ordinary catabolic stresses, such as moderate infections or labor and delivery in a pregnant mother with MSUD, can precipitate clinical crises.
- Liver transplantation effectively treats MSUD.

(II) Disorders of Ammonia Disposal

Inherited enzymatic deficiencies have been described for each of the steps of urea synthesis.

Neonatal screening does not currently detect all of the disorders in the urea cycle.

i) Ornithine carbamoyltransferase (OTC)

- X-linked recessive disease.
- If the enzyme is nonfunctional, there is no OTC activity in affected males, who are likely to die in the neonatal period.
- Affected females are heterozygous and, because of **lyonization**, can have variable severity.
- Clinical manifestations range from lethal disease in the male (coma, encephalopathy) to clinical normalcy in a high percentage of females.
- Late-onset forms in males also occur.
- Manifestations in clinically affected females include recurrent emesis, lethargy, seizures, developmental delay, mental retardation, or episodic confusion.
- Affected females may spontaneously limit their protein intake.
- Confirmatory testing for OTC includes a plasma amino acid profile, which may show reduced citrulline and arginine concentrations with increased glutamate and alanine.
- A urine organic acid profile shows increased excretion of orotic acid after a protein load.
- Mutation testing, deletion testing, and sequencing of the entire coding region of the related genes can be used.

ii) Treatment of Hyperammonemia

- During episodes of symptomatic hyperammonemia:
    - Protein intake is reduced,
    - Intravenous glucose is given in sufficient quantity (to suppress catabolism of endogenous protein)
    - Sodium benzoate and sodium phenylacetate trap NH_3 and are excreted in the urine.

- Supplemental arginine
- When ammonia levels are very high (>1000 μM) or refractory to therapy, direct removal of ammonia using hemodialysis or hemofiltration (but not peritoneal dialysis) is required.
- The neurologic status must be followed closely and cerebral edema treated promptly.

- Early liver transplantation has increased survival, especially in males with severe OTC deficiency.
- Restriction of dietary protein intake to daily needs is the mainstay of ongoing treatment for urea cycle defects.
- Crystalline essential amino acids can be supplied in amounts just sufficient to support protein synthesis.
- Arginine is an essential amino acid when arginine synthesis via the urea cycle is grossly impaired; thus arginine must be supplied except in the case of arginase deficiency.
- Citrulline needs to be supplied for some urea cycle disorders.
- For OTC deficiency and carbamoyl phosphate synthase deficiency, treatment with phenylbutyrate (which is metabolized to phenylacetate) prevents accumulation of ammonia.

(III) Disorders of Amino Acid Transport

i) Cystinuria

Cystinuria is a disorder of **renal tubular transport** of cystine, lysine, arginine, and ornithine.

Cystinuria, *Aide mémoire: COLA*
Cystine
Ornithine
Lysine
Arginine

- The concentration of cystine exceeds its solubility product and results in significant renal stones (can be **radiolucent**).
- Evaluation and diagnosis are based on the pattern of amino acid excretion in the urine.
- Mutation testing can be done.
- Treatment is based on increasing the solubility of cystine by complexing it with compounds such as penicillamine.

ii) Hartnup disease

- **Intestinal transport** of tryptophan is impaired in Hartnup syndrome;
- *Pellagra-like signs and symptoms (e.g. pellagroid rash etc) usually result from this deficiency.*
- Diagnosis is based on the amino acid pattern in urine.
- Treatment with tryptophan is successful.

CHAPTER 21 β-OXIDATION DISORDERS

- Fatty acids are derived from hydrolysis of triglycerides and catabolism of fat.
- The catabolism of fatty acids (β-oxidation) proceeds involves serial, oxidative removal of two carbons at a time as acetyl groups (each as acetyl-CoA).
- ***These disoders come under high suspicion by classical hypoketotic hypoglycemia and clinical picture.***
- The reactions are catalyzed by a group of enzymes that exhibit specificities related to the chain length and other properties of the fatty acids:
    - Very long chain acyl-CoA dehydrogenase (VLCAD),
    - Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD),
    - Medium-chain acyl-CoA dehydrogenase (MCAD), and
    - Short-chain acyl-CoA dehydrogenase (SCAD).

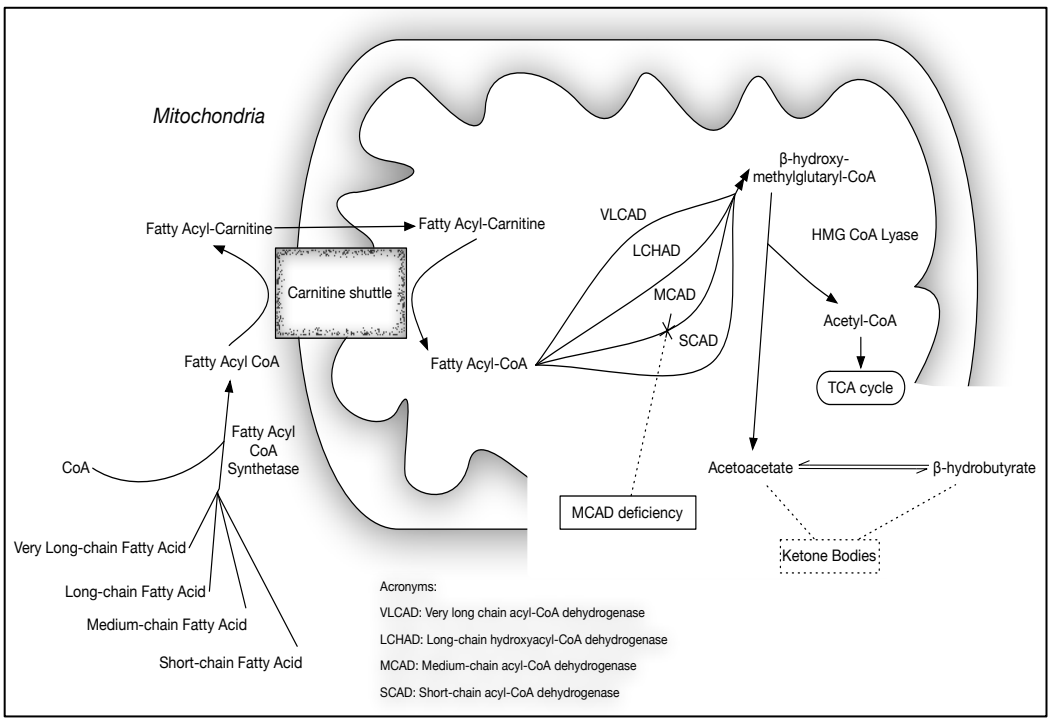


Figure. β-oxidation and associated disorders.

i) MCAD deficiency

MCAD deficiency is the most common inborn error of β-oxidation. A single mutation at position 985 (A→G) accounts for a significant percentage of cases.

- ***Hypoketotic hypoglycemia***
- Fatty infiltration of the liver.
- Sometimes *Reye syndrome–like* illness with hypoglycemia and elevated liver enzymes may be seen.
- Family history is usually positive.
- Risk of sudden infant death syndrome is increased with MCAD deficiency, presumed to be due to hypoglycemia.

ii) VLCAD and LCHAD deficiency

- VLCAD deficiency and LCHAD deficiency result in significant *myopathy and cardiomyopathy*.
- LCHAD deficiency is accompanied by a retinopathy in later childhood.
- Results in weakness and muscle pain, along with myoglobinuria in some people.

iii) HMG-CoA lyase deficiency

- Hydroxymethylglutaryl-CoA lyase deficiency, ***not a disorder of β-oxidation***, impairs hepatic adaptation to fasting by impairing ketogenesis.
- The clinical manifestations are those of MCAD deficiency, except carnitine which is not depleted.

(II) Investigations

In addition to hypoketotic hypoglycemia, the following labs help confirm the diagnosis:

- Urinary organic acid and acylglycine profiles,
- Plasma acylcarnitine,
- Free fatty acid profiles.
- Enzyme measurements and DNA testing
- Acylcarnitines profile in cultured skin fibroblasts— if others inconclusive.
- Carnitine depletion can occur (in β-oxidation disorders) through excessive urinary excretion of carnitine esters of the incompletely oxidized fatty acids. *Hence measuring plasma carnitine is helpful in monitoring.*

Management

- Avoidance of fasting,
- Fluid and calorie supplementation during illnesses and metabolic stress
- Medium-chain triglycerides must be avoided in MCAD deficiency.
- In the long-chain fatty acid metabolic disorders, provision of medium-chain fatty acids improves muscle energy metabolism.

CHAPTER 22 NEONATOLOGY

(I) Definitions

i) Neonatal period

It is from birth till the end of 1st month of life.

Early N.P.: first 7 days, Late N.P.: day 8 to day 28.

ii) Abortion

Expulsion of dead fetus before age of viability.

iii) Still birth

Expulsion of dead fetus after the age of viability.

iv) Statistical definitions

a) Perinatal Mortality Rate

$$\text{PMR} = \frac{\text{Still births} + \text{early Neonatal deaths}}{1000 \text{ live births}}$$

PMR in Pakistan is 50-90/1000.

b) Neonatal Mortality Rate

$$\text{NMR} = \frac{\text{Total deaths in first 28 days of life}}{1000 \text{ live births}}$$

NMR in Pakistan is about 50/1000.

c) Infant Mortality Rate

$$\text{IMR} = \frac{\text{Total deaths in first 365 days of life}}{1000 \text{ Live births}}$$

v) Weight at birth

Low birth weight: Neonate < 2500 g weight.

Very low birth weight: Neonata < 1500 g.

Extremely low birth weight: Neonate < 1000 g.

Incredibly low birth weight: Neonate < 750 g.

vi) Gestational age

Preterm: Birth before 37 weeks gestation.

Full term: Birth between 37-42 weeks gestation.

Post term: Birth after 42 weeks gestation.

vii) Weight and gestation

Appropriate for Gestational Age (AGA): Between 10th & 90th centile weight for gestational age.

Small for Gestational Age (SGA): <10th centile weight for gestational age.

- Symmetric SGA: If weight, length and circumference are all less than 10th centile, it denotes prolonged nutritional insufficiency.
- Asymmetric SGA: If weight is less than 10th centile, but length and head circumference are appropriate for gestational age. It denotes acute recent decrease in nutritional supply.

Large for gestational Age (LGA): > 90th centile weight for gestational age.

(II) Assessment of fetal health

- Serial maternal urinary estriol estimations give an indication of fetal health. A decrease > 35% indicates fetal and placental compromise.
- β-hCG reflects placental function.
- Doppler blood flow monitoring and fetal cardiotocography (high risk cases) can indicate stress response.
- Ultrasonography is helpful in monitoring growth.
- Amniocentesis is usually done at 12-14 weeks.
    - It provides sample of fetal cells in amniotic fluid for karyotyping, DNA analysis, Rh isoimmunization, and Inborn errors of metabolism.
    - Lecithin:Sphingomyelin ratio in amniotic fluid can also be used to determine fetal maturity.
    - Elevated AFP in amniotic fluid is associated with:
        - Anencephaly
        - Spina bifida
        - Exomphalos
        - Congenital nephrosis
        - Esophageal and duodenal atresia
        - Down's syndrome
        - Intrauterine death
- Chorionic villous sampling is usually done at 10-12 weeks gestation.
    - It provides sample of placental tissue via transabdominal/transcervical ultrasound guided sampling for karyotyping, molecular and genetic diagnostic procedures.
- Fetoscopy can be used to perform invasive procedures.
    - Fetal blood obtained via fetoscopy procedure can be use to diagnose thalassemia.
    - It can also provide skin or liver biopsy samples.

(III) Neonatal hip examination

Pelvis is stabilized with one hand, and the middle finger of the other hand is placed over the

greater trochanter and the thumb around the femur. ***The hip is flexed***, then:

- **Barlow manoeuvre** is carried out to check if the hip is *dislocatable*. The femoral head is gently pushed downwards. If dislocatable, the femoral head will be pushed out with a clunk.
- **Ortolani manoeuvre** to carried out to see if the hip is *dislocated* and can be relocated into the acetabulum. The hip is abducted and upward pressure applied by the finger on the greater trocanter. If the hip were dislocated, it would clunk back into position.

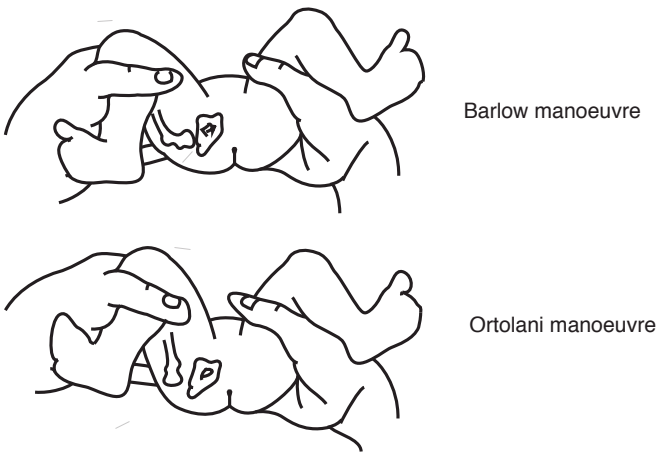


Figure. Ortolani and Barlow maneurvre

(IV) Neonatal reflexes

Persistence of primitive reflexes suggests significant neurodevelopmental dysfunction.

i) Righting reflex

- If the head is rotated to one side, the trunk is rotated to the same side.
- It is present from 34 weeks gestation onwards.

ii) Rooting reflex

- Light touching of the angle of mouth causes the neonate to turn head to same side, open his mouth and protrude his tongue.
- It is present near term and disappears in the first 4-5 months.

iii) Doll's eye reflex

- In newborns, eyes move in the direction of movement. Normally, eyes do not move with the head beyond 3 weeks of age.

iv) Moro's reflex

- If the head of a neonate is allowed to fall 10-15° below, characteristic abduction and extension of arms, opening of hands, followed by adduction and flexion of the arms is seen bilaterally as in an embracing posture.
- It disappears at 3-4 months of age. If absent, it indicates poor function of CNS. Absence in one limb indicates local disease like nerve injury, fracture etc.

v) Grasp reflex

- Light touching of the palms or soles causes flexion of of fingers and toes in a grasping manner.
- Disappears by 4-5 months of age
- If it persists beyond 5 months age, it indicates cerebral palsy.

vi) Suckling reflex

- It is weak in immature infants.

vii) Swallowing reflex

- Milk placed in the mouth is promptly swallowed.
- It may be absent in very preterm (< 28 weeks), paralysis of palate, and neurological dysfunction.

viii) Withdrawal reflex

- If the sole of the foot is pricked, the leg is lexed, and withdrawn. It indicates the integrity of the sensory and motor nervous systems.

ix) Asymmetrical tonic neck reflex

- If the baby's head is turned to one side, there is ipsilateral extension of limbs and contralateral flexion of limbs. This is also known as "fencing reflex".
- It appears after 2-4 months of age.

x) Stepping reflex

- If the infant is held with both hands upright and sole of foot is brought in contact with flat surface, flexion and extension posturing as seen in an attempt to walk are seen in both limbs.
- It disappears after 6 months of age, its persistence indicates cerebral palsy.

xi) Glabellar reflex

- Taping on the glabella produces momentary closure of eyes. It persists from birth onwards.

xii) Gallant reflex

- If the baby is stroked in the paraspinal region, ipsilateral curvature of spine is noted.

xiii) Landau reflex

- Infant is held prone by placing the hands underneath the abdomen.
- The normal response consists of slight extension of the head, trunk and hips, and on flexion of the head, there is flexion of the trunk and hips.
- It appears at 6-8 months of age and disappears at 15 months to 2 years.

xiv) Parachute reflex

- Infant is held prone as above, and allowed to fall few centimeters by displacing the hands downward. There is extension of arms, hands and fingers as if he is going to fly.
- It appears at 6-8 months of age and never disappears.

Reflex	Appear	Disappears	Comments
Rooting/sucking	Birth	3-4 months	Absence indicates prematurity or poor function of CNS
Grasp/plantar	Birth	4-6 months	Persistence > 5 months indicates cerebral palsy
Moro	Birth	4-6 months	
Stepping/placing	Birth	4-6 months	Persistence > 6 months indicates cerebral palsy
Tonic neck	Birth	4-6 months	Persistence > 6 months suggests spastic cerebral palsy
Glabellar	Birth	Persists	
Gallant	Birth	6-9 months	
Landau	6-8 months	15– 24 months	
Parachute	6-8 months	Persists	

(V) Care of normal newborn

i) Temperature regulation in newborn

- Maintain abdominal skin temperature between 36.2°C and 37.0°C when baby is in incubator.
- Vernix caseosa should not be removed and even the initial bath can be delayed if baby is hypothermic.
- Kangaroo (skin-to-skin) care is recommended.

Figure. Kangaroo (skin-to-skin) care

ii) Nutritional management of newborn

- A caloric intake of atleast 120 Kcal/kg/day and a protein intake of 3-4 g/kg per 2 hours.
- Prevention of aspiration is of the utmost importance. Special high caloric formula can be used for preterm infants.
- Vitamin K 0.5 mg I/V should be given as birth.
- Vitamins A, C, D in the form of drops should be given from the age of 1 week. Ferrous sulphate started from 6th week, and vitamin E is given for first 3 months.

(VI) Maternal diseases affecting newborn

Table. Maternal Conditions And Fetal Outcome	
Disease	**Outcome/Comment**
Bronchial asthma	IUGR; Feal goiter and hypothyroidism (due to drugs- beta agonists)
Chronic cardiac disease	IUGR, abortion, asphyxia, prematurity
Chronic renal disease	IUGR, prematurity
Hypertension	Placental vasculopathy, IUGR
Thyroid disorders	Maternal hypothyroidism may cause congenital hypothyroidism
SLE	Congenital complete heart block, IUGR
Smoking	IUGR/LBW; Sudden infant death syndrome (SIDS); Increased orofacial clefts in the fetus. Developmental lag for first few years of life: adverse effects on language skills and visual and spatial abilities

i) Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome (APLA) is notorious for causing recurrent miscarriages.

ii) SLE

Congenital heart block may be seen in neonates born to born with SLE.

iii) Diabetes / Infant of diabetic mother

These infants are LGA but born before term.

They are plymp with pink color and rounded moon face giving a false appearance of being healthy. This occurs because of transfer of large amount of glucose through placenta from the mother with consequent high insulin levels and fat deposition in the baby.

Problems occurring in infants of diabetic mothers include:

- General
- Macrosomia
- Birth trauma
- Metabolic
- Hypoglycemia
- Hypocalcemia
- Hyperbilirubinemia
- Cardiovascular
- Persistent fetal circulation
- Respiratory distress syndrome (RDS)
- Birth asphyxia

- Polycythemia
- Congenital anomalies
- Transposition of Great Vessels (TGV),
- Sacral agenesis,
- Neural Tube Defects, etc.

(VII) Neonatal problems

i) Asphyxia Neonatorum (Birth asphyxia)

Failure of neonate to cry or start adequate respiration within one minute of birth is known as asphyxia neonatorum. It can be prevented if care and attention is given to the four 'A's: Anticipation, Assessment, Action, and Aftercare.

a) Anticipation

Fetuses at high risk of developing asphyxia should be anticipated.

b) Assessment

Apgar scoring is used for assessment at 1 minute (**determines need for resuscitation**), and 5 minutes (**reflects neurodevelopmental outcome**) after birth.

Table. Apgar Score

Signs	Points		
	0	**1**	**2**
Heart rate	0	<100/min	>100/min
Respiration	None	Weak cry	Vigorous cry
Muscle tone	None	Some extremity flexion	Arms, legs well flexed
Reflex irritability	None	Some motion	Cry, withdrawal
Color of body	Blue	Pink body, blue extremities	Pink all over

Asphyxia livida

It is said to occur if neonate is cyanosed with gasping or apnea. The mucle tone is normal or increased and heart rate is above 100/minute with good pulsations. Apgar score is about 4-7.

Asphyxia pallida

Neonate is pale, hypotonic and apneic. Heart rate is below 100, pulsations in umblical cord are weak and there is no response to stimulation. Indicates prolonged intrauterine hypoxia/ischemia. Apgar score is about 0-3.

c) Action (Neonatal Resuscitation)

As soon as the head is delivered, nostrils and throat should be cleared with a mucus extractor. Resuscitation is attempted after birth asphyxia is noted.

Ventilation Correction Steps:

"**MR. SOPA**" mnemonic is used to remember these steps.

M- adjust Mask in the face

R- Reposition the head to open airway

---Re-attempt to ventilate...if not effective then

S- Suction mouth then nose

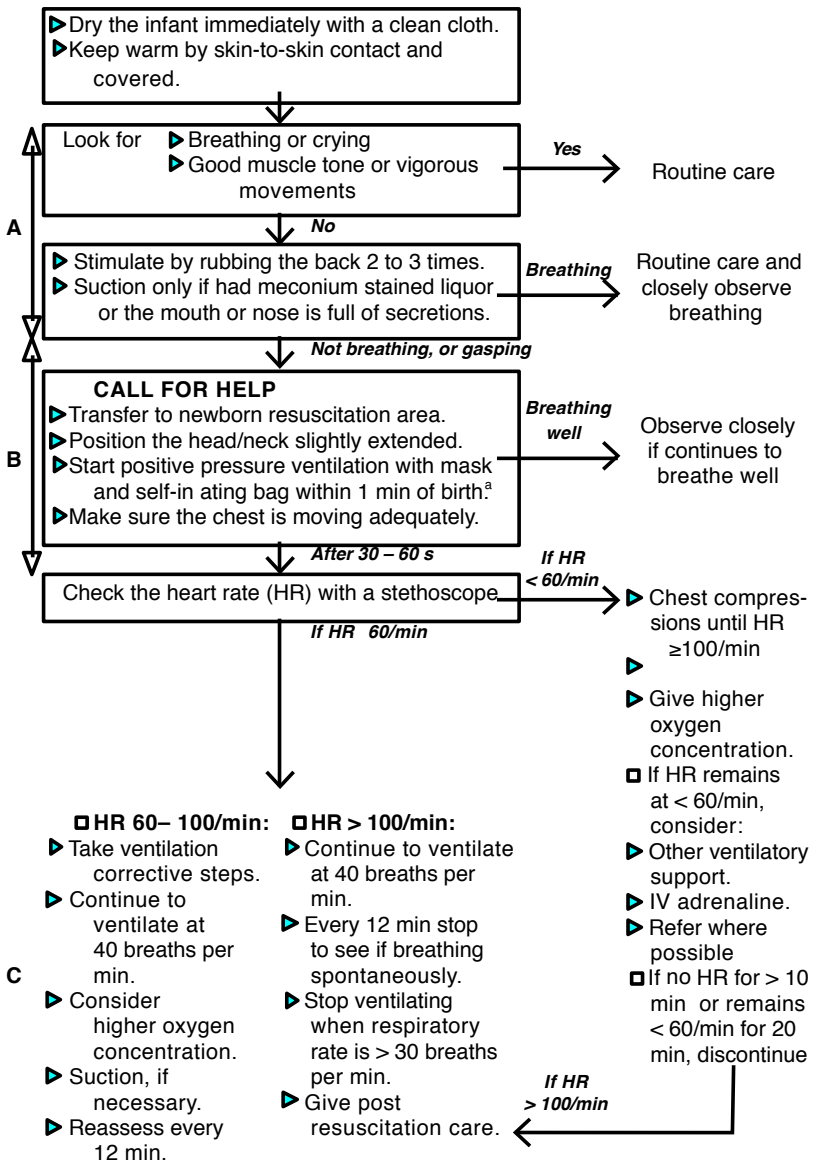
O- Open mouth and lift jaw forward

---Re-attempt to ventilate...if not effective then

P- gradually increase Pressure every few breaths until visible chest rise is noted

---If still not effective then

A- Artificial Airway (ETT or LMA)



a Positive pressure ventilation should be initiated with air for infants with gestation > 32 weeks. For very preterm infants, it is preferable to start with 30% oxygen if possible.
A and **B** are basic resuscitation steps

d) Aftercare

Neonates requiring resuscitation are kept under observation for 24 hours for signs of multi-organ dysfunction that occurs with hypoxic-ischemic injury.

ii) Birth trauma

a) Caput succedaneum

Edematous swelling that crosses suture lines. No treatment is required.

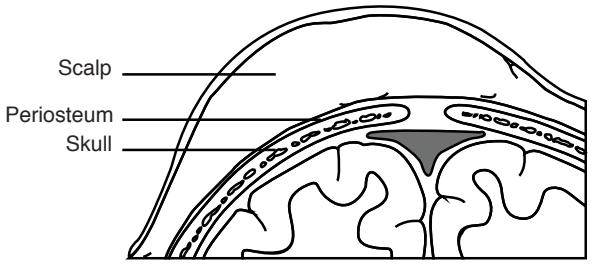


Figure. Caput succedaneum

b) Cephalohematoma

- There is hemorrhage under the periosteum of cranial bones which are adherent to the cranial sutures. Hence, the hematoma does not cross the suture lines.
- It appears a few days after birth. Resolution takes 3-4 weeks, and hyperbilirubinemia may develop due to breakdown of hemoglobin in the extravasated fluid.

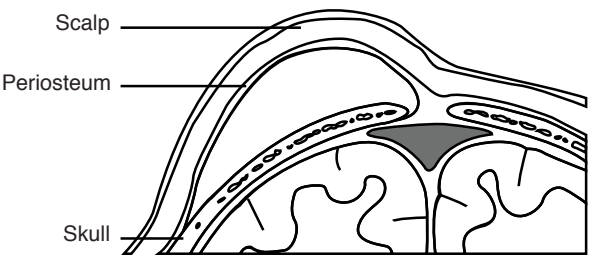


Figure. Cephalohematoma

c) Subaponeurotic hemorrhage

- It is a firm, fluctuant mass over the aponeurosis covering of scalp.
- Resolution takes 2-3 weeks, and hyperbilirubinemia may develop due to breakdown of RBCs in the hematoma.

d) Skull fracture

Fractures that affect neurological function require specific treatment.

- Elevation of fracture is carried out for depressed fracture.
- Linear fractures without neurological involvement require no therapy.
- Leptomeningeal cyst may occur.

e) Brachial plexus injuries

Erb's palsy

- It is also known as waiter's tip hand. The arm is adducted with extended elbow. The forearm is in pronation with a flexed wrist. Ipsilateral Moro's, biceps, and brachioradialis reflexes are absent.
- It is due to injury of 5^{th} and 6^{th} cervical spinal roots.

Klumpke's palsy

Injury to 7th, 8th and 1st thoracic spinal roots affects the intrinsic muscles of the hands as:

- It causes loss of ipsilateral grasp reflex.
- Biceps, and brachioradialis reflexes are normal.
- The brachial plexus injuries are usually awaited for spontaneous recovery with reduction in passive movement in 7-10 days.
- Physiotherapy and wrist splintage after 1-2 weeks can be carried out but lack of improvement after 6 weeks is a poor prognostic sign.

f) Facial nerve injury

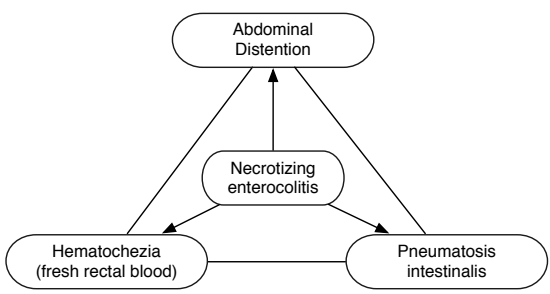
- Forceps delivery increases the risk of developing this condition.
- There is loss of nasolabial fold and depressed angle of mouth on the affected side. Blinking is affected.
- Treatment is to await spontaneous resolution with eye care to prevent keratitis. Spontaneous resolution can be expected from one to several weeks.

g) Clavicular fracture

- It is most frequent fractured bone during labor. There is a higher risk with breech and shoulder dystocia.
- It may manifest as pseudoparalysis of limb on affected side. Reduction in movements at the site is required Recovery is complete.

iii) Necrotizing enterocolitis

- This occus more commonly in the preterm LBW infants given hypertonic solutions and those with ublical catheterization, RDS, infection, polycythemia, and birth asphyxia.
- Intestinal necrosis occurring primarily in watershed distributions,
- It is seen in infants upto 2 months of age;
- Prematurity and congenital heart disease are risk factors;
- Clinical features include fever, vomiting, abdominal distention, *rectal fresh blood*. There may be jaundice and signs of shock.
- Radilogic studies may show air in bowel wall (***pneumatosis intestinalis***), air under the diaphragm, hepatobiliary/ portal air.



- Treatment:
    - Keep nill per oral (NPO)
    - Aspirating stomach frequently

- Parenteral fluids and feeds
- Broad-spectrum antibiotics
- Maintenance of serum electrolytes
- Surgey may be needed with:
  - Clinical deterioration
  - Intestinal obstruction
  - Intestinal perforation
  - Peritonitis

iv) Jaundice in newborn

Jaundice is visible at bilirubin levels of 4-6 mg/dL.

a) Physiological jaundice

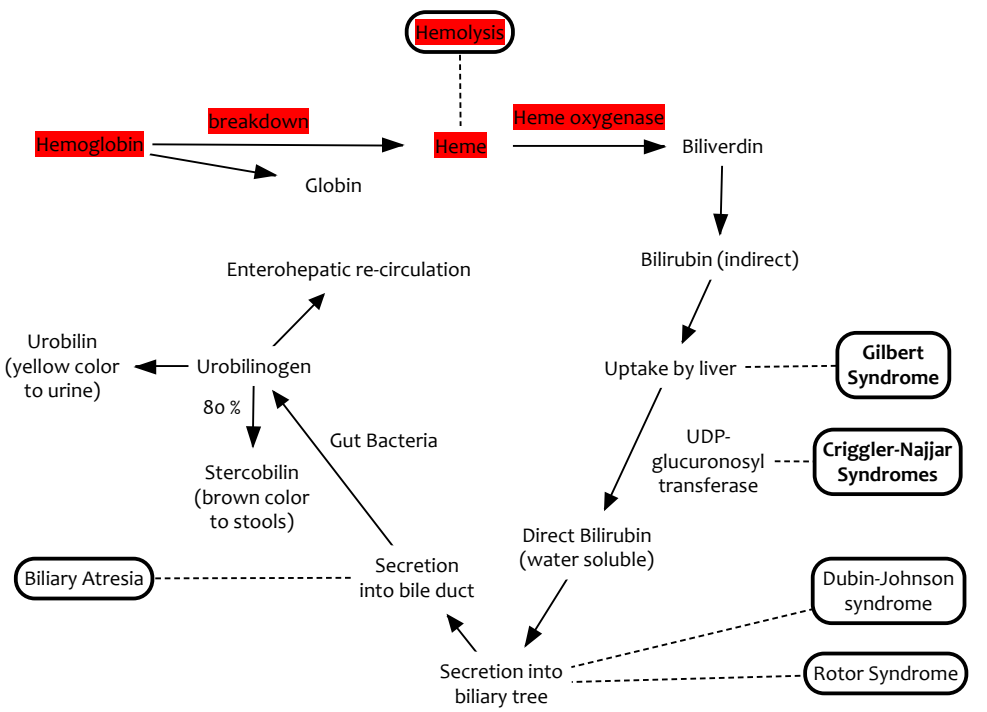
- Immature UDP-glucuronosyltransferase in neonates.

It is characterized by a gradual rise in serum unconjugated bilirubin concentration to a level of 6-8 mg/dL between 72-90 hours of age, followed by a fall to 1 mg/dL by 10th day in an otherwise healthy child. Other characteristics are:

- Total bilirubin rises less than 5 mg/dL
- Total bilirubin not higher than 12.9 mg/dL in term, and 15 mg/dL in preterm.

b) Pathological jaundice

Any jaundice seen on the first day of birth is considered pathological and must be investigated.



Unconjugated hyperbilirubinemia

It usually due to hemolysis, hypothyroidism, breast-milk jaundice or Criggler-Najjar syndrome.

There are two types of Criggler-Najjar syndrome:

- Type 1: complete enzyme deficiency of UDP-glucurosyl transferase
- Type 2: partial enzyme deficiency of UDP-glucurosyl transferase

Conjugated hyperbilirubinemia

It is usually due to viral hepatitis, biliary atresia, or autosomal recessive conjugated hyperbilirubinemia syndromes, i.e. Dubin-Johnson and Rotor syndrome.

c) Kernicterus

- It is a complication of unconjugated hyperbilirubinemia.
- High circulating levels of unconjugated bilirubin, immature blood-brain barrier lead to accumulation and destruction of neuronal tissue particularly basal ganglia.
- There may be lethargy, hypotonia, and poor suck, vomiting, high pitchd cry. Infant may develop seizures. There is high risk of death.
- Signs of neuronal damage due to kernicterus include chorea, athetosis, paralysis of conjugate upward gaze, and high tone deafness.

d) Treatment

Treatment is centered on the cause.

For unconjugated hyperbilirubinemia, phototherapy with white or blue light (420-470 nm wavelength), and exchange transfusion are most commonly used treatment modalities. Phototherapy converts some unconjugated bilirubin into water-soluble isomers, which are excreted in urine.

v) Neonatal metabolic problems

a) Neonatal Hypoglycemia

Blood glucose falls under 40 mg/dl, regardless of the gestational age of the neonate.

Clinical manifestations in symptomatic hypoglycemia include:

- Sweating,
- Lethargy,
- Irritability,
- Jitteriness,
- Tachycardia,
- Tremors,
- Seizures,
- Apneic spells.

Treatment:

- Bolus IV 2ml/kg of 10% dextrose solution, followed by IV drip of 10% dextrose should be given.
- If infant can, then feeds should be immediately started enterally.
- Diazoxide or somatostatin can be administered in refractory cases with suspected nesidioblastosis or hyperinsulinism.

Prevention:

Baby friendly hospital initiate recommends breastfeeding to be started early after birth. Avoid hypothermia.

b) Neonatal Hypocalcemia

Hypocalcemia in neonates is defined as:

- Less than 8 mg/dl in full-term, or
- Less than 7 mg/dl in pre-term

Causes:

- Prematurity
- Poor nutrition
- Excessive phosphate intake

Clinical features:

- Irritability
- Tremors
- Twitching
- Seizures
- Lethargy

Investigations:

- Serum Ca^{2+}, phosphorus and magnesium, alkaline phosphatase
- ECG: QT interval may be prolonged
- PTH levels

Treatment:

- Treatment is required if there is:
    - Symptomatic hypocalcemia < 7 mg/dL, or
    - Asymptomatic hypocalcemia < 6 mg/dL.
- 10% calcium gluconate is given by slow IV infusion. Oral therapy may be considered. Treat the underlying cause.

c) Late Hypocalcemia

- Most common cause of late hypocalcemia is ingestion of milk with high phosphate content (e.g. fresh cow's milk or infant formula without adequate reduction).
- The neonatal kidney is unable to excrete the high phosphate load.

vi) Congenital malformations

a) Meningo-myelocele

- It comes under the spectrum of neural tube defects.
- Hydrocephalus is associated in upto 80% cases. Depending on the spinal level of lesion, there may be complications like weakness or paralysis of lower limbs, bladder and anal sphincters.

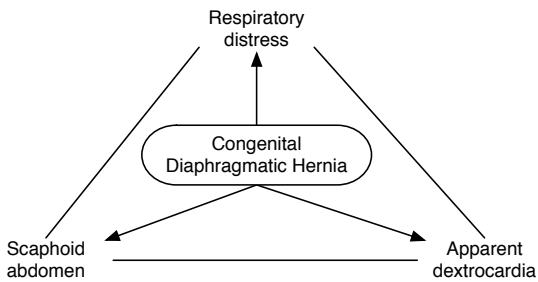
- Treatment is surgical closure for lower lesions with little evidence of sphincteric and bladder involvent.
- Prognosis for lesion lower in sacral region is better than other higher lesion.

b) Congenital diaphragmatic hernia

It is most commonly seen as at the foramen of bochdalek (failure of fusion of pleuroperitoneal canal) on the left side. Colon is the common hernia content.

Clinical features

Classic triad of respiratory distress, apparent dextrocardia and a scaphoid abdomen.



Investigations:

- Chest Xray
- Barium enema or meal
- ABGs

Treatment

- Oral feeds should be withheld and stomach aspirated continuously via a large bore nasogastric tube.
- Intravenous feeding is started.
- Bag and mask ventilation should not be used as it distends the herniated stomach further and increases respiratory embarrassment.
- Positive pressure ventilation may be needed through an endotracheal tube.
- Early surgical dissection and closure is essential. Pulmonary hypoplasia is the major cause of morbidity and mortality.

(VIII) Neonatal hematology

i) Hemolytic disease of the newborn

a) ABO-hemolytic disease

- It is more common and less severe.
- Occurs when maternal blood group is O and fetus is either group A or B.
- IgG antibodies produced as a result of previous exposure cross and destroy fetal red cells in the later half of pregnancy.

b) Rh Isoimmunization

- IgM does not cross placenta; IgG does cross placenta.

- Rh– mothers exposed to fetal Rh+ blood (often during delivery) may make anti-D IgG. In subsequent pregnancies, anti-D IgG crosses the placenta → hemolytic disease of the newborn (erythroblastosis fetalis) in the next fetus that is Rh+. Prevented by administration of RhoGAM to Rh– pregnant women during third trimester, which prevents maternal anti-Rh IgG production.
- Rh– mothers have anti-D IgG only if previously exposed to Rh+ blood.
- Direct coomb's test is positive.

Kleihauer Betke test (KB test)

The KB test is the standard test for detecting fetal - maternal hemorrhage. It is used to measure the amount of fetal hemoglobin transferred from a fetus to a mother's blood stream, quantifying the fetal - maternal hemorrhage.

It is usually performed on Rh-ve mothers to determine the required dose of Rho (D) immunoglobulin to inhibit formation of Rh antibodies in the mother and prevent Rh hemolytic disease in future Rh - positive children.

A standard blood smear is prepared from the mother's blood and exposed to an *acid bath*. This removes adult hemoglobin, but not fetal hemoglobin, from the red blood cells. Subsequent staining makes fetal cells (containing HbF) appear rose pink, while adult red cells are only seen as ghosts.

ii) Hemorrhagic disease of the newborn

In an otherwise healthy neonate, bleeding from any site (nasogastric, rectal, umblical etc) due to a deficiency of vitamin K. Intracranial hemorrhage can occur, but is uncommon.

Investigations:

- CBC
- PT/INR, APTT
- PIVKA (Protein Induced by Vitamin K absence/antagonist)

Treatment of bleeding resulting from vitamin K deficiency involves intravenous administration of 1 mg of vitamin K. If severe, life-threatening hemorrhage is present, fresh frozen plasma also should be given

iii) Anemia in the newborn

Anamia in prematurity: anemia in premature infant may be early or late.

Early anemia occurs within first 8-12 weeks of age.

The large RBC mass before birth (to carry oxygen) is no longer required and hence hemolysis of RBC's occurs while the bone marrow is in a resting stage. The premature infant also grows rapidly exaggerating this normochromic anemia.

If Hb falls below 10 g/L a packed cell transfusion of 5-10 ml/kg body weight should be given, especially if there is an illness. It cannot be corrected by iron, as the resting bone marrow cannot utilize it.

Late anemia occurs when bone marrow starts active erythropoiesis around 8-12 weeks of age, it results from low iron supply from the small iron reserves stored in the body before birth and a greater demand due to rapid growth.

Treatment is by oral iron supplements from the age of 6-8 weeks onwards.

(IX) Respiratory disease of newborn

i) Respiratory distress in newborn

Features of respiratory distress in a neonate:

- Tachypnoea (RR > 60/min)
- Expiratory grunting
- Nasal flaring
- Recession (intercostals, subcoastal, and suprasternal)
- Cyanosis

Causes:

- RDS
- Meconium aspiration
- Aspiration pneumonia
- Congenital heart disease
- Esophageal atresia
- Diaphragmatic hernia

a) Idiopathic Respiratory Distress Syndrome

There is deficiency of surfactant production due to immature lung type 2 pneumocytes. Prenatal Lecithin:sphingomyelin ratio of < 2 can in amniotic fluid can indicate this.

Investigations:

- CBC
- Blood C/S
- Pulse Oximetry
- ABGs
- Chest Xray (air bronchograms on ground glass lungs)

Management:

- Surfactant replacement: Administered via the endotracheal tube.
- Ventilatory support – oxygen, CPAP or positive pressure ventilation as needed
- Antibiotics if infection is suspected

ii) Transient tachypnea of newborn

It is a benign self-limiting condition secondary to delayed clearance of lung fluid that may cause tachypnea or minimal respiratory distress usually in full-term neonates delivered by cesarean section. Chest radiograph shows prominent vascular markings (as streaky shadowing radiating out of hila), interlobar fissure, and parenchyma (as horizontal lines at bases). Resolves spontaneously in 24-48 hours.

iii) Meconium aspiration syndrome (MAS)

The most common presentation of MAS is a postmature infant with *staining of nails, skin and*

umbilical cord with meconium and neurological and respiratory depression followed by varying degree of respiratory distress that may persist for several weeks.

a) Diagnosis

Chest radiograph shows overinflated lungs, flat diaphragm, and coarse hilar shadows with streaky shadowing, segmental collapse, bilateral pneumonia and signs of air leak syndromes.

b) Treatment:

If meconium staining is seen as birth, then mouth, nose and pharynx should be suctioned as soon as possible to prevent further aspiration. Humidified O_2 and mechanical ventilation may be required. Broad spectrum antibiotics are also added.

Complications:

- Airleak syndromes: Pneumothorax, interstitial emphysema, pneumomediastinum
- Persistent pulmonary hypertension of the newborn
- Hypoxic-ischemic encephalopathy
- Pulmonary/cerebral hemorrhage
- Superadded bacterial sepsis

(X) Neonatal neurology

i) Neonatal seizures

About 50% of all neonatal seizures are subtle which may manifest as eye movements (blinking, fluttering, deviation with jerking, eye opening sustained with ocular fixation), orobucolingual movements, rowing, apneic spells and pedalling movements.

a) Etiology

Seizures in the newborn reflect some form of brain injury:

- Hypoxic-ischemic injury (HIE),
- Stroke,
- Intracranial infection,
- Hypoglycemia,
- Inborn errors of metabolism,
- Brain malformations

b) Diagnosis

The diagnosis of neonatal seizures is challenging ongoing seizure activity might be very mild and subtle and in many cases is even absent.

- Electroencephalogram (EEG)
- Focused investigations for uunderlying cause of seizure activity.

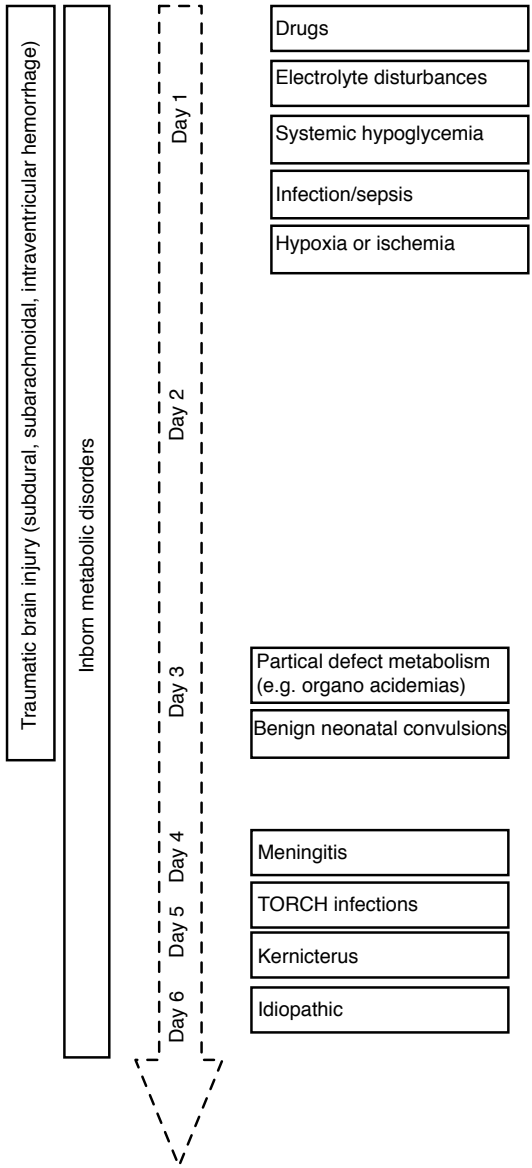


Figure. Causes of neonatal seizures according to their classical day of presentation.

c) Management

- Controlling seizure activity
    - Phenobarbital is the most commonly used first line antiepileptic in term and preterm neonates.
    - Lorazepam, Levetiracetam
    - Lidocaine— useful in case of ongoing continuous seizures activity
- Treat the underlying cause of seizure activity if treatment is available.

d) Complications

- Seizures can cause neuronal cell death in *term* infants.
- Seizures in the *immature* brain may in addition alter neuronal circuitry, resulting in impaired learning and memory and enhanced susceptibility to further seizures.

ii) Intracranial hemorrhage (ICH)

These tend to occur in LBW neonates more often.

a) Subarachnoid hemorrhage

- Most common form of ICH. Usually occurs due to injury during birth. Source of blood is bridging veins of subarachnoid space or from ruptured leptomeningeal vessel.
- Anticonvulsants may be needed for seizures.
- Resolves without sequelae mostly.

b) Subdural hemorrhage

- It is seen in cases of precipitate delivery, mid cavity forceps or delivery of a large baby leading to venous bleeding.
- Signs with an early presentation are those of increased intracranial pressure (bulging fontanelles, increasing FOC, neurological signs) due to accumulation of blood in anterior or posterior cranial fossae. Treatment is required only if there is progressive increased intracranial pressure.
- Treated with subdural tap or open evacuation.

c) Intraventricular hemorrhage (IVH)

- Hemorrhage in periventricular subependymal germinal matrix followed by flow into ventricular system.
- It is primarily seen in preterms < 1500g or < 34 weekers. If it occurs within 72 hours of birth it is called early IVH, after which it is called late IVH.
- The germinal matrix between caudate and thalamus is a watershed zone (supplied by end arteries). This is area is prone to damage in hypoxic-ischemic injury.

Ultrasonographic staging of IVH	
Grade 1	Germinal matrix hemorrhage
Grade 2	IVH without ventricular dilatation
Grade 3	IVH with ventricular dilatation
Grade 4	Intraventricular hemorrhage with parenchymal involvement.

iii) Perinatal asphyxia & Hypoxic-Ischemic Encephalopathy (HIE)

Hypoxia is insufficient arterial oxygen concentration; ischaemia is insufficient blood flow to the cells.

a) Pathophysiology of HIE

Hypoxia-ischemia is associated with two phases – *primary* and *secondary* energy failure – that culminate in brain injury:

- Perinatal hypoxia-ischemia can cause **primary** neuronal injury and cell necrosis as a response to low cerebral blood flow, low energy (↓ ATP). This is termed as **primary energy failure**.
- The hypoxic-ischemic insult as well as reperfusion elicit an inflammatory response with increased levels of pro-inflammatory cytokines and delayed brain injury. The continued generation of free radicals is contributes to **secondary energy failure** continuing

over several days to weeks.

- The interval between primary and secondary energy failure is called **''therapeutic time window''**. Therapeutic interventions in this phase help to protect the neonatal brain from further injury. It is thought to be about 6 hours.

b) Diagnosis

The diagnostic criteria for hypoxic-ischemic encephalopathy in term newborn infants require:

(1) Signs of perinatal or postnatal asphyxia:

a. Obstetrical causes of hypoxia-ischemia

b. Low apgar score at birth ,

c. Need for resuscitation, and

(2) Signs of encephalopathy characterized by abnormal neurological scores (sarnat or thompson score) and presence of seizure activity.

- Electroencephalographic (EEG) evidence of abnormal cerebral function
- A combination of neurological scores (in particular the Thompson score), continuous electroencephalographic assessment by EEG and neuroimaging methods (MRI) predicts neurological outcomes.

c) Treatment:

- Induced hypothermia— first established neuroprotective strategy to reduce HIE in full-terms.
    - Total body cooling (involves cooling to ~33.5°C for 72 hours with gradual re-warming over 6 h)
    - Selective head cooling.
- The beginning of treatment during *therapeutic window* has been shown to be successful in reducing the injury and delay of > 6 hours reduces the neuroprotective potential.
- Other preventive and supportive strategies include:
    - Avoidance of hypocapnia,
    - Hypotension,
    - Metabolic disturbances (acidosis, electrolyte imbalance, hypoglycemia), and
    - Treatment of seizure activity, if present.

d) Complications

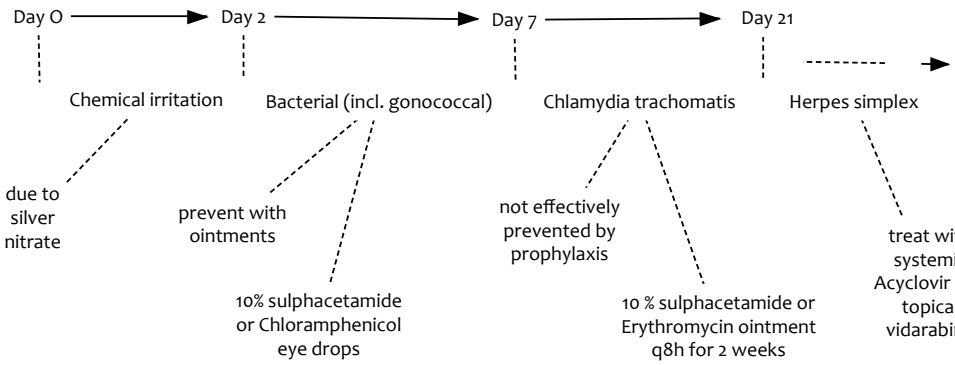
- Perinatal asphyxia and its long-lasting consequences are a huge burden to the child, family, and produce a worldwide burden of disability.
- Neonatal seizures

(XI) Neonatal infections

i) Superficial Infections

- Pyoderma: localized skin infection by staphylococci
- Umblical sepsis: a purulent discharge or inflamed periumblical area raises suspicion. Treat with topic antisepsis with spirit/alcohol or parenteral therapy may be indicated.

- Conjunctivitis:



- Oral thrush: White patches on tongue or buccal mucosa. Treat with topic nystatin drops or 1% gentian violet.

ii) Systemic infections

iii) TORCH infections

Infection	Description	Diagnosis	Treatment	Prevention
Toxoplasmosis	Convulsions, intracranial Calcifications, Chorioretinal scar (*Aide mémoire: 3 C's).* Hydrocephalus, ring enhancing lesions on head CT	Initial: IgM Most accurate: PCR	Pyrimetham rimethamine, sulfadiazine.	Avoid exposure to cat feces during pregnancy; avoid undercooked meat
Rubella	Deafness (MC) '*Bluberry muffin' rash*, Cataracts and 'salt and pepper' chorioretinitis, PDA and multiple Pulmonary stenoses, tis (periventricular calcification) maximum fetal transmission if infected between 6-8weeks of pregnancy.	Elevated maternal IgM with clinical picture	None	Immunize mother prior to pregnancy
Cytomegalovirus	Petechial rash, periventricular calcifications, microcephaly, chorioretinitis	Initial: Urine/saliva viral titers. Most accurate: PCR	Ganciclovir Acyclovir	
Herpes	Skin, eye and mouth vesicles, can progress to severe systemic infection or encephalitis.	Initial: Tzanck smear. Most accurate: PCR	Acyclovir	Avoid exposure, C-section if mother has active lesions
Syphilis	Maculopaular skin rash, lymphadenopathy, 'snuffles' peri-osteitis, Interstitial keratitis If infected during first trimester (maximum risk of abortion)	Initial: VDRL/RPR. Most accurate:FTA-Abs/ Dark field microscopy	Penicillin	Treat seropositive mothers with penicillin

a) Neonatal sepsis

- The most common causative organisms are: *E. coli*, klebsiella and enterobacter, pseudomonas, proteus, and staphylococci. The last three more commonly cause late-onset sepsis.
- The diagnosis is made by multiple blood cultures in light f supportive tests like CBC, CRP, ESR.
- Treatment is usually broad spectrum for the most common organisms in the specific age group till culture sensitivities are available. Usually a third generation cephalosporin with an aminoglycoside combination is used.

b) Neonatal meningitis

- It has similar presentation, usually with fever, neck stiffness, bulging fontanelles.
- Blood cultures are required in addition to cerebrospinal fluid D/R and C/S.
- Treatment is similar to neonatal sepsis. But duration of treatment may be longer.

c) Neonatal tetanus

It occurs in the newborn by contamination of the umbilicus by clostridium tetani, which produces a spastic neurotoxin. Inability to suck and trismus (lock jaw) are first to occur. Risus sardonicus, opisthotonus, and neck retraction may develop. Generalized tonic clonic seizures may occur triggered by sudden noise or stimulation.

Treatment

- Antibiotics- IV penicillin for 7-10 days
- Tetanus immune globulin
- Anti-tetanus serum

Prevention

An effective method of prevention is to give mother 2 doses of tetanus toxoid a month apart and only one injection in subsequent pregnancies. The antibodies from maternal serum cross placenta and prevent tetanus.

Dose of TT or Td	When to give	Duration of protection
1	At first contact or as early as possible in first pregnancy	None
2	Atleast 4 weeks after TT1	1-3 years
3	Atleast 6 months after TT2 or during next pregnancies	Atleast 5 years
4	Atleast 1 year after TT3 or during next pregnancy	Atleast 10 years
5	Atleast 1 year after TT4 or during next pregnancy	For all childbearing age years & possibly longer

The WHO recommends the above-mentioned schedule of dosing to protect unvaccinated mothers for the ***complete duration of their reproductive lives.***

CHAPTER 23 HEMATOLOGY

(I) Anemia

Table. Mean Hb values in pediatrics age groups.	
Age	**Mean hemoglobin**
First days after birth (full term)	18.5 mg/dL
1 month	14
2-6 months	11.5
6 months-2 years	12
2 years-6 years	12.5
6-12 years	13.5
12-18 years	12-14

Table. Anemia criteria based on WHO guidelines		
Age group	**Hemoglobin less than:**	**Hematocrit less than:**
6 months to 5 years	11 g/dL	0.33
5 to 11 years	11.5 g/dL	0.34
12 to 14 years	12 g/dL	0.36

i) Microcytic anemias

a) Iron deficiency

(Refer to chapter on Vitamins and Minerals)

b) Thalassemia

- Thalassemia is a hemoglobinopathy due to mutations in the gene coding for Hemoglobin chains.
- Adult haemoglobin (Hb A_1) is a tetramer, composed of 2 α-globin chains and 2 β-globin chains.
- In α-thalassemia there is diminished synthesis of α-globin chains, leading to a relative excess of β- or γ- chains:
    - In fetal life, excess γ-chains (predominant HbF) form tetramers (γ_4)—known as **Hemoglobin Barts.** Barts haemoglobin in unable to release oxygen to tissues and causes severe hypoxia, extravascular hemolysis and non-immune hydrops in the fetus.
    - Beyond neonatal period, excess β-chains (predominant HbA) form tetramers (β_4)— known as **Hemoglobin H.**
- An opposite phenomenon occurs in β-thalassemia, in which excess α-chains accumulate

and form aggregates. This leads to RBC membrane damage and rapid hemolysis.

- β° Thalassemia → complete absence of β-chain
- β^{+} Thalassemia → Partial reduction β-chain

Table. Hemoglobin types and constituent chains	
Hemoglobin	**Constituent chains**
Hb A_1	$\alpha_2 \beta_2$
Hb F	$\alpha_2 \gamma_2$
Hb A_2	$\alpha_2 \delta_2$
Hb Barts	γ_4
Hb H	β_4

β-Thalassemia

There are 3 forms of β-thalassemia.

Thalassemia Minor (β-Thalassemia trait)

- Individual has only one copy of β-chain genes (Heterozygous)
- Mildest form - patient are usually asymptomatic

Thalassemia intermedia

- Condition intermediate between major and minor
- Individuals may rarely need occasional transfusion

Thalassemia major (Cooley's anemia)

- Homozygous for β-Thalassemia genes.
- Severe transfusion dependent
- Manifests at 6-9 months as haemoglobin synthesis switches from HbF to HbA.

Clinical Features

- There is progressive pallor, growth failure, jaundice of varying degree and enlargement of liver and spleen starting soon after birth.
- Recurrent respiratory infections are common.
- Physical retardation of growth may be accompanied by hypogonadism.
- Thalassemic or hemolytic facies refer to characteristic facial appearance as:
  - Frontal bossing
  - Prominent maxillae
  - Depressed bridge of nose
  - Malocclusion of teeth
- By adolescent age, cardiomyopathy due to chronic anemia and progressive myocardial iron deposition as a result of increased iron turnover may be seen

Investigations

- Peripheral Blood Smear

- Anisocytosis (Variation in size of RBCs)
- Poikilocytosis (variation in shape of RBCs)
- Microcytic hypochromic RBCs
- Target cells (Hemoglobin collects in centre of RBCs)
- Basophilic stippling
- Fragmented RBCs

- Xray imaging of skull may show hair-on-end appearance during to hematopoiesis
- Other supportive labs show:
  - MCV ↓, MCH ↓ and MCHC ↓
  - Serum Iron ↑, Serum Ferritin ↑
  - HbA2 ↑
  - HbF ↑

Treatment

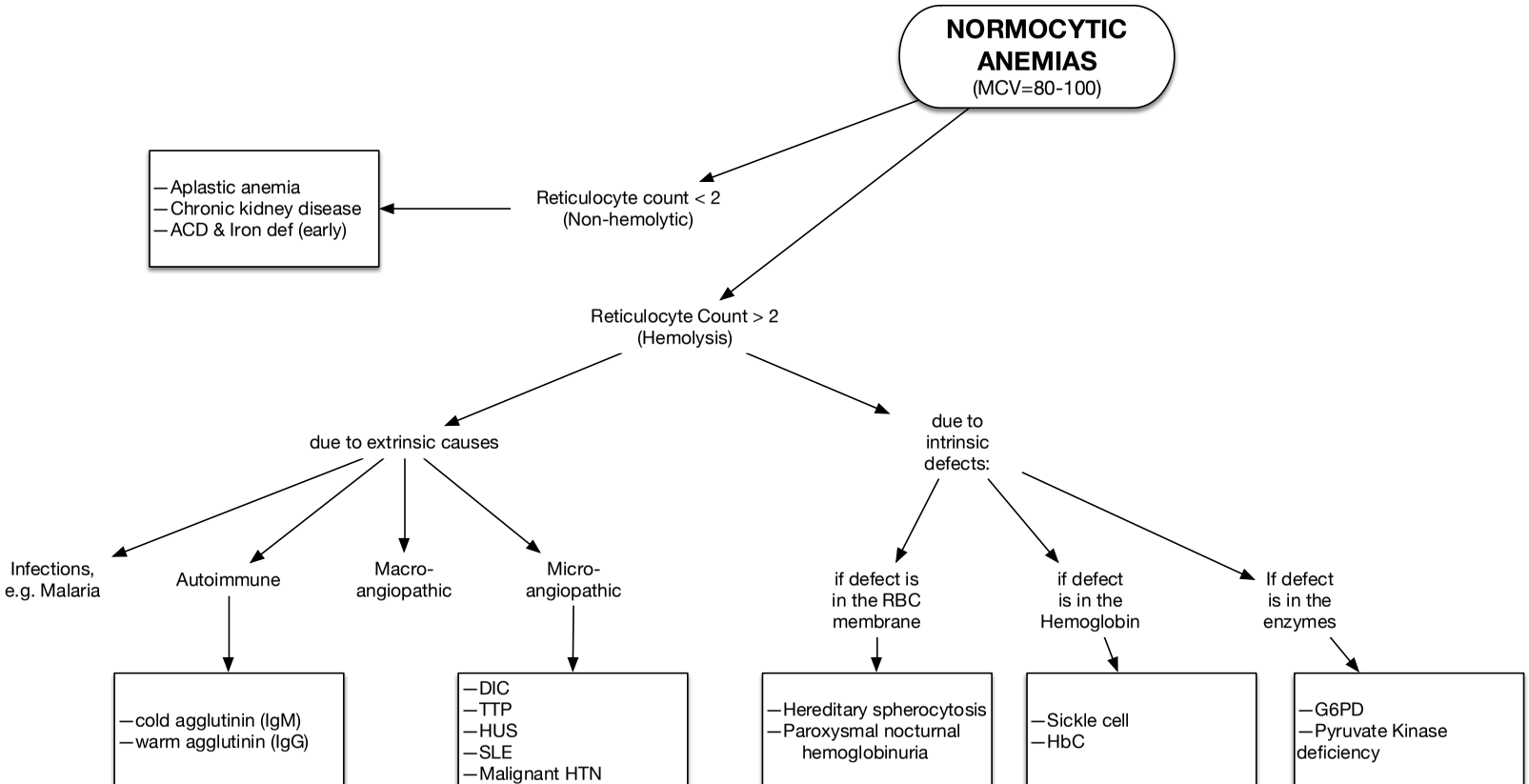
- Transfusions-chelation (desferrioxamine) therapy is effective.
  - Desferrioxamine is effective for chelation of excess iron (maintain ferritin <1000 ng/ml)
  - Vitamin C also enhances excretion of iron by chelation
  - *Blood is transfused regularly to maintain Hb of atleast ~10.5 g/dL*
- Deferoxamine to chelate excessive iron
- Splenectomy may be required for splenomegaly
- Allogenic bone marrow transplantation using a matched sibling donor is curative.

Prognosis

- Prognosis depends on treatment in the form of high transfusion program and adequacy of chelation therapy.
- By adolescent age, cardiomyopathy due to chronic anemia and progressive myocardial iron deposition as a result of increased iron turnover may be seen

ii) Normocytic anemias

(*continued*)


NORMOCYTIC ANEMIAS
(MCV=80-100)
Reticulocyte count < 2
(Non-hemolytic)
—Aplastic anemia
—Chronic kidney disease
—ACD & Iron def (early)
Reticulocyte Count > 2
(Hemolysis)
due to extrinsic causes
due to intrinsic defects:
Infections, e.g. Malaria
Autoimmune
Macro-angiopathic
Micro-angiopathic
if defect is in the RBC membrane
if defect is in the Hemoglobin
If defect is in the enzymes
—cold agglutinin (IgM)
—warm agglutinin (IgG)
—DIC
—TTP
—HUS
—SLE
—Malignant HTN
—Hereditary spherocytosis
—Paroxysmal nocturnal hemoglobinuria
—Sickle cell
—HbC
—G6PD
—Pyruvate Kinase deficiency

a) G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common X-linked disorder.

G6PD catalyzes the first reaction in the oxidative pentose phosphate pathway, through which red cells' glucose is metabolized to provide a continuous supply of the reduced NADPH. NADPH converts oxidized glutathione (GSSG) to its reduced form (GSH).

Reduced glutathione (GSH) is directly involved in detoxification and reduction of the various free radicals accumulating in the red cells (e.g. H_2O_2).

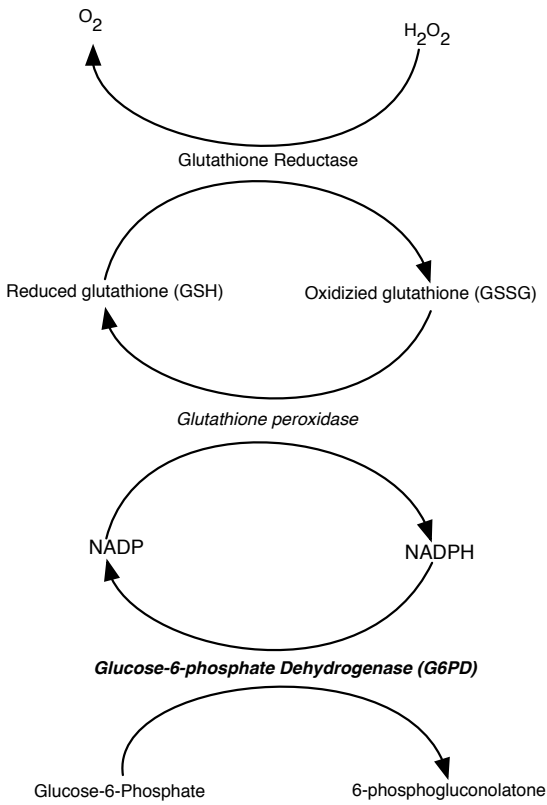


Figure. Glucose-6-phosphate dehydrogenase (G6PD) biochemistry

Clinical Features

- Most commonly presents as an episodic crisis upon exposure to oxidants, or in the neonatal period as jaundice mostly without anemia.
- Children with G6PD deficiency develop episodic hemolysis (leading to hemolytic anemia) upon exposure to oxidants, e.g.
    - Sulfa drugs,
    - Antimalarials,
    - Infections (hepatitis, pneumonia, typhoid, etc.)
    - Fava beans (*favism*)
- This hemolysis can begin within a few hours to 3 days after the exposure to offending agent as manifesting as:
    - Jaundice,
    - Abdominal pain,
    - Vomiting

- G6PD deficiency confers some degree of protection from the potentially lethal malaria parasite probably due to shortened lifespan of RBCs and/or enhanced macrophage-recognition of the parasite-infected G6PD deficient RBCs, and accelerated removal of the cells (suicidal infection).

Investigations

- *The diagnosis is straight forward if there is a classical history of fava bean ingestion, or anti-malarial use leading to hemoglobinuria*
- Children are usually asymptomatic and hematology labs CBC, platelets and antibody testing may be normal normal in between episodes.
- Spectrophotometric analyses—detection of NADPH in RBCs (WBCs and Platelets give false negatives) is the specific test for diagnosis.
- Supportive blood smear testing shows:
    - Heinz bodies (hemoglobin denatured by oxidative stress)
    - Bite cell (due to eating of hemoglobin leaving behind defects that look like bites on the cell).

Treatment

Acute hemolysis

- Hemolytic crisis is self-limited and resolves spontaneously.
- Children with severe anemia or ongoing hemolysis should be considered for transfusion.
- Splenectomy— effective in hypersplenism and decreases the need for frequency of transfusions.

Complications

- Cataracts: the lens of the eye is composed of non-nucleated cells (and hence relatively more deficient in G6PD), which might be the site of developing juvenile cataracts in young people.
- Renal failure in hemolytic crisis

Prevention

- Genetic counseling and prenatal diagnosis should be considered in severe cases.
- It is recommended to test for G6PD status before starting primaquine.

iii) Megaloblastic anemias

(Refer to chapter on Vitamins and Minerals)

(II) Bleeding disorders

i) Normal physiology

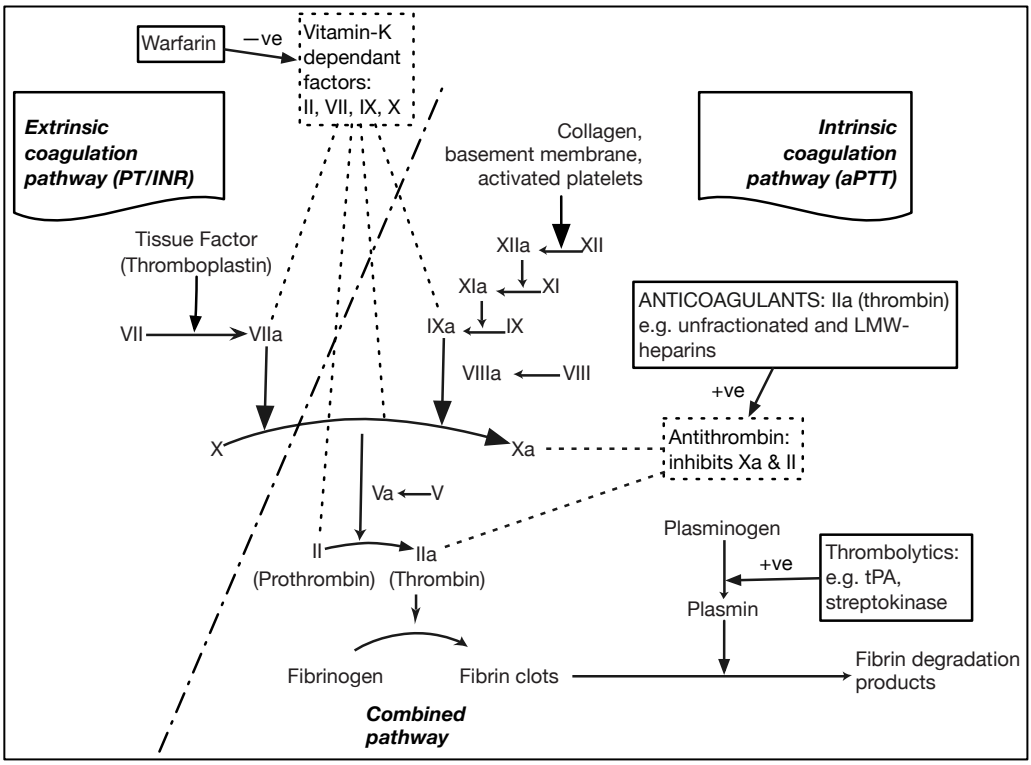


Figure. The clotting cascade

ii) Idiopathic thrombocytopenic purpura (ITP)

- It is the most common acquired platelet disorder of childhood.
- It is characterized by decrease in platelet count (<100,000) is seen in the absence of other causes.
- It is most often preceded by a nonspecific viral infection severeal weeks earlier in age group 1-4 years mostly.
- It is thought to be due to autoantibodies against platelet antigens. It of two types:
- Acute ITP: is realtively common, and and tends to resolve within 2 months. Platelets counts can very low (<20,000).
- Chronic ITP: persists for 6 months without a specific cause, usually seen in adults and persists for months to years. Platelet counts are usually in range of 30,000 to 80,000.

a) Clinical features

- Most common presentation— spontaneous appearance of petechiae and bruises.
- Epistaxis
- Hematuria
- Oral mucosal bleeding
- **Absence of splenomegaly is an essential diagnostic criteria**

b) Investigations

CBC shows normal RBC, and WBC counts with low platelet counts, sometimes <20,000

Bone marrow biopsy shows normal-to-increased megakaryocytes

c) Treatment

- Transfusion is usually not need unless life-threatening bleeding (platelet antibodies will bind to transfused platelets as well)
- No specific treatment if platelets > 20,000 and ***no active*** bleeding
- If very low platelets, ongoing bleeding that is difficult to stop or life-threatening:
    - Intravenous immunoglobulin (IVIG) for 1–2 days
    - If inadequate response with IVIG, then prednisone may be used
    - Splenectomy reserved for older child with severe disease

iii) Hemophilia and Von-Willebrand's Disease

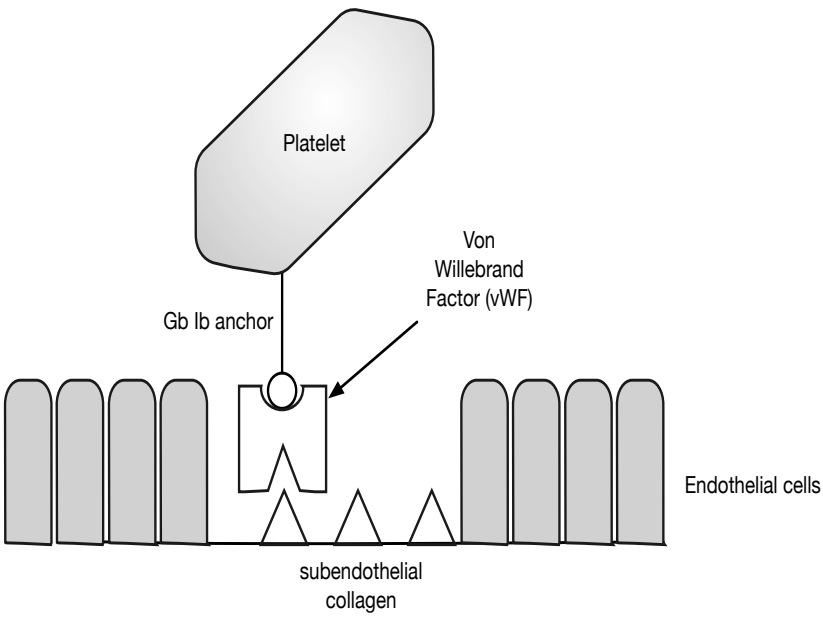


Figure. Physiology of the von-Willebrand's factor.

a) Clinical Features

- Mucous membrane and skin bleeding manifestations (petechiae, small ecchymoses~superficial bleeding) are seen in:
    - Platelets dysfuntion
    - Von-Willebrand's disease (vWD)
- Deep bleeding with more extensive ecchymoses and hematomas (e.g. haemarthroses) are seen in cases of clotting factor deficiencies:
    - Hemophilia A (Factor VIII deficiency)
    - Hemophilia B (Factor IX deficiency, also known as Christmas disease)

Table. Hemophilia A and Von Willebrand's disease characteristics.			
		Hemophilia A	**Von Willebrand's disease (vWF)**
Transmission		X-linked	Autosomal dominant
Defect		Factor VIII	Von willebrand factor
Site of bleeding		***Operative, joint***	***Mucous membranes, skin***
Platelet adhesion		Normal	Defective
Investigations	PT/INR	Normal	Normal
	APTT	Prolonged	Prolonged
	Bleeding time	Normal	Prolonged
	Factor VIII levels	Low	Low or normal
	vWF activity (Ristocetin testing)	Normal	Low
Management		Factor VIII concentrates, Desmopressin	Fresh Frozen Plasma transfusions, cryotherapy, Desmopressin

b) Management

- Replacement of the deficient clotting factor in cases of clotting factor deficiencies.
- Replacement of both vWF and Factor VIII may be required in vWD (vWF protects Factor VIII from degradation).
- Desmopressin induces release of vWF from patient's own Weibel-Palade bodies in endothelial cells. Can also increase factor VIII in mild hemophilia A disease.

iv) Differential diagnosis based on coagulation profile

Table. Usual causes of abnormal coagulation profile		
Abnormal PT and aPTT	**Abnormal aPTT only**	**Abnormal PT/INR only**
Vitamin K deficiency Liver dysfunction Warfarin therapy DIC	Hemophilia Von-Willebrand's disease	Warfarin therapy Factor VII deficiency

CHAPTER 24 GI AND LIVER DISEASES

(I) Congenital gastrointestinal malformations

i) Intussusception

- It refers to the telescoping of a bowel segment in to itself.
- There is a high risk of arterial occlusion, intestinal segment necrosis.
- Affects children 4 months to 2 years of age
- MC cause of bowel obstruction in first 2 years of life; ***usually ileocecal;***
- Presents as paroxysmal abdominal pain, palpable **sausage shaped mass**, ***'currant jelly' stools*** (due to blood and mucus), bilious vomiting;
- Barium enema is both diagnostic and theraputic;
- Associated with Henoch-schonlein purpura and cystic fibrosis

ii) Volvulus

- Volvulus occurs in the background of malrotated gut as predisposing condition. The gut can twist on itself due to incomplete fixation to the posterior abdominal wall.
- Tends to occur in first 2 years of life.
- When midgut volvulus occurs, venous drainage of bowel segment is impaired → congestion → ischemia, pain, tenderness, distention, and often with bloody emesis, stools and peritonitis. The child may have toxic look.
- A decreasing platelet count is a common indicator of bowel ischaemia.
- Immediate surgery to reduce ischemic injury and necrosis.

iii) Exomphalos and gastroschisis

- These conditions present with congenital herniation of abdominal contents
    - Exomphalos is the herniation through umbilicus. Bowel and viscera covered with membranous sac. Associated with other congenital abnormalities
    - Gastroschisis: Herniation through abdominal wall defect lateral to umbilicus. Bowel is not covered with membrane.
- First step in management is covering the abdomen with to conserve body heat and fluid loss especially with gastroschisis.
- I.V fluid replacement and nasogastric tube as required.
- Definitive treatment is primary surgical closure if it is a small defect; while gradual reduction may be needed with silastic silo if the defect is large.

iv) Meckel's diverticulum

- A remnant of omphalomesenteric duct that persists as an outpouching of the distal ileum; can contain ectopic gastric mucosa.
- Meckel's diverticulum can predispose to intussusception, obstruction or volvulus.
- Acute inflammation of the diverticulum may mimic appendicitis-like presentation.

Rule of 2s for Meckel's diverticulum
2% of population affected
2 inches long,
Within 2 feet of ileocolic junction,
Presents in the first 2 years of life.

- Presentation is variable. Can be asymptomatic throughout life, or cause massive, painless GI bleeding. Ectopic gastric mucosa may cause mucosal ulceration in the ileum.
- Meckel scan (technetium radionucide scan) can detect ectopic gastric mucosa. other investigations include ultrasound, barium enteroclysis and laparoscopy.
- Definitive treatment is with surgical removal.

v) Meconium ileus

- In cystic fibrosis, meconium plug obstructs intestine preventing stool passage.
- Affects children 0-2 weeks; may cause late feculent vomiting, rectal prolapse

vi) Pyloric stenosis obstruction;

- Hypertrophy of pylorus - gastric outlet obstruction.
- Affects first-born male infants more often around 2 week- 4 months of age.
- **Nonbilious projectile vomiting**, palpable olive shaped mass in epigastrium; hypochloremic, hypokalemic metabolic alkalosis due to excessive vomiting.
- Ultrasound imaging is gold standard for diagnosis.
- Management is by first correcting dehydration and metabolic abnormalities due to excessive vomiting.
- Definitive treatment is Ramstedt's pyloromyotomy procedure.

vii) Duodenal Atresia

- Affects infants 0-1 week;
- Early **bilious vomiting** with proximal stomach distension (**"Double bubble" sign on X-ray**). Associated with *Down's syndrome*.
- Treatment: duodenoduodenostomy

viii) Tracheoesophageal fistula (TEF)

- Most common type is a blind ending atretic esophageal pouch and fistula between distal esophagus and trachea.
- Presents in the first few hours of life with copious salivation, choking, cyanosis, respiratory distress; aspiration pneumonia; gastric distension from air occurs.
- Prenatal polyhydramnios may be observed.
- If a nasogastric tube is inserted, may show coiling of the tube in upper esophagus due to atresia of the segment.
- Treatment is mainly surgical correction.
- TEF is associated with other VACTERL anomalies, and should be examined for.

"VACTERL" associated anomalies
Vertebral anomalies
Anal atresia
Cardiac defects
TracheoEsophageal fistula
Renal anomalies
Limb abnormalities

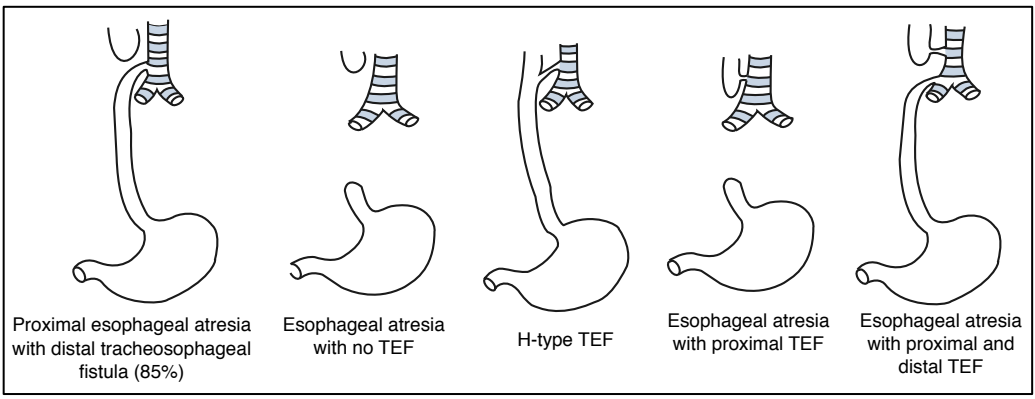


Figure. Tracheosophageal fistula types, arranged in decreasing frequency of occurrence.

ix) Hirschsprung's disease

- Also known as "aganlionic megacolon".
- Full thickness biopsy of segment shows absence of ganglion cells/enteric nerve plexuses (Auerbach's and Meissner's) in the affected segment of colon;
- Narrowing of anganglionic segments with dilation of proximal normal colon.
- Presents at infancy or within first 2 years of life;
- Failure to pass meconium, abdominal distension, chronic constipation;
- Staged procedure with initial diverting colostomy and later resection when infant is > 6 months old.

(II) Congenital Biliary Atresia

- This is failure of canalization or obstruction of biliary ducts early in life.
- Some studies suggest association with Reovirus type-3 infection as the trigger.
- Jaundice appears in 2nd or 3rd week of life and progresses slowly.
- *The urine is dark yellow and stools are clay colored due to decreased fat absorption.*
- There is gross hepatomegaly. Other complications seen may be due to fat-soluble vitamin deficiencies (Vitamins A, D, E and K).

i) Diagnosis

- Technetium-99 scan shows failure of dye to be excreted into the intestine
- Liver biopsy

ii) Treatment

- Surgical- Kasai's procedure (porto-enterostomy) **within first 8 weeks.** *Prognosis is unfavorable after 8 weeks.*
- Liver transplant may be considered.

(III) Viral Hepatitis

i) Hepatitis A

It is an RNA virus transmitted by feco-oral route and contaminated water and food. There the virus elicits an inflammatory response that leads to hepatocellular necrosis.

a) Clinical Features

- Clinical disease manifests in phases
- After exposure, the incubation period lasts 28 days on average.
- **Prodromal phase** that can include fever, nausea, vomiting, malaise, & abdominal pain.
- A minority of children may then enter a 1–2 week **jaundiced (icteric) phase**, during which they exhibit jaundice and often have tender hepatomegaly. Although majority remains asymptomatic.
- This is followed by a **convalescent phase** during which their clinical symptoms and signs improve and resolve over 2–4 weeks.
- Acute liver failure or fulminant hepatic faiure can occur rarely

b) Investigations

- Diagnosis is mainly clinical with supportive labs show:
    - ↑ --hepatic alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
    - They peak 3–10 days after the onset of clinical symptoms and can remain abnormal for 2–4 weeks.
    - Hyperbilirubinemia
- Liver biopsy is rarely done but shows— acute inflammation of the liver parenchyma and include hepatocellular necrosis and regeneration, leukocyte invasion of the parenchyma and portal tracts, and proliferation of bile ducts and Kupffer cells.
- Specific diagnosis is based on:
    - Anti-HAV antibodies— IgM confirming recent infection in symptomatic and IgG confirming exposure previously.
    - Anti-HAV IgG persists and confers lifelong protection. Testing a patient's stool for HAV virus in culture or genetic material is often of little use because the virus is so common.

c) Treatment

It is supportive to prevent dehydration, and spread of disease

More aggressive supportive therapy is needed for complications like acute hepatic failure, and may include parenteral nutrition, fluid management, coagulation factors, and sometimes liver transplantation.

d) Prevention

- Improved water sanitation,
- Vaccination
- Postexposure prophylaxis can be given to individuals with possible hav exposure to prevent symptoms and spread of the virus.
    - Anti-HAV vaccine is sufficient for post-exposure prophylaxis for children > 12 months of age.
    - Anti-HAV immune globulin should be given to infants <12 months and those who are immunocompromised.

ii) Hepatitis B

Hepatitis B virus (HBV) is a DNA virus spread by parenteral blood-to-blood contact, or via sexual contact.

Acute infection includes intracellular viral replication and causes an inflammatory response, which causes hepatocellular necrosis and degeneration.

a) Clinical Features

- The incubation period is highly variable, lasting 4–26 weeks before viral antigens appear in the serum.
- Clinical signs and symptoms of acute infection may be absent or may be similar to those of Hepatitis A.
- A prodromal phase may include headache, nausea, vomiting, abdominal pain, malaise, and fever.
- An **icteric (jaundiced) phase** then follows and *can include* jaundice, pruritus, dark urine, and pale- stools. Lymphadenopathy, a tender right upper quadrant, and hepatomegaly may also be seen.
- Sometimes a serum-sickness like picture with HBV is seen as:
    - Fever,
    - Arthralgias or arthritis,
    - Erythematous maculopapular rash.
- Acute HBV infection is also associated with vasculitis (most commonly polyarteritis nodosa) and membranous glomerulonephritis (type of nephrotic syndrome),
- Age, immune status, viral genotype, and the HBV infecting dose all affect the clinical outcome of HBV infection. Infection is more likely to become chronic with ***young age at exposure*** to the virus, occurring in up to 90% of exposed neonates. I
- 30% of children ages 1–5 years develop chronic HBV infection.
- Most infections that occur in the perinatal or young childhood period are asymptomatic in the acute period, and clinical signs of disease rarely arise before the second or third decade of life.

b) Investigations

- Acute cases should be be screened for HDV, which can coinfect persons with HBV,
- Diagnosis and determination of chronicity and infectivity depend primarily on serology

Table. Serology in Hepatitis B infection		
HBsAg	Hepatitis B surface antigen	First serological marker; usually becomes undetectable at 6 months
HBsAb	Hepatitis B surface antibody (Anti -HBs)	Detectable once HBsAg clears; remains indefinitely
HBcAg	Hepatitis B core antigen	*Not detected routinely*
HBcAb	Hepatitis B core antibody (Anti-HBc)	Detectable 1–2 weeks after HBsAg (IgM initially, then IgG)
HBeAg	Hepatitis B e antigen	Occurs shortly after HBsAg; correlates with viral replication and infectivity
HBeAb	Hepatitis B e antibody (Anti-HBe)	Correlates with ↓ viral replication and infectivity
HBV DNA	Hepatitis B DNA testing by PCR	Quantifies viral replication

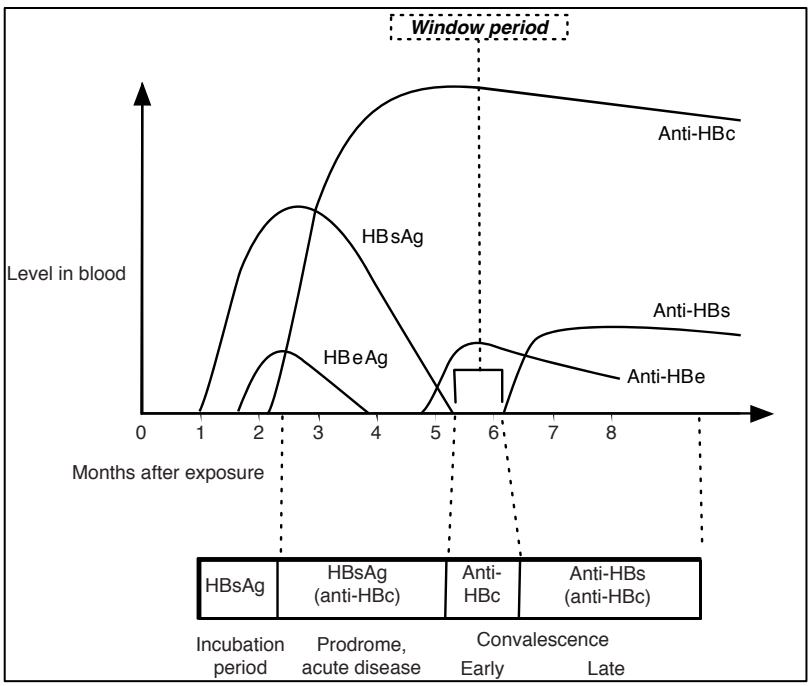


Figure. Hepatitis B virus serologies.

- *Detection of HBcAg or HBsAg in the absence of vaccination confirms infection.*
- There is a window mperiod Antibodies to HBsAg, and HBeAb, anti-HBs, anti-HBc and anti-HBe, are "**window period**" during which HBsAg may be negative before anti-HBs is detectable. Anti-HBc antibodies of the IgM type can be very helpful in diagnosing recent infection, whereas IgG antibodies to any of the antigens indicate past infection only. Advances in polymerase chain reaction (PCR) techniques allow detection of lower levels of HBV DNA.
- Should be screened for HDV, which can coinfect persons with HBV,
- Regular monitoring of ALT and HBeAg in HDV coinfections should be done for evidence of active liver disease and seroconversion.
- Abdominal ultrasound can be useful in evaluating for hepatocellular carcinoma.
- Liver biopsy helps assess severity of damage and complications, e.g. hepatocellular carcinoma.

Table. Serology of different forms of Hepatitis B exposure						
	Non-infected non-immune	Vaccinated	Acute infection	Chronic infection		Resolved infection
				High infectivity	Low infectivity	
HBsAg	–	–	+	+	+	–
HBeAg	–	–	+/–	+/–	–	–
Anti HBs IgG	–	+	–	–	–	+
Anti HBc IgM	–	–	+	–	–	–
Ani HBc IgG	–	–	–	+	+	+
Anti HBe IgG	–	–	–	–	+	+/–

c) Treatment

- Generally, the treatment is generally supportive for acute HBV infections.
- Therapy is focused to slow or stop viral replication (normalization of liver transaminases and clearance of HBV DNA and HBeAg) and reduce morbidity and mortality with chronic infection.
    - Specific treatment indicated in:
        - Chronically infected children with active liver disease (↑ ALT) and active viral replication (↑ HBV DNA).
        - Cirrhosis,
        - Coinfection with HDV,
        - Acute deterioration in liver function
    - Drugs for use in children include:
        - Interferon-α, or its pegylated form
        - Lamivudine.

d) Complications

- Acute Injury may subside and symptoms usually resolve over the course of 6–8 weeks.
- ***Chronic hepatitis, caused primarily by HBV, Hepatitis C and D viruses (HCV, HDV), is characterized by persistent elevations of liver aminotransferases, hyperbilirubinemia, and detectable viral antigens and genetic material.***
- There is a higher risk of acute liver failure with HBV and HBV+HDV coinfections.
    - Coinfection with Hepatitis D virus increases a patient's risk of developing this serious complication.
    - Extensive liver necrosis can be fatal.

e) Prevention

- Three doses of vaccine at 6, 10 and 14 weeks after birth.
- Postexposure prophylaxis is for infants born to chronically infected mothers requires administering HBV vaccine + HBV immune globulin (HBIG), within 24 h after delivery.
- HBIG is **very effective** in reducing the risk of mother to child transmission.

iii) Hepatitis C

The hepatitis C virus is also transmitted parenterally and causes chronic infection and serious sequelae.

a) Clinical Features

- Children with hepatitis C are generally asymptomatic, but may have mild nonspecific malaise, anorexia, or abdominal pain.
- Hepatomegaly is the most frequent sign of disease in young children.
- Clinical progression of disease in those with chronic HCV infection is often slow, with fluctuating serum liver function tests and recurrent or chronic evidence of inflammation, but leads to cirrhosis in up to a quarter of cases.
- Pruritus, ascites, growth failure, digital clubbing, palmar erythema, cutaneous xanthomas, and prominent abdominal vessels are few of the stigmata of chronic liver disease.

b) Investigations

- Diagnosis is based on detection of viral RNA, which can be done by PCR or other assays.
- ***Chronic infection is determined by detecting HCV RNA in serum twice, at least 6 months apart.***
- Measuring anti-HCV antibodies is useful to screen for past exposure, but they may be absent in recent infection, and in infants, may represent maternally transmitted antibody up to 18 months of age.
- Genotype determination is helpful prognostically— genotypes 2 and 3 are more responsive to antiviral treatment

c) Treatment

- Management of patients with chronic hepatitis C infection reduces the risk of morbidity and mortality due to long-term sequelae including cirrhosis, liver failure, and hepatocellular carcinoma.
- Liver function tests and HCV RNA are used to monitor the course of illness.
- Liver biopsy can be helpful in evaluating degree of liver injury
- Ultrasound surveillance is recommended hepatocellular carcinoma in adults (rare in childhood)
- Antiviral therapy reduces the risk of transmitting infection, severe liver disease or hepatocellular carcinoma.
- These risks, weighed against the risks of therapy and the possibility of spontaneous viral clearance, inform decisions about whether and when to treat.
- Patients with genotypes 2 and 3, rather than genotype 1, and those with lower pretreatment HCV RNA levels respond better to therapy.
- Subcutaneous Interferon injections or Pegylated interferon (better) is used in combination with ribavirin.
- Duration of therapy for children in most cases is 48 weeks. Therapy can be stopped after 24 weeks in patients who do not show adequate response to therapy.

d) Complications

- Patients should be monitored for adverse effects of antiviral therapy, which include leu-

kopenia, neutropenia, and autoimmune hypothyroidism

- Chronic infection carries a high risk of development of
    - Cirrhosis and other stigmata of chronic liver disease
    - Hepatocellular carcinoma

e) Prevention

- Immunization against HAV and HBV in all.
- The most effective measure –widespread screening of blood products for HCV
- Avoidance of high-risk behaviors eg. multiple heterosexual or homosexual partners, I.V drug abuse, sharing razors etc.
- Screening is *not* recommended for pregnant women because there are no available measures to prevent mother-to-child vertical transmission. There is not sufficient evidence regarding a *relatively* increased risk of transmission with breastfeeding in HCV.

(IV) Fulminant hepatic failure

Fulminant hepatic failure in children is a clinical syndrome that evolves over a period of 8 weeks from the onset of signs and symptoms of liver disease.

- The synthetic, excretory, and detoxifying functions of the liver are all severely impaired, presenting in coagulopathy, jaundice, and hepatic encephalopathy.

Table. Causes of fulminant liver failure
Infection
Viral: Hepatitis A, B, C, D, and E
Drugs: Acetaminophen (dose-dependant), Halothane
Toxins
Metabolic
Autoimmune hepatitis
Vascular/ischemic
Budd–Chiari syndrome
Infiltrative
Leukemia, lymphoma

i) Clinical Features

- These include:
    - Progressive jaundice,
    - Fetor hepaticus,
    - Fever,
    - Anorexia,
    - Vomiting, and
    - Abdominal pain.
- Early stages of encephalopathy (thought to be related to cerebral edema) manifest as:
    - Irritability,
    - Poor feeding,

- Change in sleep habits,
- A characterisitic flapping tremer (asterixis) may be seen in older children.

Table. Clinical grades of hepatic encephalopathy	
Grade 1	Confused; altered mood or behavior, psychometric defects
Grade 2	Drowsy; irritability, poor feeding, disturbance of sleep
Grade 3	Stuporous but speaking and obeying simple commands; inarticulate speech; marked confusion
Grade 4	Coma

- Bleeding from the gastrointestinal tract and easy bruising, as a result of severe coagulopathy is a common finding.
- Pruritus, ascites, growth failure, digital clubbing, palmar erythema, cutaneous xanthoma, and prominent abdominal vessels suggest a chronic liver condition.

ii) Investigations

The cause of fulminant failure should always be investigated guided by clinical suspicion. Supportive labs include:

- Hepatic transaminases are markedly elevated.
- Serum direct and indirect bilirubin levels are increased.
- A coagulopathy is always present with prolongation of the prothrombin time, which does not improve after the parenteral administration of vitamin K.
- *Liver biopsy* may be helpful but is usually contraindicated due to coagulopathy. Patchy or confluent, massive necrosis of hepatocytes is commonly found on liver biopsy.

iii) Treatment

- The treatment of fulminant hepatic failure is primarily supportive with intensive care as needed.
- Lactulose is administered in a dose sufficient to produce several acidic loose bowel movements daily.
- Plasmapheresis or perfusion of the patient's plasma through an ion-exchange resin or a column of charcoal has been used in several studies.
- Gastrointestinal hemorrhage, infection, electrolyte imbalance, and hypovolemia may exacerbate hepatic encephalopathy and should be prevented/aggressively treated.

Table. Extrahepatic complications of fulminant hepatic failure
Cerebral edema
Coagulopathy
Hepatic encephalopathy
Acid–base disturbances
Gastrointestinal bleeding
Electrolyte imbalances
Renal failure
Sepsis
Hypoglycemia

- Mechanical ventilation and the administration of oxygen are often required.
- Prevent hypoglycemia.
- FFP or platelets may be necessary in cases of active heavy bleeding or in preparation for urgent surgery.
- Ascites may be managed by fluid restriction and diuretics
- Specific therapies are centered on the cause of failure, e.g.
    - NAC for acetaminophen overdose,
    - Removal of galactose-containing formula in children with galactosemia,
    - Intravenous glucose and avoidance of fasting for children with inherited defects in fatty acid oxidation,
    - Activated charcoal and high-dose intravenous penicillin for mushroom poisoning;
    - Lamivudine or entecavir for acute hepatitis B;
    - Acyclovir for herpes simplex virus infection;
    - Hemodynamic support for shock or ischemic liver injury;
    - Decompressive surgery or transjugular intrahepatic portosystemic shunts (tips) for acute budd–chiari syndrome,
- Liver transplantation— most effective treatment

iv) Complications

- Cerebral edema
- A functional form of renal failure – so-called **hepatorenal syndrome** – can occur in patients with liver failure and carries a poor prognosis.

v) Prognosis

- The prognosis varies and depends on the etiology of the hepatic injury, age, and stage of encephalopathy.
- Jaundice for more than 7 days prior to the onset of encephalopathy is associated with poor outcome.

(V) Wilson's Disease

Hepatolenticular degeneration (Wilson disease) is an **autosomal recessive** disorder of abnormal hepatobiliary copper excretion.

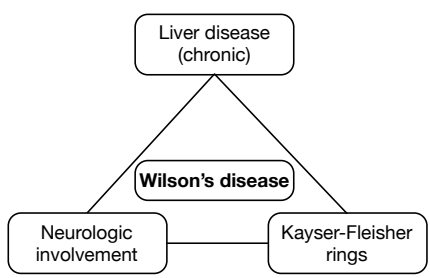


Figure. Classical triad associated with Wilson's disease is characterized by liver disease, neurologic involvement and Kayser-Fleischer rings.

i) Clinical features

The clinical features are reflect the stage of disease and sites of copper deposition

- Hepatomegaly, due to excessive accumulation of copper, is the earliest manifestation.
- Neurologic manifestations include
    - Personality and behavioral changes
    - Tremors of outstretched arms and wrists.
    - Dysarthria and dystonia (advanced stage)
- Jaundice, splenomegaly, and other stigmata of chronic liver disease may occur with long-standing untreated disease.
- Kayser–Fleischer rings occur due to copper deposition in cornea, best observed on slit-lamp examination of the eye.

ii) Investigations

- Best initial test: serum ceruloplasmin (decreased)
- 24 hour urinary copper excretion is increased (exponential increases are seen after penicillamine dosing).
- Liver biopsy shows periportal copper deposition confirms the diagnosis. Liver tissue copper exceeds 400 mcg/g dry weight.
- To assess other organ involvement: slit lamp eye examination, MRI, ECG, echo, EEG, EMG (electromyogram)

iii) Treatment

Prognosis is improved over the years due to early diagnoses, and prompt therapy.

- Low copper diet (aim for <1mg/kg/day intake, avoid liver, nuts, chocolate, shellfish etc)
- D-penicillamine (chelates copper), pyridoxine (vitamin B6) should be supplemented
- Liver transplantation may be considered in fulminant liver failure.

(VI) Diarrheal illness

- Diarrhea is defined as frequent passage of loose stools.
- Diarrhea occurs when the stool volume exceeds the normal value of approximately 10 g/kg/day in infants and toddlers, and 200 g/day in older children and adults.
- It can be classified into acute and chronic:
    - The WHO defines acute diarrhea as less than 14 days in duration and persistent diarrhea episodes as 14 days or longer in duration. It reflects an infectious cause (bacterial, viral, or parasitic infections), and is usually self-limited.
    - Chronic diarrhea refers to the persistence of loose stools (with or without an increase in stool frequency) for at least 14 days.
    - Such a distinction can help in forming a differential diagnosis, and thus impact management, as well as prognosis.
- Normally, the secretory process in intestines is balanced by fluid absorption. Diarrhea occurs when there is an imbalance between those two processes. This can occur through two basic mechanisms: *secretory or osmotic*.

- Osmotic diarrhea occurs when poorly absorbed osmotically active solutes are present in the gut lumen. These solutes draw water into the intestinal lumen with resulting watery stools and diarrhea.
    - The essential characteristic of osmotic diarrhea is that the stool output is proportional to the intake of the unabsorbable substrate, and the ***diarrhea disappears with fasting or cessation of ingestion of the offending substance.***
    - The most common cause of osmotic diarrhea is lactose intolerance.
- Secretory diarrhea occurs secondary to upregulation of the mechanisms involved in the active secretion of intestinal fluids, resulting in high-volume, extremely watery stools.
    - The most common cause for secretory diarrhea is infection. Enterotoxins from microbes bind to specific receptors on the enterocytes and activate secretory process, (e.g. Cholera toxin, *Escherichia coli* toxins, etc.)
    - Secretory diarrhea continues with fasting.
- Diarrhea can be further classified according to the stool characteristics into watery, fatty, or inflammatory.
    - Watery diarrhea implies a defect primarily in water absorption, and as discussed earlier, can either be secretory or osmotic.
    - Fatty diarrhea implies a defect in fat absorption.
    - ***Inflammatory diarrhea characterized by the present of mucus and pus in the stools, imply an infectious or inflammatory etiology.***

i) Assessment

On examination, the following should be looked for:

- Signs of dehydration:
    - Restlessness or irritability
    - Lethargy or reduced level of consciousness
    - Sunkeneyes
    - Skin pinch returns slowly or very slowly
    - Thirsty or drinks eagerly, or drinking poorly or not able to drink

Classification	Signs or symptoms	Treatment
Severe dehydration	≥ 2 of: - Lethargy/unconsciousness - Sunken eyes - Unable to drink or drinking poorly - Skin pinch goes back v.slowly (≥ 2 s)	- Diarrheal treatment **plan C in hospital**
Some dehydration	≥ 2 of: - Restlessness, irritability - Sunken eyes - Drinking eagerly, thirsty - Skin pinch goes back slowly	- Diarrheal treatment **plan B** - After rehydration, counsel on home treatment and when to return immediately.
No dehydration	Not enough signs to classify as some or severe dehydration	- Diarrheal treatment plan A at home
Always counsel when to return immediately, otherwise followup in 5 days if no improvement		

- Blood in stools and grading. Grading of stools can provide prognostically helpful information about effectiveness of treatment.

Table. Grading of stools in diarrheal illness	
Grade 1	Normal formed stools
Grade 2	Soft stools
Grade 3	Liquid stools taking the shape of container
Grade 4	Watery stools with flakes, appears opaque in glass container
Grade 5	Watery stools with few flakes, appears translucent in container.

- Signs of severe *malnutrition*
- Abdominal mass
- Abdominal distension.
- The degree of dehydration is graded according to symptoms and signs that reflect the amount of fluid lost.

ii) Investigations

- CBC
- Urea, creatinine, electrolytes
- Blood cultures
- Stool for:
    - pH and reducing substances
    - Leucocytes and RBCs
    - Ova and parasites
    - *E. coli* bioassay
    - Culture and sensitivity
    - Rota virus testing ELISA

iii) Management

- Oral rehydration solution (ORS) can be made:
- By mixing one WHO standard ORS packet in 1 liter of water and mixing well.
- Alternatively (if WHO standard packets are unavailable), homemade "salt-sugar solution" can be prepared by adding 2 finger pinch of salt and one large teaspoon of sugar to 200 mL of clean drinking water).

a) Antibiotic therapy

▶ FOR DYSENTERY AND CHOLERA:
Give recommended antibiotic for 5 days.
FIRTS-LINE ANTIBIOTIC — CIPROFLOXCIN
SECOND-LINE DRUG — METRONIDAZOLE (REFER TO FOLLOW UP BOX)

	CIPROFLOXCIN ▶ Give two times daily for 3 days		METRONIDAZOLE ▶ Give three times daily for 5 days	
AGE or WEIGHT	TABLET 500 mg	SYRUP 250 mg per 5 ml	TABLET 200 mg	SYRUP 200 mg per 5 ml
2 months up to 4 months (4 - <6 kg)				
4 months up to 12 months (6 - <10 kg)	1/5	1.5ml		
12 months up to 3 years (10 -< 14 kg)	1/3	3.5 ml	1/2	2.5 ml
3 years up to 5 years (14 - 19 kg)	1/2	5 ml	1	5 ml

b) Diarrheal treatment plans

Diarrhoea treatment plan A: Treat diarrhoea at home

COUNSEL THE MOTHER ON THE FOUR RULES OF HOME TREATMENT: GIVE EXTRA FLUID. GIVE ZINC SUPPLEMENTS. CONTINUE FEEDING. KNOW WHEN TO RETURN TO THE CLINIC.

1. Give as much extra fluid as the child will take.

Tell the mother to:
–Breastfeed frequently and for longer at each feed.
–If the child is exclusively breastfed, give ORS or clean water in addition to breast milk
–If the child is not exclusively breastfed, give one or more of the following: ORS solution, food-based fl uids (such as soup, rice water and yoghurt drinks) or clean water.

It is especially important to give ORS at home when:
–the child has been treated according to plan B or plan C during this visit.
–the child cannot return to a clinic if the diarrhoea gets worse.

Teach the mother how to mix and give ORS. Give the mother two packets of ORS to use at home.

Show the mother how much fl uid to give in addition to the usual fl uid intake:
< 2 years: 50–100 ml after each loose stool
> 2 years: 100–200 ml after each loose stool

Tell the mother to:
–Give frequent small sips from a cup.
–If the child vomits, wait 10 min. Then continue, but more slowly.
–Continue giving extra fl uid until the diarrhoea stops.

2. Give zinc supplements.

Tell the mother how much zinc to give:
> 6 months: half tablet (10 mg) per day for 10–14 days
> 6 months: one tablet (20 mg) per day for 10–14 days

Show the mother how to give zinc supplements:
– For infants, dissolve the tablet in a small amount of clean water, expressed milk or ORS in a small cup or spoon.
– Older children can chew the tablet or drink it dissolved in a small amount of clean water in a cup or spoon.

REMIND THE MOTHER TO GIVE THE ZINC SUPPLEMENT FOR THE FULL 10–14 DAYS.

3. Continue feeding.

4. Know when to return to the clinic.

Diarrhoea treatment plan B: Treat some dehydration with oral rehydration salts

GIVE THE RECOMMENDED AMOUNT OF ORS IN THE CLINIC OVER 4 H

Determine amount of ORS to give during fi rst 4 h:

Age[a]	≤ 4 months	4 - 12 months	12 months to 2 years	2 years to 5 years
Weight	< 6 kg	6 – < 10 kg	10 – < 12 kg	12 –19 kg
	200–400 ml	400–700 ml	700–900 ml	900–1400 ml

[a] Use the child's age only when you do not know the weight. The approximate amount of ORS required (in ml) can also be calculated by multiplying the child's weight (in kg) by 75.

If the child wants more ORS than shown, give more.

Show the mother how to give ORS solution.

– Give frequent small sips from a cup.
–If the child vomits, wait 10 min, then continue, but more slowly.
–Continue breastfeeding whenever the child wants.

After 4 h:

– Reassess the child and classify him or her for dehydration.
–Select the appropriate plan to continue treatment.
–Begin feeding the child in the clinic.

If the mother must leave before completing treatment:

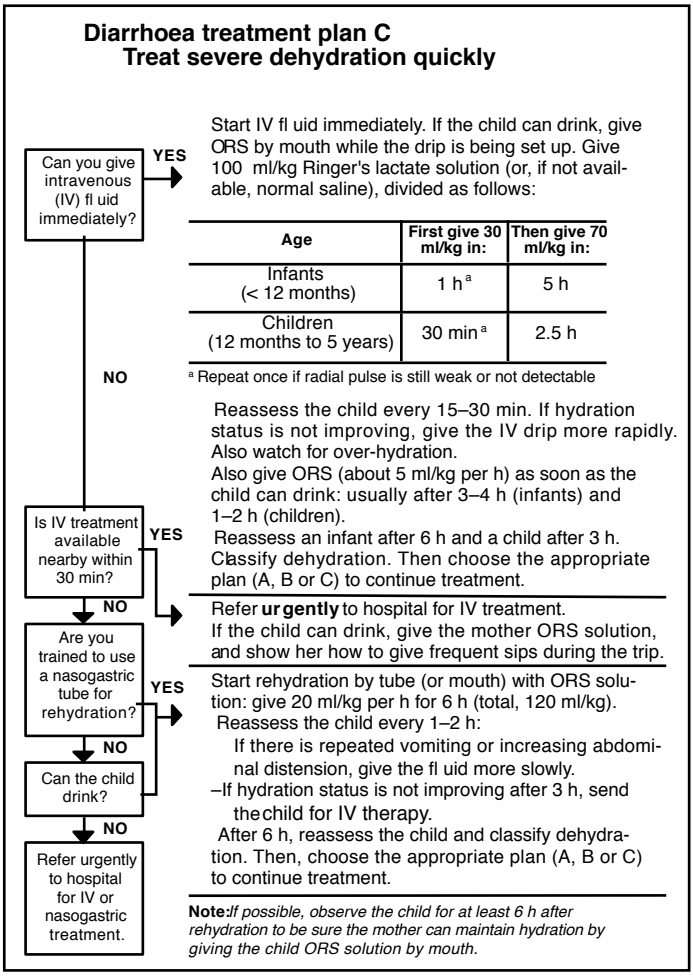
– Show her how to prepare ORS solution at home.
–Show her how much ORS to give to fi nish the 4-h treatment at home.
–Give her enough ORS packets to complete rehydration. Also give her two packets as recommended in plan A.
–Explain the four rules of home treatment:

1. Give extra fl uid.

2. Give zinc supplements.

3. Continue feeding.

4. Know when to return to the clinic.



iv) Chronic Diarrhea

a) Etiology

- Infectious causes:
    - Bacterial: The most common causes of infectious persistent diarrhea are bacterial microorganisms (enteroadherent *E. coli*, enteropathogenic *E. coli*, *Shigella*, *Cryptosporidium*, and *Cyclospora*).
    - Viral: Rotavirus, cytomegalovirus, Torovirus, and astrovirus have been associated with chronic diarrhea. Also HIV infections
    - Protozoal: Intestinal protozoa and parasites can also cause persistent diarrhea, while viruses typically cause acute diarrhea, though prolonged symptoms may occur due to postinfectious enteritis.
        - *Giardia lambilia*, *Entamoeba histolytica, Cryptosporidium*
- *Postinfectious enteritis* is a relatively common complication of acute viral and bacterial infections.
- *Dietary protein-induced enteropathy*: It occurs in infants with hypersensitivity to cow's milk protein.
- *Eosinophilic gastroenteritis* is a disorder of unknown etiology, thought to be related to environmental or dietary allergens. It is characterized by eosinophilic infiltration of

one or more areas of the gastrointestinal tract, usually the stomach and the small intestine.

- *Celiac disease* (*gluten-sensitive enteropathy*)
- *Acrodermatitis enteropathica*
- Carbohydrate Intolerance
    - Disaccharidase deficiencies can be congenital, late-onset (primary), or secondary.
    - Late-onset adult lactase deficiency
    - Secondary lactase deficiency
- Inflammatory Bowel Diseases Including Crohn's Disease, Ulcerative Colitis, and Indeterminate Colitis
- Pancreatic Diseases
- Cystic fibrosis
- Bile acid deficiency
    - Cholestatic liver diseases (e.g., biliary atresia, primary biliary cirrhosis),
    - Diseases affecting the terminal ileum (where bile acid absorption takes place), and following extensive resection of the terminal ileum.
    - Bile acid can also be deconjugated by bacteria in patients with small bowel bacterial overgrowth.
- Motility Disorders
    - *Functional diarrhea* (also known as chronic nonspecific diarrhea of childhood, or *toddler's diarrhea)*— diarrhea only during waking hours and not during sleep.
- Irritable bowel syndrome (IBS)
- Other Causes
    - *Drugs*
    - *Neuroendocrine tumors*— secretory diarrhea.
    - *Gastrinoma* (*Zollinger–Ellison syndrome*)
    - *VIPomas*— WDHA syndrome (**W**atery **D**iarrhea, **H**ypokalemia, **A**chlorydria)

b) Investigations

- Certain investigations may be required, depending on clinical assessment.
- FBC, ESR, Coagulation studies, especially prior to jejunal biopsy.
- UCEs,
- Serum calcium, phosphate, alkaline phosphate, ferritin and folate.
- Trace metals (especially zinc).
- Antigliadin antibodies, endomysium antibodies.
- Stool for
    - Micrbobial testing (including testing for ova and parasites)
    - Quantification of fecal fat
    - Fecal elastase

- Specific testing includes:
    - Sweat testing— for cystic fibrosis
    - Radiological investigations may be of help in some cases:
        - Abdominal xray,
        - Barium meal and follow-through,
    - Autoimmune antibody testing,
    - Jejunal biopsy.
    - Pancreatic function tests, e.g. stool chymotrypsin etc.
- Other tests:
    - Colonoscopy and biopsy,
    - Thyroid function tests,
    - Congenital infection screen,
    - Gastrointestinal hormone profile

c) Treatment

- The most important step in managing a child with chronic diarrhea is to assess and stabilize the hydration and nutritional status.
- Children with severe malnutrition should be treated in an inpatient setting. (Refer to Chapter on Malnutrition for treatment guidelines)
- Further treatment depends on the specific etiology of the chronic diarrhea.

d) Prevention

- Control of sanitary conditions decreases the risk of infectious diarrhea.
- Breastfeeding, especially exclusive breastfeeding, protects is protective. WHO recommends exclusive breast-feeding for first 6 months of life.
- Treating cyst carriers can prevent shedding and spreading bacteria, protozoa and parasites.

(VII) Celiac Disease

- Celiac disease is a malabsorption syndrome induced by the introduction of gluten to the diet of susceptible patients. Gluten is a large complex molecule that has four heterogenous classes of protein: gliadins, glutenins, etc.
- Gliadin is recognized as a toxic molecule to patients with celiac disease.
- Gluten is the protein found in wheat, barley, oats, and rye.
- Gluten-containing diet in Celiac disease increases local and systemic immunoglobulin (Ig) A and IgG antigliadin antibodies accompanied by autoantibodies against structural proteins of the small intestinal mucosa, leading to autodestruction.
- Some autoimmune diseases are also associated with Celiac:
    - Type I diabetes mellitus
    - The disease is associated with HLA DQ2 and DQ8
    - Juvenile rheumatoid arthritis
    - Hyperparathyroidism

i) Investigations

- Intestinal biopsy is essential for the diagnosis of celiac disease.
- It is taken first, second, and third part of the duodenum.
- Flat or convoluted mucosa (atrophic villi) is characterisitically seen. Absence of identifiable brush border, crypts hyperplasia, and increased intraepithelial lymphocytes are also seen.

ii) Clinical Features

- Age of onset of celiac disease is variable, and can manifest in early and later ages.
- The classic signs and symptoms most often encountered in young children are:
    - Chronic diarrhea,
    - Failure to thrive,
    - Abdominal distention
    - Short stature
    - Dermatitis herpetiformis— may subside when gluten is removed from diet.

iii) Investigations

- Routine labs show anemia (iron deficiency > megaloblastic).
- Coagulation profile may be altered in the face of Vitamin K deficiency.
- ↓ serum albumin and globulin proteins due to malabsorption and protein-losing enteropathy
- Fecal fat testing shows significant steatorrhea (>10% of fat intake)
- Genetic testing (HLA-DQ2 & HLA-DQ8) is useful in the diagnosis of CD especially when the small intestinal biopsies and/or serology are inconclusive.
- Antibody testing:
- Antiendomysial antibodies are best in untreated cases.
- IgG antigliadin antibodies (less specific), IgA antigliadin antibodies (more specific).
- Tissue transglutaminase (tTG) antibodies

iv) Diagnosis

- Histological confirmation of small intestinal biopsies— gold standard for diagnosis.
    - These are taken from first, second, and third part of the duodenum.
    - Flat or convoluted mucosa (atrophic villi) is characterisitically seen. Absence of identifiable brush border, crypts hyperplasia, and increased intraepithelial lymphocytes are also seen.
    - Repeated biopsies and gluten challenge are indicated only when in doubt.
- Circulating antibodies (IgA antigliadin, antiendomysial antibodies, etc.) *at diagnosis* and *their disappearance on a gluten-free diet supports the diagnosis.*
- Definitive diagnosis is made when there is complete symptom resolution after treatment with a strict gluten-free diet in a previously symptomatic individual with characteristic histological changes on small intestinal biopsy.

v) Treatment

- A gluten-free diet produces rapid improvement, and lifelong avoidance prevents relapses.
    - All foods containing wheat or rye should be excluded from the diet.
    - Oats and barley are better avoided.
    - Corn, and rice are safe.
- Supplementation calcium, folate, and vitamins for 2 months

vi) Complications

- Lymphoma
- ***Celiac crisis*** is severe diarrhea, abdominal distention and weight loss and often accompanied by hypokalemia, and prolonged prothrombin time. It is treated with:
    - IV fluids, gluten-free diet, and
    - Corticosteroids as needed.

(VIII) Rectal bleeding

i) Presentation

- Determine whether bright red blood is being passed around, after or mingled with the stool as in the case of bleeding from the colon, or
- Is the blood altered as melena— signifies a more proximal bleeding source.

ii) Invetigations

- Assess the degree of blood loss by history and hemoglobin levels.
- Per rectal examination.
- Although direct visualization of the stool may reveal fresh blood or melena, but sometimes occult blood testing is needed to confirm the proximal source.

iii) Etiology

- It is important to exclude swallowed blood (e.g. bleeding fissures of nipple during breastfeeding) as a cause of rectal bleeding in infants.
- The etiology of bleeding per rectum is influenced by the age of the patient and also by the mode of clinical presentation.
- Thus, a child with chronic constipation who passes bright red blood *on the surface of the stool* may have an associated anal fissure, while the infant
- Colicky abdominal pain, passage of 'red currant jelly stools' ± shock points to intussusception.
- Acute vomiting and bloody diarrhea may herald the onset of intestinal infection and the presence of hematuria and proteinuria may suggest Henoch–Schönlein purpura or the hemolytic uremic syndrome.
- Chronic blood loss with the painless passage of bright red blood is suggestive of a colonic polyp, hamartoma or a polyposis syndrome.

Table. Causes of rectal bleeding in childhood
Anal fissure
Infective colitis (*Salmonella, Shigella, E. coli etc.)*
Intestinal polyposis (e.g. Juvenile polyps, Peutz–Jeghers syndrome etc.)
Bleeding disorders
Inflammatory bowel disease
Rectal prolapse
Intussusception
Meckel's diverticulum/gut duplication
Henoch–Schönlein purpura
Hemangioma/angiodysplasia/telangiectasia
Upper gastrointestinal bleeding

iv) Investigations

- Depend upon the clinical presentation.
- For slow bleeding presentations:
    - CBC, ESR, serum iron and ferritin estimation and clotting studies help narrow down causes.
    - Stool culture is mandatory (in bloody diarrhea)
    - Plain abdominal X-ray
- For more acute presentations (e.g. shock)
    - Urgent plain abdominal X-ray or ultrasound studies
    - Air contrast enema should be done to exclude intussusception.
- *The most useful investigation is colonoscopy*, allows direct visualization, control of bleeding, and multiple biopsies to be obtained for histopathlogy studies.
- Technetium isotope scanning helps identify ectopic gastric mucosa in either a Meckel's diverticulum or in a duplication of the intes- tine,
- **Nuclear Tagged RBC studies** are find for occult gastrointestinal blood loss.
- Capsule endoscopy may be helpful in visualizing more proximal sources of bleeding.
- Less commonly, angiography, laparotomy.

CHAPTER 25 INFECTIOUS DISEASES

(I) Definitions

i) Pyrexia without a focus

It is fever without localizing signs (fever without a focus), frequently occurring in children younger than 3 years of age, in which a history and physical examination fail to establish a cause

ii) Pyrexia of unknown origion (PUO)

It is defined as fever for >14 days without an identified etiology despite history, physical examination, and routine laboratory tests or after 1 week of hospitalization and evaluation

(II) Fever with a rash

Childhood exanthems are characterized by fever and rash.

Table. The six original exanthematous illnesses	
First disease	Measles
Second disease	Scarlet fever
Third disease	Rubella (German measles)
Fourth disease	Duke's disease (scarlantinella), now Scalded skin syndrome
Fifth disease	Erythema infectiosum
Sixth disease	Exanthem subitum (Roseola infantum)

Table. Periods of Infectivity In Childhood Infectious Disease		
Disease	**Incubation periods**	**Infectious periods**
Measles	8-12 days before to 14 days after (range 7 to 21)	1 to 2 days before onset of symptoms—from about 5 days before to 4 days after the appearance of rash—and immunocompromised persons can have prolonged excretion of contagious virus.
Chickenpox	14 to 16 days (range 10-21)	2 days before rash to 7 days after all lesions have crusted
Rubella	16 to 18 days (range 14 to 21).	2 days before rash to 5-7 days after
Sarlet fever		10-21 days after onset of rash (shortened to 1 day by penicillin)
Whooping cough	7 to 17 days	
Parvovirus B19	Incubation period is typically 4 to 14 days and rarely may last 21 days.	

i) Measles (Rubeola)

a) Etiology

- Measles is an RNA paramyxovirus (one antigenic type) is transmitted by droplets or the airborne route and is highly contagious.
- Infects the upper respiratory tract, regional lymph nodes then spread systemically.

b) Clinical Features

- Measles infection is divided into four phases: incubation, prodromal (catarrhal), exanthematous (rash), and recovery.
- The manifestations of the 3-day prodromal period are cough, coryza (runny nose), and conjunctivitis.
- **Koplik spots** (gray-white, dots on a red base on the buccal mucosa adjacent to the lower molar teeth) are pathognomonic.
- **Stimson Line**: a characteristic transverse line of inflammation along the eyelid margin.
- The macular rash from the hairline downwards over most of the body in over 24 hours.
- **Black measles:** petechial or hemorrhagic rash.
- As the rash fades, it undergoes brownish discoloration and desquamation.
- **Modified measles** refers to mild cases of measles occurring in persons with partial protection against measles. It occurs in those:
    - Vaccinated before 12 months of age
    - Infants with disease modified by transplacental antibody, or
    - Immunoglobulin receipients.

c) Investigations

- Serologic testing for IgM antibodies.
- Multinucleate giant cells (Warthin-Finkleday cells) on histopathology— pathognomonic.
- Identification of measles RNA via reverse transcriptase-polymerase chain reaction (PCR).
- Measles virus culture
- Supportive investigations may show characteristic leucopenia.

d) Treatment

- Routine supportive care includes maintaining adequate hydration and antipyretics.
- High-dose vitamin A supplementation has been shown to improve the outcome of infants with measles in developing countries.
- Routine administration of vitamin A for 2 days to all children with acute measles is recommended by WHO.

e) Complications

- Otitis media is the most common complication.
- **Giant cell (Hecht) pneumonia** (in those with impaired cell-mediated immunity)
- Appendicitis due to enlarged lymph nodes blocking appendiceal lumen.

- Encephalomyelitis
    - Early encephalitis is due to direct viral infection of brain tissue,
    - **Subacute sclerosing panencephalitis** (SSPE): This late onset encephalitis (upto 10 years after infection) is a rare (1 in 1 million) demyelinating immunopathologic phenomenon. Progressive behavioral and intellectual deterioration and eventual death may occur.

f) Prevention

- Vaccination at 9 months (as measles), 15 months and 5-7 years of age (as MMR) is recommended.
- Recommended for all HIV-infected persons (without evidence of severe immunosuppression),
- **Postexposure prophylaxis** with measles vaccine within 72 hours of exposure or immunoglobulin within 6 days of exposure.

ii) Rubella (German or 3-Day Measles)

- Rubella, also known as **German measles** or **3-day measles,** is caused by a togavirus.
- Rubella virus infects the respiratory mucosa initially and then disseminates.
- Rubella virus is most contagious through direct or droplet contact with nasopharyngeal secretions from 2 days before until 5 to 7 days after rash onset, although virus may be present in nasopharyngeal secretions from 7 days before until 14 days after the rash.
- Infection **in utero** during first trimester may manifest as **congenital rubella syndrome (CRS)** in the newborn. Cataracts, patent ductus arteriosis (PDA), deafness and a **"Blueberry muffin rash" (**due to extramedullary hematopoiesis**)** may be seen.

a) Clinical Features

- The characteristic signs of rubella are maculopapular rash with retroauricular, posterior cervical, and posterior occipital **lymphadenopathy**.
- The rash begins on the face and moves downwards (clearing as it spreads), lasting for ~3 days and less prominent than that of measles.
- Petechiae on the soft palate, known as **Forchheimer spots,** may be seen but are nonspecific.
- Low-grade fever, pharyngitis, anorexia, headache, malaise may occur.

b) Investigations

- Diagnosis is mainly clinical, and confirmed by serologic testing for IgM antibodies or by a fourfold or greater increase in specific IgG antibodies in paired acute and convalescent sera.
- Supportive labs may show normal or low WBC count.

c) Treatment

- Supportive care mostly with antipyretics and fluids.

Prevention

- Vaccination at 15 months and 5-7 years of age (as MMR) is recommended.
    - Pregnancy is considered a contraindication to rubella immunization.

- Prenatal serologic testing in all pregnant women to determine their immune status to rubella, and susceptible mothers should be vaccinated after delivery.

iii) Roseola Infantum (Exanthem Subitum)

a) Etiology

- **Roseola infantum (exanthem subitum, sixth disease)** is caused primarily by human herpesvirus type 6 (HHV-6). The incidence increases as maternally derived antibody levels in the newborn decline.

b) Clinical Features

- **Roseola** is characterized by high fever (often >40° C) with an abrupt onset that lasts 3 to 5 days.
- A maculopapular, rose-pink colored rash erupts as the fever goes down.
- Rash usually lasts 1 to 3 days.
- Nasal congestion and cough may occur.

c) Investigations

- Diagnosis is mainly clinical and routine labs are nonspecific.
- Diagnosis can be confirmed with:
  - Serologic testing showing a fourfold rise in acute and convalescent sera.
  - HHV-6 DNA by PCR in the cerebrospinal fluid.

d) Treatment

- There is no specific therapy for roseola.
- Routine supportive care includes maintaining adequate hydration and antipyretics.

e) Prognosis and complications

- Disease resolves spontaneously in short duration in almost all cases.
- A rare **hemophagocytosis syndrome** can occur and has high mortality.

iv) Erythema Infectiosum (Fifth Disease)

a) Etiology

- **Erythema infectiosum (fifth disease)** is caused by the human parvovirus B19 (previously Erythrovirus),
- The cell receptor for parvovirus B19 is the **erythrocyte P antigen,** present on erythroid precursors. The virus replicates in actively dividing erythroid stem cells, leading to cell death. This destructive affinity for red blood cell progenitor cells explains *aplastic crisis* in patients with hemolytic anemias, including **sickle cell disease**, spherocytosis, and thalassemia.

b) Clinical Features

- Initial nonspecific illness characterized by fever, malaise, myalgias, and headache.
- In some cases, the characteristic rash appears 7 to 10 days later:

- The initial stage is typically a **"slapped cheek" rash** with circumoral pallor.
- An erythematous symmetric, maculopapular, truncal rash appears 1 to 4 days later. This fades as central clearing takes place, giving a distinctively diffuse **lacy, reticular rash** on the extremities that waxes and wanes over 2-3 weeks.
- Children with erythrocyte comorbidities (e.g. sickle cell anemia) may develop a ***transient aplastic crisis*** characterized by ineffective erythroid production typically lasting 7 to 10 days.

c) Investigations

- Hematologic abnormalities can include:
    - Anemia,
    - Thrombocytopenia,
    - Lymphopenia, and neutropenia.
- Serologic tests showing IgM antibody to parvovirus are diagnostic
- Parvovirus B19 can be detected by
    - PCR
    - Electron microscopy of erythroid precursors in the bone marrow.

d) Treatment

- Routine supportive care including adequate hydration and antipyretics.
- Transfusions may be required for transient aplastic crisis and intrauterine hydrops fetalis.
- IV Immunoglobulins may be considered for immunocompromised.

e) Complications

- The prognosis for erythema infectiosum is excellent. Transient aplastic crises is rare.
- *In utero* may result in fetal hydrops, heart failure, and fetal death.

v) Varicella-zoster virus infection

a) Etiology

- Chickenpox and zoster are caused by varicella-zoster virus (VZV). **Chickenpox (varicella)** is the manifestation of primary infection.
- VZV infects susceptible individuals via the conjunctivae or respiratory tract and replicates in the nasopharynx and upper respiratory tract.

b) Clinical Features

- Nonspecific prodromal symptoms with fever, and malaise.
- The characteristic rash appears initially on the trunk as small red papules that progress to oval vesicles on an erythematous base.
- The rash spreads in the centripetal fashion spreading to extremities from the trunk.
- Lesions advance quickly from clear to cloudy, progressing through macule, papule, vesicle, pustule, and crusting (scabs are not infective). These pleomorphic stages of lesions can be present at the same time (**distinguishing factor from small-pox, in which all lesions are at the same stage**).

c) Investigations

- Laboratory testing confirmation for diagnosis is usually unnecessary. PCR is the current diagnostic method of choice, and genotyping to distinguish vaccine and wild-type strains is available through the CDC.
- Detection of varicella-specific antigen in vesicular fluid by immunofluorescence using monoclonal antibodies or demonstration of a fourfold antibody increase of acute and convalescent sera is also diagnostic but not as sensitive as PCR.

d) Differential Diagnosis

- Coxsackievirus A infection (***Hand-foot-mouth disease***) has a vesiculopustular appearance, but lesions tend to occur at the oropharynx and extremities.

e) Treatment

- Symptomatic therapy of varicella includes ***nonaspirin antipyretics***, cool baths, and careful hygiene.
- Routine acyclovir is not recommended in otherwise healthy cases.
- Acyclovir or valacyclovir may be considered in those at risk of severe varicella

f) Complications

- Primary varicella usually resolves spontaneously. Disease tends to be more severe for those older than 20 years of age and for immunocompromised.
- Secondary bacterial infection of skin lesions (by streptococci or staphylococci) is the most common complication.
- Pneumonia
- Myocarditis, pericarditis
- Reye syndrome (avoid Aspirin use)
- Neurologic complications include:
    - Encephalitis,
    - Cerebellar ataxia, nystagmus, and tremor.
- A severe form of neonatal varicella may develop in newborns of mothers with varicella (but not shingles) occurring 5 days before to 2 days after delivery.

g) Prevention

Varicella zoster immunoglobulin, 1.25 to 5 ml given within 72 hours of exposure will modify or prevent the disease.

A live attenuated varicella vaccine—two doses (at 1 year of age and 4-5 years booster).

Post-exposure immunity can be provided by VZIG, if given with 96 hours of exposure to prevent severe disease in high-risk individuals.

vi) Whooping cough

It is an infection caused by bacterium *Bordetella pertussis*. It is uncommon due to vaccination.

a) Clinical features

The course of the disease spans 6-8 weeks. It is subdivided into 3 phases:

Catarrhal phase

- This phase is characterized by coryza-like illness, with runny nose, sneezing etc. There is gradual worsening of symptoms, with a additional complains of dry cough at night.
- Lasts 7-10 days.

Paroxysmal (or spasmodic) phase

This phase lasting several weeks is characterized by:

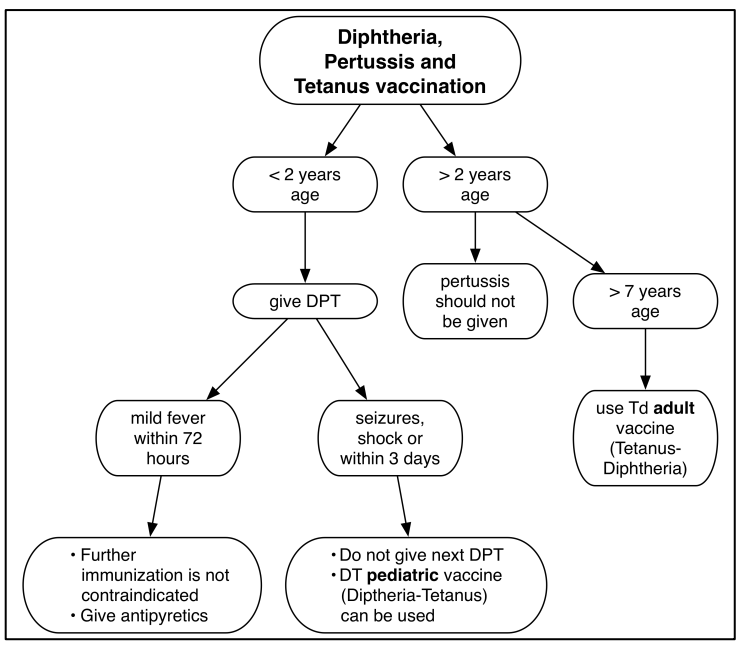
- Paroxysms— bouts of short, very severe cough, accompanied by expectoration of tenacious white sputum with congested face or cyanosis.
- Inspiratory whoop— as the spasm ends (absent in neonates)
- Between paroxysms, the child does not have respiratory symptoms.
- Post-tussive emesis

Convalescent (recovery) phase

This phase is characterized by:

- ↓ paroxysms
- ↓ whoop

After 8-10 weeks of illness, the child improves.



b) Complications

- Convulsions
- Secondary bronchopneumonia
- Subconjunctival hemorrhages
- Intracranial hemorrhage (rare)

c) Treatment

- Oxygen
- Antitussives
- Sedatives
- Oral erythromycin 4 times daily for 14 days—affects shedding of the bacteria only, minimal effect on severity of coughing and course of disease

d) Prognosis

All cases undergo recovery over time. But mortality rate is high in age < 6 months (upyo 40%) due to secondary complications.

e) Prevention

- Immunization is not recommended after 7 years of age.
- Unimmunized exposed infants should receive erythromycin prophylaxis (for 10 days).

vii) Scarlet fever

This is a rare sequela of infection with streptococci that possess the **erythrogenic toxin**.

After an incubation period of a week, this illness manifests as:

- High fever with chills
- Sore throat
- Headache
- Vomiting
- The hallmark of this condition is a diffusely erythematous "coarse ***sand-paper like***" rash develops 12-48 hours later with superimposed red punctate macules or fine papules starting localized in axillae, groin and neck, and then generalizing. On the face, cirumoral pallor is seen.
- On examination, following may be noted:
    - Swollen beefy-**red strawberry** tongue (a white strawberry tongue may be seen earlier)
    - Pharyngeal congestion
    - Inflamed tonsils
- The fever peaks on second day of illness and gradually lowers to normal over the coarse of a week.
- This sequela is now rare due to use of antibiotics.

(III) Typhoid Fever

It is caused by *Salmonella typhi* and *Salmonella paratyphi* species. Infection by these species result in a severe form of salmonellosis known as ***Enteric fever.*** It is spread by feco-oral transmission via contaminated food or water

i) Clinical features

Classically after an incubation of 10-14 days,

- Fever which follows a stepladder pattern starting to increase gradually until it reaches a maximum of 40– 41°C in 5–7 days.
- During the first week of illness, most patients are constipated;
- By the second week, diarrhea develops.

Rose spot rashes usually appear by end of the first week as faint *blanching* macular erythematous or rose-colored 2-3 mm lesions over the chest and upper abdomen. They last for 2–3 days and then disappear. Splenomegaly may also be observed.

- Fulminant illness with high fever, drowsiness, anemia, and shock, but this is rare.
- There is an accentuation of all manifestations, with an intermittent fever- by third week.
    - Diarrhea, abdominal pain and distention may be severe
    - Hemorrhage or perforation of intestinal ulcers more likely to occur at this stage.
    - **Typhoid psychosis**: mental status changes

ii) Investigations

The gold standard method of diagnosis is isolating the organism from infected specimens.

- Widal test— titers peak between 3rd and 5th week (unreliable and can be nonspecific): >1:80 titer of "O" antigen is considered significant.
- Typhidot IgM and IgG antibody detection.
- Salmonella can be isolated from blood during the first week and from **stool *or urine*** by the second week of illness. However, bone marrow remains the most sensitive specimen for isolating the organism even if pretreated with antibiotics.
- Serology

iii) Treatment

- Stabilization and high dependency care as needed.
- I.V Fluids
- Dexamethasone used initially with antibiotics for short duration improves mortality.
- Antibiotics used are based on C/S results (due to resistance) for 10-14 days but chloramphenicol, ampicillin or trimethoprim-sulfamethoxazole can be used.
- Third-generation cephalosporins (e.g. ceftriaxone) and ciprofloxacin are effective for resistant strains. Ciprofloxacin is generally contraindicated in children < 18 years of age.
- Carries state can be eradicated by 4-6 weeks of high dose ampicillin (or amoxicillin) +probenecid, or Trimethoprim-sulfamethoxazole. Ciprofloxacin can also be used.

iv) Complications

- Intestinal hemorrhage and perforation (the most common)— 2nd – 3rd week of illness.
- Osteomyelitis (esp. in Sickle cell disease),
- Pneumonia,
- Typhoid encehalopathy etc.
- Hepatitis, cholecystitis, and pancreatitis can also occur.
- **Carrier state— due to persistence of infection in biliary tract.**

(IV) Dengue virus infection

i) Etiology

Dengue virus (DENV) is an RNA virus of the genus Flavivirus. Four serotypes, DENV-1, -2, -3, and -4, have been discovered.

ii) Clinical Features

Dengue is a dynamic disease beginning with a nonspecific, acute febrile illness lasting 2 to 7 days (febrile phase), progressing to severe disease during fever defervescence (critical phase), and ending in a convalescent phase.

Typically, after an incubation period of 4-6 days the patients develop:

- Abrupt onset high grade fever, biphasic

- Headache, retro-orbital pain, vomiting, facial fushing, injected oropharynx
- Petechiae
- Plasma leakage attributed to increased vascular permeability manifests as:
    - Ascites,
    - Pleural effusion on chest x-ray, or
    - Hypoalbuminemia

A minority of patients develops severe dengue infections, which is associated with a second or other subsequent infections.

a) Dengue Fever (DF)

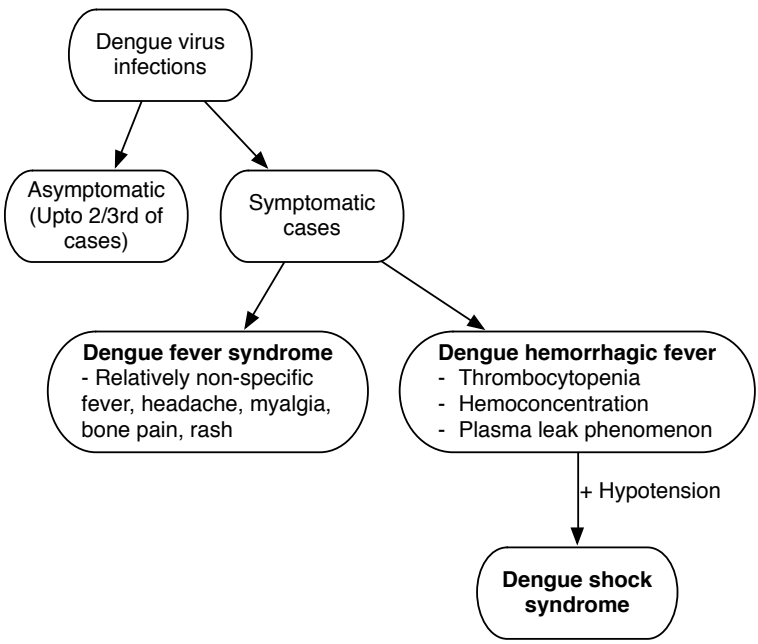
Dengue fever (DF) is characterized by biphasic "saddle-back" fever (fever for few days, then no fever for one or two days followed by reappearance of fever), myalgia, arthralgia and rash.

b) Dengue Hemorrhagic Fever (DHF)

The presence of thrombocytopenia with concurrent hemoconcentration and evidence of plasma leak are considered features of Dengue Hemorrhagic Fever (DHF).

c) Dengue Shock Syndrome (DSS)

DHF with hypotension is called Dengue Shock Syndrome (DSS).



iii) Diagnosis

Routine labs may show:

- Thrombocytopenia
- *Hemoconcentration* - hematocrit elevated at least 20% above baseline
- Leucopenia

Laboratory confirmation of a clinical diagnosis of dengue depends on when a serum sample is obtained during the course of illness and which investigation is ordered.

Table. Diagnostic investigations for dengue virus	
DENV nonstructural protein 1 (NS-1) antigen	First 10 days of illness.
DENV RNA by reverse-transcriptase polymerase chain reaction (RT-PCR) assay	Positive during febrile phase
IgM antibodies by enzyme immunosorbent assay (EIA), [can be false-positive due to previous exposure or cross-reaction]	4 to 5 days after illness onset.
Less commonly used	Reciprocal IgG anti-DENV titer Hemagglutination inhibition test IgM anti-DENV in CSF.

iv) Treatment

- No specific antivirus therapy exists as yet. Management is mainly supportive with:
    - I/V Ringer's lactate bolus and infusion.
    - Blood transfusions
    - Intensive palliative care as needed
- Most patients recover in 2-3 days without sequelae in non-severe cases.

v) Control measures

- No chemoprophylaxis, antivirals or vaccines are available to for dengue.
- Aedes mosquitoes bite during the daytime, so bed nets are indicated for children sleeping during the day.
- Use of mosquito repellents containing up to 50% N,N-diethyl-meta-toluamide (DEET) for adults (including pregnant women) and up to 30% DEET for children older than 2 months of age is recommended when used accordingly to directions on product.

CHAPTER 26 PEDIATRIC CARDIOLOGY

(I) Congenital heard diseases

i) Coarctation of aorta (CoA)

- In infantile form, preductal stenosis proximal to insertion of ductus is seen.
- Postductal form is relatively more common in adult form.
- *Associated with Turner syndrome.*

a) Clinical findings

Physical examination findings may show:

- Hypertension in upper extremities,
- Weak/absent pulses in lower extremities,
- Radiofemoral delay.

b) Investigations

- Echocardiography
- Untreated chronic coarctation of aorta may show characterisitic ribs-notching (due to collaterals) on chest xray with long standing disease.
- Electrocardiography (ECG) may show:
    - Right ventricular hypertrophy (RVH) in neonate,
    - Left ventricular hypertrophy (LVH) in older child.

c) Treatment

- Surgical resection and anastomosis.
- Balloon dilatation/stenting.

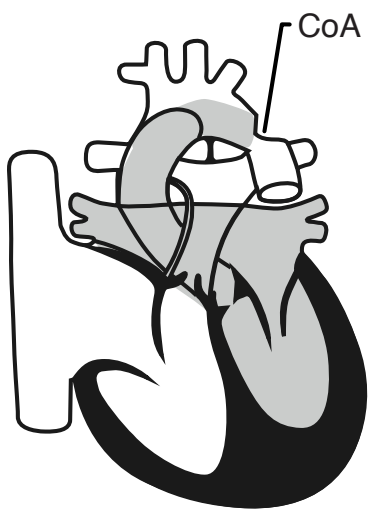
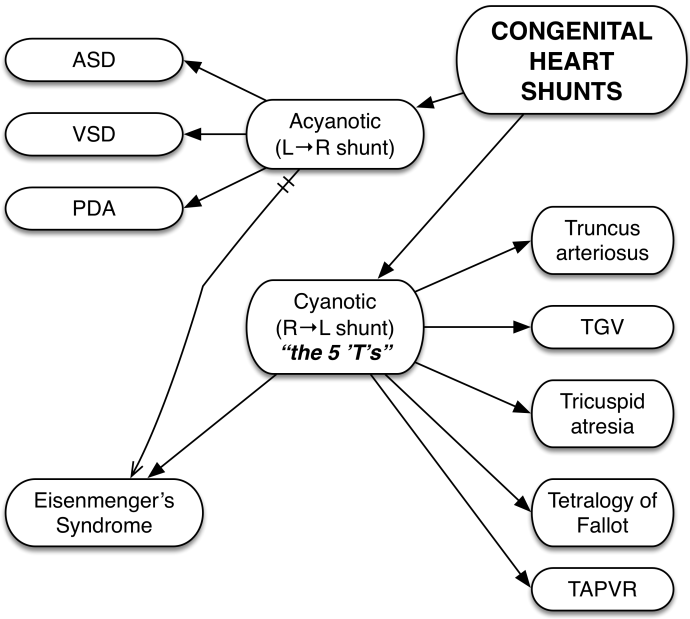


Figure. Illustration of a postductal form of coarctation of aorta

ii) Congenital Heart Shunts



a) Cyanotic shunts (R → L, blue babies)

Tetrology of Fallot (ToF)

Primary defect is deviation of the infundibular septum that separates aortic and pulmonary outflows. This gives rise to the four characterisitic components of ToF:

- Obstruction to right ventricular outflow (pulmonary stenosis)
- Right ventricular hypertrophy
- Ventricular septal defect (VSD)
- Aorta overriding the ventricular septum

Clinical Features

- Cyanosis
- Acyanotic/pink tetralogy of fallot: when obstruction to right ventricular outflow is mild-moderate and a balanced shunt across the VSD, the patient is not cyanotic.
- Ductal dependent pulmonary blood flow in infants.
- Older children: presentation with cyanosis, clubbing and dyspnea on exertion.

Clinical examination findings:

- A systolic thrill/ systolic murmur in left sternal 3rd - 4th parasternal space. It is caused by turbulence through right ventricular outflow tract.
- Single 2nd heart sound or soft pulmonary component.

Investigations

- Chest X-ray shows **Boot shaped heart** due to cardiac **apex elevation** (due to right ventricle hypertrophy).
- Echocardiography

Treatment of Cyanotic Spell

- Placement of child in knee chest position (It increases systemic vascular resistance and decrease venous return. This decreases right to left shunt, and improves symptoms).
- Oxygen administration
- Morphine subcutaneous at dose not exceeding 0.2 mg/kg
- Intravenous soda bicarbonate if metabolic acidosis present
- Intravenous phenylephrine - increase systemic vascular resistance, decrease right ' left shunt and improves symptoms.

Surgical Management

- Palliative surgery - Blalock - Taussig shunt (subclavian artery and pulmonary artery) performed to augment pulmonary artery flow. It is indicated Infants with less severe cyanosis without cyanotic spells and with good growth.
- Corrective surgery
    - Electively between 4-6 months of age in case of less severe cyanosis without spells
    - Immediately in infants with severe cyanosis (marked right ventricular outflow obstruction).

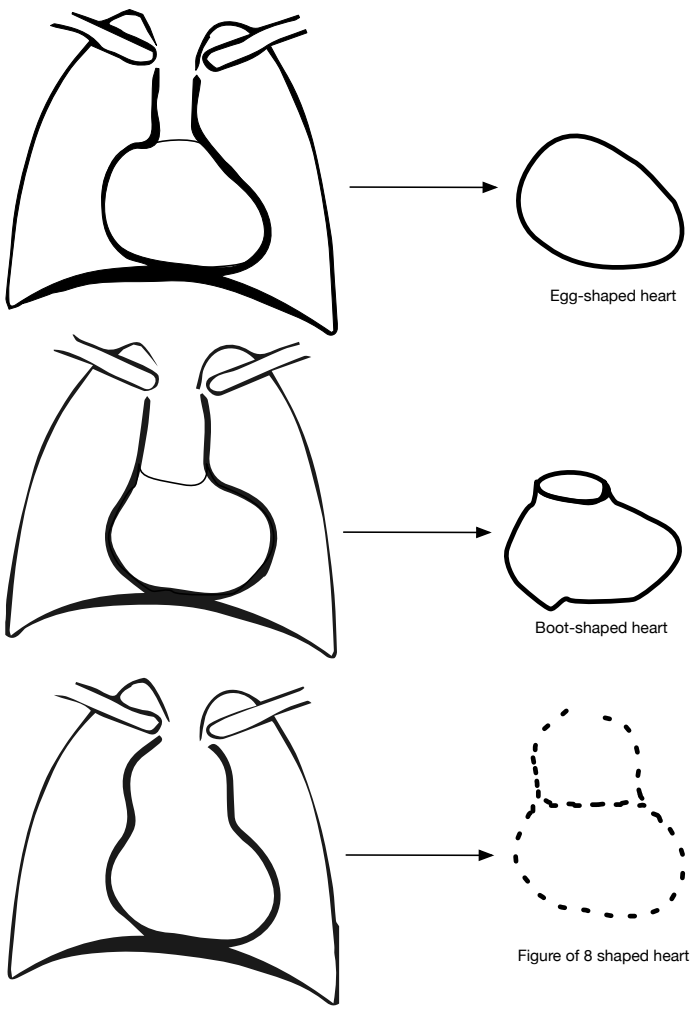


Figure. Characteristic cardiac silhouette findings in congenital heart diseases.

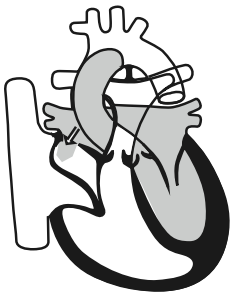
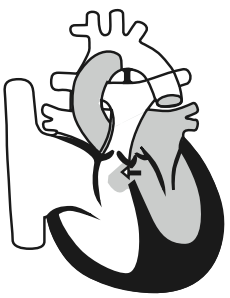
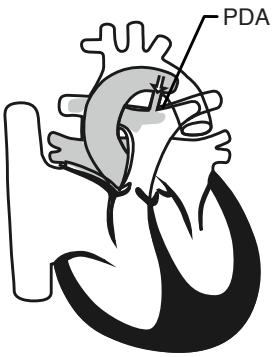
Table. Cyanotic shunts		
Conditions	**Features**	**Findings**
Transposition of Great Vessels	Cyanosis from birth or shortly after, proportional to shunt through foramen ovale, ductus arteriosus or VSD. Associated with maternal diabetes	Cyanosis persists in 100% oxygen that may even worsen cyanosis by causing closure of ductus. - Single Heart sound - **CXR: Egg on side/string appearance**
Tetralogy of Fallot	Infant: progressively deeper cyanosis, weeks or few months old. Cyanotic spells from infundibular spasm. Children assume squatting position after exertion to overcome dyspnea. *Squatting cause compression of femoral arteries increase pressure threby decrease the right to left shunt and directing more blood from the RV to the lungs*	Central cyanosis, clubbing, right ventricular heave. Single S2 Ejection systolic murmur **- CXR: boot shaped heart due to RVH** **Surgical treatment**: Blalock-Taussig shunt connecting pulmonary artery to subclavian artery
Truncus arteriosus	Neonate may present with breathless, cardiac failure	Minimal cyanosis, Bounding pulse, Single S2, short systolic murmur
Total anomalous pulmonary venous return (TAPVR)	The heart has no direct pulmonary venous connection into the left atrium. Presents as Breathless, FTT	Cyanosis NOT improved in 100% oxygen. Poor pulse. Loud S2. Murmur often absent, tachypnea, right ventricular heave. **CXR: *figure of 8 (snowman) shaped heart.***

Eisenmenger's syndrome

- Uncorrected VSD, ASD, PDA increase pulmonary vascular resistance due to arteriolar thickening → pulmonary hypertension.
- As pulmonary resistance increase the shunt reverses from L → R to R → L shunt, which causes late cyanosis.

b) Acyanotic shunts (Left → Right)

Table. Acyanotic shunts

Condition	Features	Findings
ASD 	Ostium secundum defect of fossa ovalis (Most common type). Ostium primum type more common in **Down's syndrome**. Children may be asymptomatic. Breathlessness may occur due to pulmonary hypertension in long-standing.	• Left parasternal heave (RVH) • Widely fixed split S2 • Ejection systolic murmur over pulmonary area may be heard.
VSD 	90% in membranous part of septum. Majority close spontaneously. May present with failure to thrive, *respiratory infections*, or reversal of shunt in later life (Eisenmenger's syndrome).	• Pansystolic murmur at left sternal border • Split S2 sound • CXR: biventricular hypertrophy
PDA 	Normal during fetal life (R → L); should close in few days of neonatal period, if not lung resistance decreases and shunt becomes abnormally L → R with subsequent right ventricular hypertrophy and failure. Associated with maternal rubella in 1st trimester. Indomethacin is used to close PDA. PGE (alprosatdil) is used to keep PDA open, which may be necessary to sustain life in conditions like TGV.	• Continuous machinery murmur in left infraclavicular area (Gibson's murmur) • Cyanosis occurs in PDA with reversal of shunt

(II) Cardiac failure

Table. Causes of cardiac failure in children

Congenital causes	1-4 weeks age	Lage PDA
		Coarctation of aorta
	4-6 weeks	Large VSD
		Large PDA
Acquired causes	Acute rheumatic carditis	
	Rheumatic heard disease	
Non-cardiac causes	Anemia	
	Bronchopneumonia	
	Acute glomerulonephritis	

CHAPTER 27 RESPIRATORY SYSTEM

(I) ARIs

i) ARI Programme

The Acute Respiratory Infections programme in collaboration with WHO has been launched in Pakistan an integral part of IMNCI. It aims to reduce mortality with pneumonia and rational use of antibiotics and other drugs in ARI. Lower ARIs (larynx and below) should be distinguished from upper URIs (80% of the cases) so they may be treated in timely and standardized manner.

The upper ARIs do not need antibiotics. Recommended home remedies in such cases include:

- Luke warm water with honey
- Green tea
- Joshanda
- Qehwa

ii) Bronchiolitis, Croup and Epiglottitis

Features	Bronchiolitis	Laryngotracheo-bronchitis: Croup	Acute epiglottitis
Medical emergency	No	No	Yes
Cause	Respiatory syncytial virus	Parainfluenza virus	*H. influenzae*
Age	Newborn – 2 years	3 months – 5 years	3 – 7 years
Clinically	Prodromal URI symptoms for few days, then tachypnea and expiratory wheezing. Can be confused with ***Cardiogenic asthma*** (wheezing associated left heart failure).	Prodromal URI symptoms for few days, then fever, ***inspiratory stridor*** that worsens with agitation; hoarseness of voice, barking cough,	Rapid onset (4-12 hours); high fever, dysphagia, drooling, muffled voice, stridor patients may be in "sniffing" position with neck hyperextended and chin protruding
Xray	Hyperinflation with patchy atelectasis	Subglottic tracheal narrowing "***Steeple sign***" on *PA view*	Swollen epiglottis "***Thumb sign***" on *lateral view*
Treatment	Humidified oxygen, bronchodilators, ribavirin (for severe cases)	Mist therapy, humidified oxygen, aerosolized racemic epinephrine, dexamethasone	Transfer to operation theatre, endotracheal intubation and IV antibiotics

(II) Pneumonia

Pneumonia is the inflammation of lung parenchyma. It typically presents with:

- Fever,
- Cough, often production sputum.
- Shortness of breath.

Following are the most likely organisms involved:

Age group	Organism
Neonate (0-28 days)	Group B Streptococci
	E. coli
3 weeks - 3 months	RSV (most common)
	Streptococcus pneumoniae
	Staphylococcus aureus
4 months - 4 years	Viruses-most common
	Streptococcus pneumoniae- most common bacteria
	Hemophilus influenza
	Mycoplasma pneumonia
5 years – 15 years	Mycoplasma pneumonia-most common
	Streptococcus pneumoniae

i) Investigations

- Chest X-ray findings (confirmatory test):
    - Viral pneumonia-hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing
    - Pneumococcal pneumonia- confluent lobar consolidation
    - Mycoplasma pneumonia- unilateral lower lobe pneumonia
    - Chlamydia- interstitial pneumonia
- Definitive diagnostic tests for:
    - Viral causes: direct fluorescent antibody testing, enzyme immunoassay, other serologies or viral cultures.
    - Bacterial causes: isolation of bacteria from blood or pleural fluid

ii) Treatment

It is guided with empiric antimicrobial therapy based on age group. For bacterial causes macrolides, amoxicillin or sometimes-respiratory quinolones (moxifloxacin) may be used in children.

(III) Asthma

It is a chronic, reversible inflammatory airway disease characterized by reversible bronchoconstriction, airway hyperresponsiveness and airway edema. In terms of pathology, asthma is considered an obstructive lung pathology, in which there is obstruction to outflow of air in smaller airways and wheezing that is typically heard during expiration.

About 80% of cases start to manifest before 6 years of age. It is more severe in younger age.

Extrinsic IgE mediated asthma occurs out of exposure to environmental factors, while intrinsic asthma is non-IgE mediated with negative skin allergen testing and low IgE levels. Skin prick testing demonstrates presence of atopy (i.e. propensity to produce IgE).

Table. Triggers for an asthmatic attack	
Tobacco smoke	Outdoor pollens and mold
Domestic dust mite allergens	Physical activity
Allergens from furry animals	Cockroach allergens

i) Clinical Features and Classification

- Characteristic expiratory wheezing with cough, dysnea, chest tightness, and relatively prolonged expiratory phase of respiration is observed.
- During an acute exacerbation, a hyperventilating child with use of accessory muslces of respiration, cyanosis, and pulsus pradoxus sitting in a tripod sitting position with or without wheezing (in severe cases) may be seen.
- Harrison's sulci and barrel-shaped chest may be seen in long-standing disease.
    - Due to long-term overuse of accessory respiratory muscles lead to remodelling of chest wall. Anteroposterior-to-transverse diameter ratio is > 0.9. Normally, AP diameter is less than transverse diameter. Also seen in other obstructive lung diseases like COPD and Emphysema.
    - If a child experiences chronic severe respiratory disease such as asthma before the bones mineralize and harden, the downward tension from the diaphragm and other accessory muscles used during increased respiratory effort can bend the ribs inward over time. Also seen in Rickets due to softening of ribs.

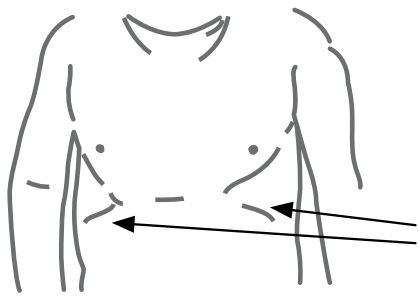


Figure. Harrisons's sulcus

ii) Investigations

The diagnosis of asthma is mainly clinical. However, supportive labs may show:

- CBC: leukocytosis and eosinophilia
- Chest xray may show some characteristic changes like: (findings similar to viral bronchiolitis)
    - Hyperinflation of lungs
    - Flattening of diaphragm
    - Peribronchial cuffing
    - In complicated cases: Lobar collapse (due to mucus plug obstruction) and Allergic bronchopulmonary aspergillosis (ABPA) can also be seen.
- Arterial Blood Gases (ABGs): during an acute attack, hypoxemia is common. Respiratory acidosis (CO_2 retention) may also occur.
- Pulmonary Function Testing (PFT) should be performed before and after inhaled bronchodilators in suspected cases to establish diagnosis.
    - Peak Expiratory Flow Rate (PEFR) is maximum speed of air outflow generated during a forceful exhalation.
    - Forced Expiratory Volume-1st second (FEV_1) is the volume of air expired in the first second during *maximal* expiratory effort.

Making a diagnosis of asthma
Compatible clinical history plus either/or:
FEV_1 ≥ 12%-15% (and 200 mL) increase following administration of a bronchodilator/trial of corticosteroids.
> 20% diurnal variation on ≥ 3 days in a week for 2 weeks on Peak Expiratory Flow diary.
FEV_1 ≥ 15% decrease after 6 mins of exercise.

iii) Treatment

This is based on asthma severity classification.

Rules of Two: daytime symptoms occurring two or more times per week or nighttime awakening two or more times per month implies a need for daily anti-inflammatory medication.

Asthma severity classification					
Clinical Features		Severity			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Daytime symptoms		<2/week	>2/week	Daily	Continuous
Nighttime symptoms		<2/month	>2/month	>1/week	Frequent
PEFR or FEV_1	% of predicted	>80%	>80%	>60%	<60%
	Variability	<20%	20-30%	>30%	>30%
PEFR: Peak Expiratory Flow Rate FEV_1: Volume expired in the first second of a forceful expiration.					

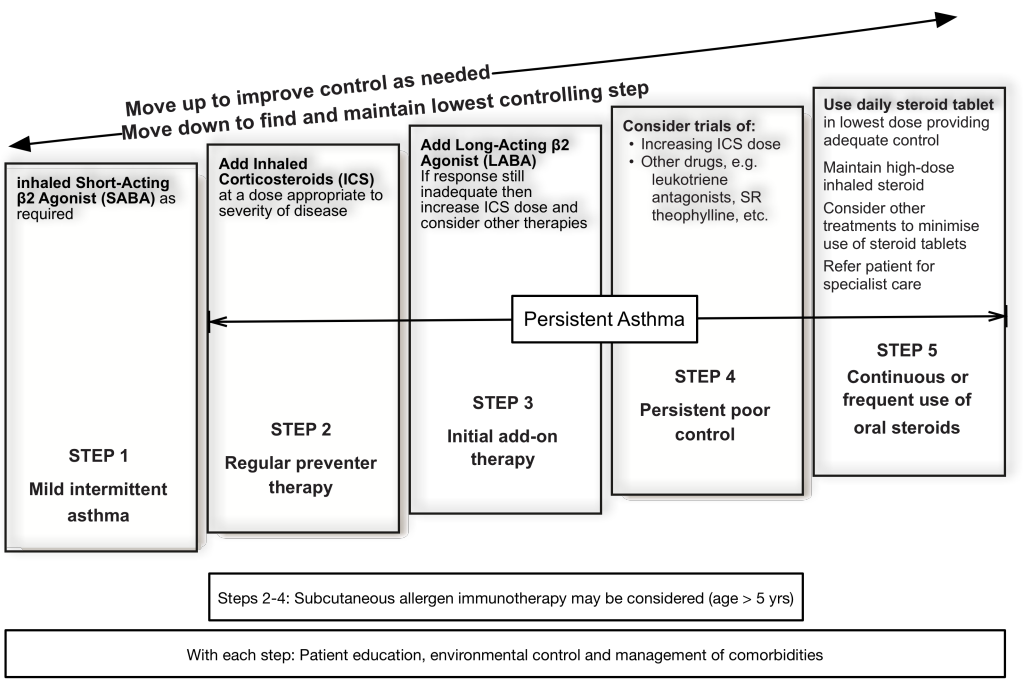


Figure. Step-up and Step-down management of asthma control.

a) Using a metered-dose inhaler

i. Remove the cap and shake the inhaler
ii. Breathe out gently and place the mouthpiece into the mouth
iii. Incline the head backwards to minimise oropharyngeal deposition
iv. Simultaneously, begin a slow deep inspiration, depress the canister and continue to inhale
v. Hold the breath for 10 seconds

b) Acute Asthma

- High concentration oxygen humidified to maintain oxygen saturation
- High dose inhaled corticosteroids. Additional ipratropium may be considered.
- Systemic corticosteroids
- Assisted ventilation may be considered in severe cases

CHAPTER 28 KIDNEYS

(I) Definitions

- Oliguria: It is defined as being present when less than 300 mL urine is passed per day., whereas anuria is deemed to exist when less than 50 mL urine is passed per day.
- Anuria: It is said to be present when there is less than 50 mL of urine passed per day.
- Polyuria is defined as a urine volume in excess of 3 L/day.
- Hematuria: it is the presence of hemoglobin in the urine.

Table. *Aide mémoire* for causes of hematuria: TICS

T	Tumor
	Trauma
	Tuberculosis
I	Infection
	Inflammation
C	Congenital
	Cystic
	Calciuria
S	Stones
	Sickle cell anemia
	Someplace other than kidney

- Kidney malformation is classified at the clinical level by gross and microscopic anatomical features. One commonly used classification system is as follows:
- Renal agenesis—congenital absence of the kidney and ureter
- Simple renal hypoplasia—small kidney with a reduced number of nephrons and normal renal architecture
- Renal dysplasia—presence of malformed kidney tissue elements

(II) Congenital conditions

i) Polycystic kidney disease

- It is of two types: autosomal-recessive type is encountered in infants
- Both kidneys greatly enlarged with many cysts through cortex and medulla
- There are cysts and fibrosis in the kidneys and fibrosis may also be seen in the liver.
- It presents classically as:
    - Bilateral flank masses in neonate or early infancy
    - May present with Potter sequence

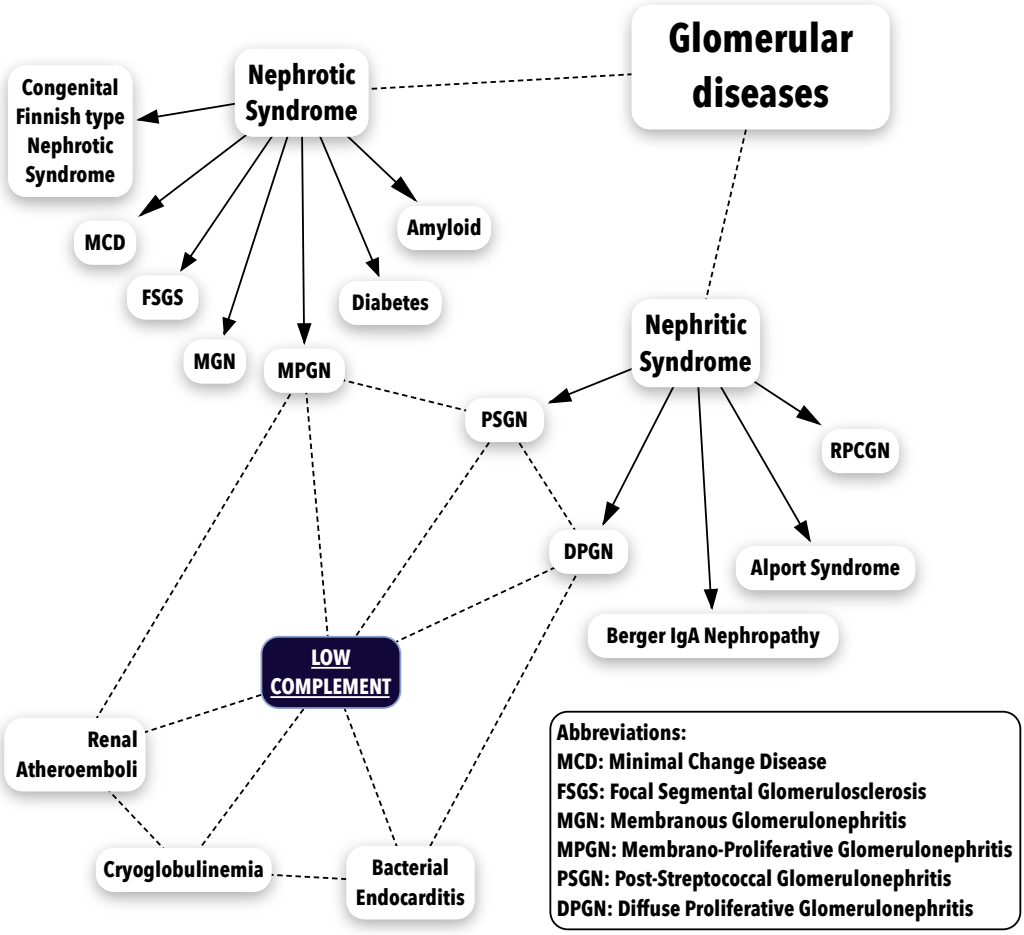
- Hypertension, oliguria, acute renal failure
- About half have liver disease in newborn period

- Diagnosis
  - Oliguria and hypertension in newborn
  - Ultrasound– shows numerous small cysts are seen (may be seen prenatally).
- Treatment and prognosis
  - Symptomatic
  - Need dialysis and transplant
  - Chronic renal failure occurs in most untreated cases

ii) Vesicoureteric Reflux

- It is the retrograde projection of urine from the bladder to the ureters and kidneys.
- Causes include:
  - **Posterior urethral valves—**
    - Most common congenital urethral obstruction
    - Classically presents in a male newborn as distended, palpable bladder with low urine output.
  - Urethral or meatal stenosis,
  - Neurogenic bladder (loss of nerve supply).
- Patients present with recurrent UTIs, typically in childhood. Prenatal ultra- sound may identify hydronephrosis.
- A "**micturating cystourethrogram (MCUG)**"— detects abnormalities at ureteral insertion sites and to classify the grade of reflux:
  - Mild reflux (grades I–II): No ureteral or renal pelvic dilation. Often re- solves spontaneously.
  - Moderate to severe reflux (grade III–V): Ureteral dilation with associated caliceal blunting in severe cases.
- *A VCUG should be obtained in all boys presenting with their first UTI, girls < 3 years of age with their first UTI or < 5 years of age with febrile UTI, and with recurrent UTIs in others.*
- Treatment is centered on preventing complicatings:
  - Antibiotic cover for active infections.
  - Treat mild reflux with daily prophylactic antibiotics [Trimethoprim-sulfamethoxazole (or amoxicillin if < 2 months of age)] till reflux resolves.
  - ***Ureteral reimplantation***— generally reserved for children with persistent high-grade (III to V) reflux.
- Untreated cases can lead to progressive renal scarring and chronic renal failure.

(III) Glomerular Diseases



i) Nephrotic syndrome

It is most commonly idiopathic. Minimal change disease subtype is most commonly seen in children.

Congenital Finnish-type nephrotic syndrome is seen in early life by 3 months of age. It is attributed to **Nephrin (NPHS1)** mutation. (*Aide mémoire: Nephrin and Finnish both have "PH" in them*).

Gene mutation associated with steroid resistant Nephrotic Sydrome is **Podocin (NPHS2).**

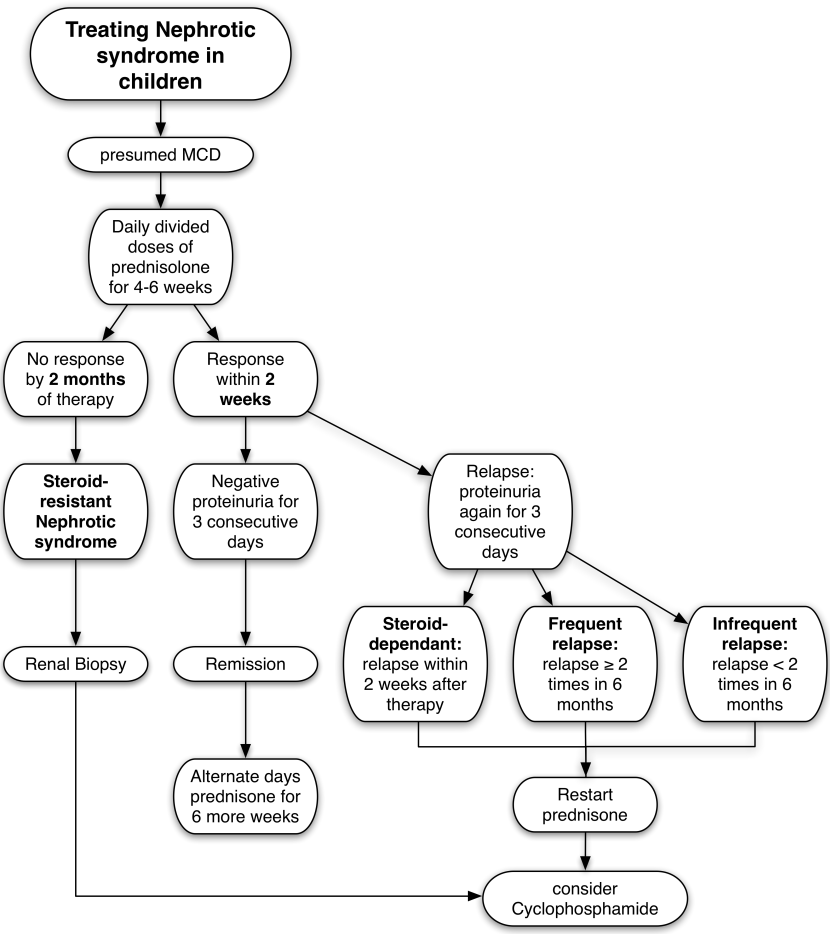
a) Clinical Features

Nephrotic syndrome characterisitics		
Protein loss in urine	Proteinuria (albuminuria, mostly)	> 1g/m²/day or 40 mg/m²/hour
Decreased proteins in serum	Hypoproteinemia	< 5.5 g/dL
	Edema	Seen when albumin < 2.5 g/dL
Compensatory hepatic anabolism	Hyperlipidemia	

b) Treatment

- Diet

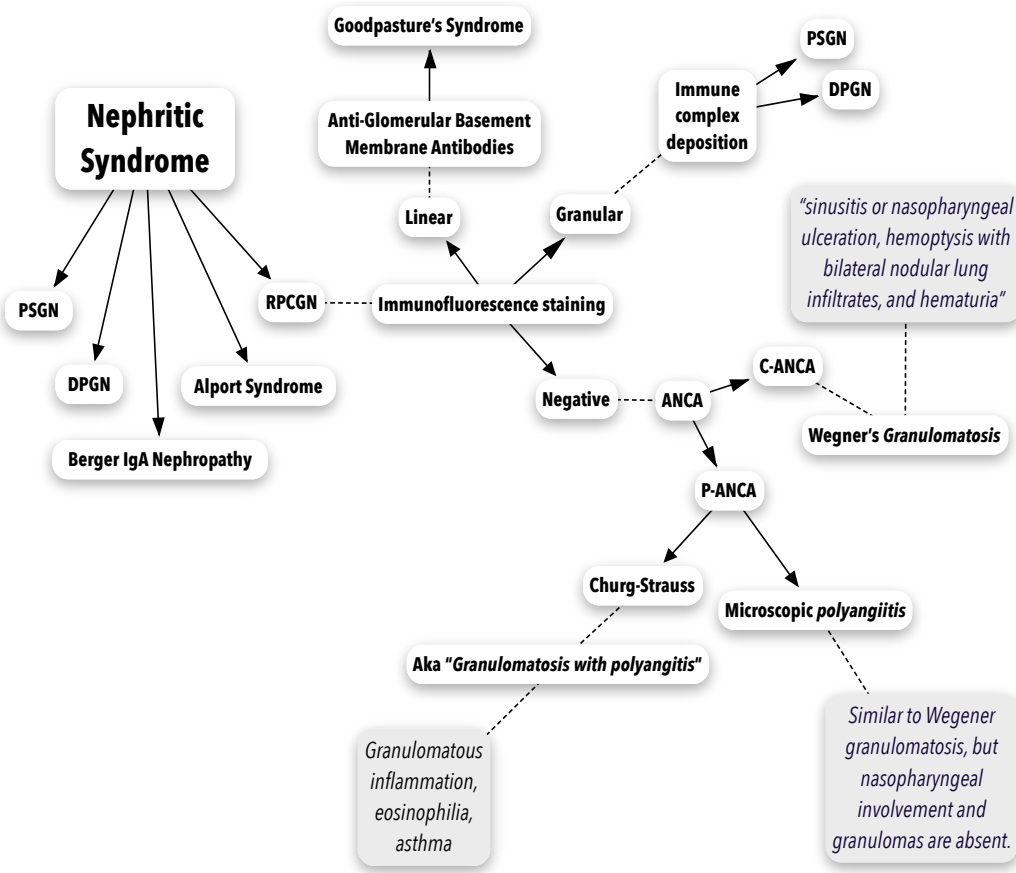
- Activity
- Immunizations: should be delayed until 6 months after remission, because of fear of relapse.
- Infection: Heavy proteinuria increases the risk of infections. High index of suspicion should be kept in mind.
- Edema
- Steroid therapy and renal biopsy (if needed)



c) Complications

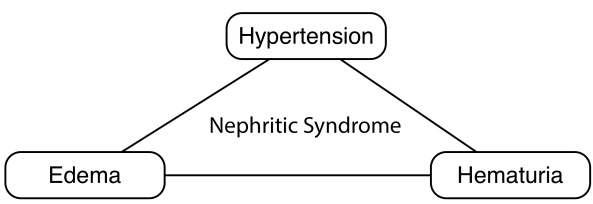
- Increased risk of infections
- Hypercoaguable state is seen due to loss of anticlotting proteins in urine.
- Acute renal failure
- Ascites and spontaneous bacterial peritonitis.

ii) Nephritic syndrome



Group A Strep Infections
Skin infections can lead to glomerulonephritis. However, only pharyngeal infections can lead to rheumatic fever. *Aide Mémoire*: Throat (pharyngitis) goes to kidneys (glomerulonephritis) and heart (rheumatic fever).

a) Clinical features



Nephrotic syndrome characterisitics		
Protein loss in urine	Proteinuria (albuminuria, mostly)	> 1g/m²/day or 40 mg/m²/hour
Decreased proteins in serum	Hypoproteinemia	< 5.5 g/dL
	Edema	Seen when albumin < 2.5 g/dL
Compensatory hepatic anabolism	Hyperlipidemia	

b) Treatment

Management is mainly centered around:

- Bed rest: (recommended during the phase of oedema and hypertension).
- Edema and Hypertension:
    - Diet: should have very little salt and proteins
    - Fluid restriction—intake should be reduced to approximately the amount of insensible losses (~400 mL/m^2).
    - Control of hypertension diuretics, calcium channel blockers, etc.
- For Vasculitis-associated glomerulonephritides, steroids and immunosuppresives (e.g. cyclophosphamide) may be used.
- Dialysis in more severe complicated cases.

CHAPTER 29 RHEUMATIC DISEASES IN CHILDREN

(I) Rheumatic Fever

It is a result of pharyngeal infection with group A β-hemolytic streptococci. Antibodies to M protein cross-react with self-antigens (molecular mimicry) in a type 2 hypersensitivity reaction affecting high-pressure valves most (mitral (70%) > aortic (25%) >> tricuspid).

Early manifestation is mitral regurgitation and Carey coomb's murmur (mitral valvulitis producing a diastolic murmur without an opening snap). Late sequelae include rheumatic heart disease mitral stenosis.

i) Investigations

- ASO titers, anti DNAase B (best test)
- Streptozyme slide test: detects antibodies to extracellular streptococcal antigens
- ECG – 1st degree heart block
- Echocardiography

ii) Diagnosis

J♥NES criteria **[(2 major or 1 major + 2 minor) + preceding streptococcal infection]**	
Major criteria	Minor criteria
Joint (migratory polyarthritis)	Fever
♥ --carditis	Arthralgia
Nodules, subcutaneous	Previous rheumatic fever
Erythema marginatum	Increased acute phase reactants (ESR, or CRP)
Sydenham chorea	Prolonged PR
A diagnosis is acceptable without Jones criteria if: --Chorea --Evidence of late onset carditis without other explanation --Rheumatic recurrence	

iii) Treatment:

- Bed rest
- Aspirin
- For pharyngitis 100,000 units/kg/day for 10 days or single dose 1.2 million units benzathine penicillin.
- Steroids --for carditis
- Chlorpromazine, haloperidol and penicillin prophylaxis –for sydenham's chorea

iv) Prevention:

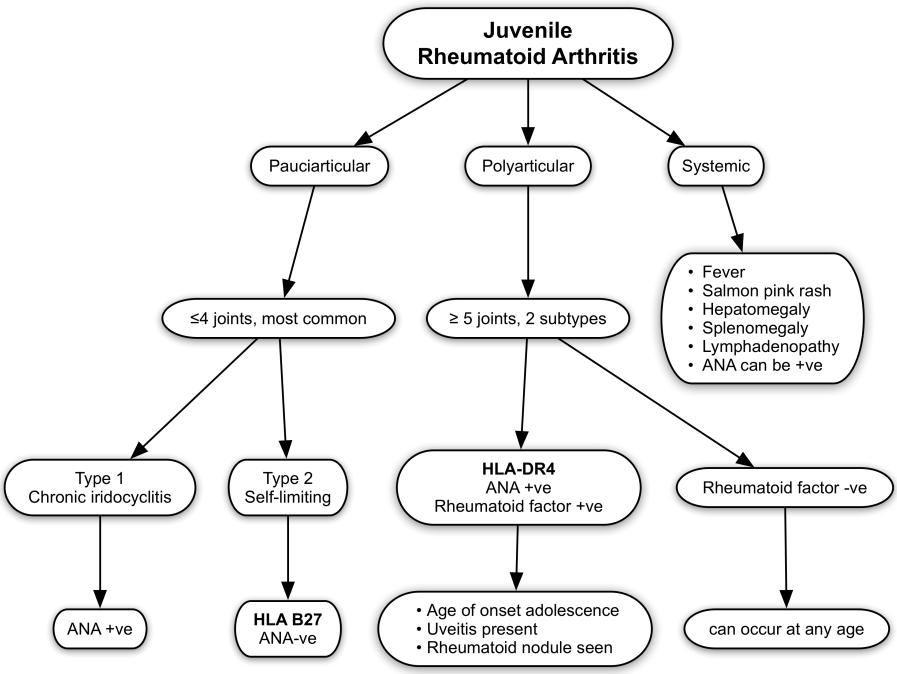
- Primary Prevention: Early antibiotic treatment can prevent rheumatic fever but not glomerulonephritis.
- Secondary Prevention: 1.2 million units benzathine penicillin at 3 weeks interval for life.

(II) Juvenile rheumatoid arthritis (JRA)

i) Clinical Features

There are 3 forms depending on number of joints and systemic involvement.

Arthritis with periarticular bone resorption is an early feature. *Morning stiffness is characteristic.* A relapsing and remitting course of disease is seen.



ii) Investiagtions

- CBC, CRP, ESR
- Rheumatoid Factor (IgM antibodies against IgG)
- Joint aspiration- decreased complement levels in joint fluid
- Radiologic features include joint space narrowing, juxta-articular osteopenia, subcondral sclerosis, and soft tissue swelling.

iii) Diagnosis

Criteria for JRA and classification
Age at onset < 16 years
Arthritis (swelling or effusion, or presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion and increased heat) in one or more joints.)
Duration of disease ≥ 6 weeks
Onset defined by type disease in the first 6 months of presentation: Pauciarticular, polyarticular or systemic.
Exclusion of other forms of juvenile arthritis

iv) Treatment

- Bed rest, warm packs
- Physiotherapy
- Aspirin, NSAIDS, Methotrexate
- Biologic therapies, e.g. Etanercept (blocks TNF-α receptors)
- Omega-3 fatty acids may be of some value

(III) Systemic Lupus Erythematosis

It is a female predominant autoimmune disease, hallmark of which is antibody production against nuclear antigens. Antigen-antibody complex deposition in various tissues also results in a type 3 hypersensitivity reaction.

ACR diagnostic criteria (4/11 should be present for diagnosis) – *Aide Mémoire:"4 RASHES"*		**Points**
4 Rashes	Malar rash	1
	Discoid rash	1
	Photosensitivity	1
	Oral ulcers	1
Renal proteinuria > 0.5g/day or ≥ 3+ on dipstick		1
Arthritis ≥ 2 joints,		1
Serositis, pleuritis, pericarditis		1
Hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia, LE cell		1
Excitation—seizures, psychoses		1
Serology	ANA	1
	Anti-dsDNA, anti-Smith, APLA, false positive VDRL	1

i) Investigations

- CBC, ESR, Coombs test,
- ANA, anti-Smith, RF, antiphospholipid antibodies (APLA)
- Completement levels-- decreased
- Urinalysis—proteinuria may be seen
- Renal biopsy— may show Diffuse Proliferative Glomerulonephritis (DPGN) type of nephritic syndrome or Membranous Nephropathy type of nephrotic syndrome.

ii) Treatment

- It is focused to the organ system most involved.
- Aspirin, NSAIDS

- Corticosteroids for acute flares
- Hydroxychloroquine is used for skin and joint manifestations is given long term
- Immunosuppressives e.g. azathioprine or cyclophosphamide for some steroid resistant forms.
- Anti-platelets for thromboembolic phenomena

(IV) Vasculitis

i) Henoch-schonlein purpura (HSP)

It is a recurring disease of skin, joints, abdomen and kidney mostly, characterized by characteristic clinical features occurring after an acute upper respiratory tract infection usually.

It is an IgA antibody mediated disease. *HSP and IgA nephropathy come under a similar spectrum of diseases.*

a) Clinical features

- Palpable purpuric rash—most common
- Cutaneous nodules over elbows and knees
- Transient arthritis
- Colicky abdominal pain (50%) ± GI bleeding (due to hemorrhage and edema involving small intestines)
- Hematuria—nephritic syndrome if renal involvement
- There should be a high suspicion for intussusception of intestines in HSP.

b) Investigations

- CBC, CRP, ESR,
- Hess's capillary-fragility-tourniquet test is normal. ***Distinguishes it from Dengue fever.***
- Serum IgA levels
- Serum complement levels
- ASO titers
- Stool D/R for blood testing

c) Treatment

- It generally supportive treatment for this self-limiting condition
- Aspirin, NSAIDs for pain
- Corticosteroids may be used in severe disease
- Penicillin may be required if ASO titers are elevated

(V) Kawasaki's disease

Also known as mucocutaneous lymph node syndrome, it is a medium-vessel vasculitis occurring predominantly in children <5 years (80%).

The inflammation in the vessel wall destroys internal elastic lamina. Consequently, there is dila-

tation and aneurysm formation. Stenosis may be seen in the vessel in the healing phase.

i) Clinical features

- Acute febrile illness (1-2 weeks)—non-specific acute illness
- Subacute phase (4 weeks)- there is an increased risk of death in this phase due to development of coronary vessel aneurysms. Desquamation and thrombocytopenia is seen.
- Convalescent phase (6-8 weeks)—recovery period.

Table. Diagnostic criteria for Kawasaki's disease	
A	Fever ≥ 5 days
B	Presence of 4 of the following 5 conditions 1. Bilateral non-purulent conjunctival injection 2. Changes in the mucosea of the oropharynx, including infected pharynx, infection and/or fissured lips, strawberry tongue. 3. Changes of the peripheral extremities, such as edema and/or erythema of the hands or feed, desquamation, usually beginning centrifugally. 4. Rash, primarily truncal, polymorphous but non-vesicular. 5. Cervical lymphadenopathy (>1.5 cm usually unilateral).
C	Illness not explained by other known disease processes

ii) Investgations

- CBC—anemia with leukocytosis and thrombocytosis is seen, ESR, CRP
- ECG—tachycardia, low voltage may be seen
- Echocardiography/ateriogram—coronary vessel aneurysms may be seen

iii) Treatment

- IV immunoglobulins single dose over 10-12 hours
- High dose aspirin
- Plasmapharesis for non-responding cases
- Corticosteroids are not helpful
- Long-term therapy with antiplatelets aspirin and dipyridamole

iv) Complications

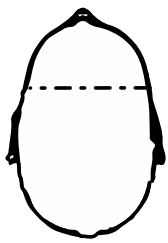
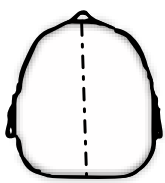
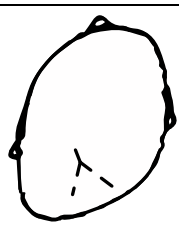
- Myocarditis
- Pericarditis
- Coronary heart disease

CHAPTER 30 CNS

(I) Head Malformations

1. Holoprosencephaly: Incomplete separation of the cerebral hemispheres. Seen in Patau's syndrome.
2. Lissencephaly: Bat like brain with no cerebral convolutions and a poorly formed sylvian fissure due to faulty neuroblast migration (agyria).
3. Schizencephaly: Unilateral or bilateral cleft in the cerebral hemispheres, microgyria.
4. Craniosynostosis: premature closure of cerebral sutures

Table. Types of Craniosynostosis

Premature fusion of	Pathology	Description
Coronal suture	 Brachycephaly	Broad, short anteroposterior diameter
Sagittal suture	 **S**caphocephaly	Elongated, thin cranium
Lambdoid suture	 Plagiocephaly	Parallelogram/trapezoidal shaped cranium

(II) Neural Tube Defects (NTDs)

During normal fetal development, the neural tube closes around 3rd – 4th week. Defects include:

- Anencephaly: Due to failure of closure of the cranial neuropore. Stillborn/die shortly after birth.
- Encephalocoele: extrusion of brain through skull defect.
- Meningocoele: normal spinal cord, defect covered with skin.
- Myelomeningocoele: abnormal spinal cord and *exposed* defect.
- Spina bifida occulta: cord covered with bone, and skin with overlying skin lesion, e.g. lipoma/sinus/hair.

(III) Mental Retardation

- Mental retardation refers to abnormalities in intellectual/adaptive function.
- Age on onset before 18 years/age of maturity
- Most common cause = Chronic anomalies (Down's syndrome)
- Most common cause in males = Down's syndrome (mild to moderate MR)
- Most common cause of severe MR in males = Fragile X syndrome.

Table. Levels of mental retardation			
Level	**ICD-10 IQ score (WHO)**		
Normal	> 90		
Borderline	70-90		
Mild	50-69	Educable mentally retarded (EMR)	
Moderate	35-49	Trainable mentally retarded (TMR)	
Severe	21-34	Able to guard, but cannot manage self	Custodial
Profound	< 20	Unable to guard self,	

(IV) Meningitis

It refers to the inflammation of the meningeal covering (dura, arachnoid and pia) of the brain. it occurs mostly due to microbial organisms.

i) Etiology

Age group	**Causative organisms**
<1 month age	Group B streptococcus
	E. Coli
	Listeria Monocytogenes
1 month—3 months	Group B streptococcus
	E. Coli
	Streptococcus pneumonia
	Hemophilus influenza type B
3 months—5 years	Streptococcus pneumonia
	Neisseria meningitides
	Hemophilus influenza type B
> 5 years age	Streptococcus pneumonia
	Neisseria meningitidis

ii) Clinical features

- Fever
- Lethargy, irritability
- Symptoms of meningeal irritation, e.g.
- Photophobia
- Neck, and back pain
- On examination:
    - Neck stiffness

- Kernig's sign: painful passive extension of the knee when hip is flexed passively at 90°.
- Brudzinski's sign: flexion of the neck elicits reflex flexion of the hip joints.

a) Meningococcemia

- It is caused by *Neisseria meningitides*
- Characterisitic petechial-purpuric rash is seen
- A fulminant infection leads to **Waterhouse-Friderichsen Syndrome (WFS)**, characterized by rapid worsening features:
  - Septic shock,
  - Acidosis
  - DIC,
  - ***Adrenal hemorrhage***

b) Tuberculous meningitis

- It caused by *Mycobacterium tuberculosis* in immunocompetent individuals. Other mycobacterial species can affect immunosuppressed individuals.
- Its clinical features are characterized in the following stages:
  - **Stage 1**: early non-specific signs and symptoms, including irritability, headache, malaise, fever, anorexia, nausea, without any alteration in level of consciousness.
  - **Stage 2:** There is altered level of consciousness in addition to focal neurological signs, cranial nerve palsies, with signs and symptoms of meningism and meningitis.
  - **Stage 3**: It is an advanced state with stupor, coma, dense neurological deficits, seizures, and posturing ± abnormal movements.

c) Aseptic/ viral meningitis

- It can be caused by a variety of viruses including:
  - Enteroviruses (most common cause)
  - Arbovirus
  - Herpes simplex virus
  - Varicella zoster— commonly presents as cerebral ataxia and encephalitis
  - Cytomegalovirus (CMV)
  - Epstein-barr virus—
- Less severe features are generally observed in comparison with bacterial meningitis.

iii) Investigations

- Blood cultures
- Lumbar puncture
  - It is contraindicated in:
    - Focal neurologic signs,
    - Poorly reactive pupils, and

- A tense fontanelle

- For diagnosis of viral meningitis
  - Viral culture
  - PCR testing of CSF is the best test

- Biopsy of brain or meninges is gold standard for *Mycobacterium tuberculosis.*

Condition	Pressure	Leucocytes (/mm)	Protein (mg/dL)	Glucose (mg/dL)
Normal	50–80	<5, ≥75% lymphocytes	20–45	>50 (or ⅔ of serum glucose)
Bacterial meningitis Organisms usually seen on Gram stain and recovered by culture.	Usually elevated (100–300)	100–10,000 or more; usually 300–2,000; PMNs predominate	Usually 100–500	Decreased, usually <40
Viral meningitis or meningoencephalitis HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF	Normal or slightly elevated (80–150)	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis (LCM) may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50–200	Usually normal;
Tuberculous meningitis Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF	Elevated	10–500; PMNs early, but lymphocytes predominate through most of the course	100–3,000;may be higher	<50
Fungal meningitis Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection	Elevated	5–500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25–500	<50;

iv) Treatment

- Choice of antibiotics is mainly empirical and based on most common organisms in that age group until culture/sensitivities are known.

- The choice of first line of antibiotics in case of suspected bacterial meningitis is:

Table. Antibiotics used in empirical therapy of bacterial meningitis	
Indication	**Antibiotic**
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 mo	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 mo	Cefotaxime, ceftriaxone or cefepime + vancomycin

- If purpuric skin rash seen: Benzylpenicillin (N. meningitidis)
- No skin rash is seen: Ceftriaxone
- A broad-spectrum empiric antibiotic cover can be done with Ampicillin + Chloramphenicol/cefotaxime/ceftriaxone.
- Dexamethasone given early (for 2-4 days) with antibiotics decreases the risk of complications like deafness and other neurologial deficits.
- Treatment of Tuberculous meningitis is:
    - Isoniazid, Rifampin, Pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampicin alone for a another 10 months.
    - Steroids are always used initially for upto 6 weeks or more with antibiotics.
- Treatment of viral meningitis is generally supportive, although acyclovir may be used for select cases of Herpes simplex virus.

Specific antibiotic therapy of CNS bacterial infections		
Organism		**Antibiotic**
Neisseria meningitides	Penicillin-sensitive	Penicillin G
	Penicillin-resistant	Ceftriaxone
Streptococcus pneumoniae	Penicillin-sensitive	Penicillin G
	Penicillin-intermediate	Ceftriaxone or cefotaxime
	Penicillin-resistant	(Ceftriaxone or cefotaxime) + vancomycin
Gram-negative bacilli (except *Pseudomonas)*		Ceftriaxone or cefotaxime
Pseudomonas aeruginosa		Ceftazidime or cefepime or meropenem
Staphylococci spp.	Methicillin-sensitive	Nafcillin
	Methicillin-resistant	Vancomycin
Listeria monocytogenes		Ampicillin + gentamicin
Haemophilus influenzae		Ceftriaxone or cefotaxime
Streptococcus agalactiae		Penicillin G or ampicillin
Bacteroides fragilis		Metronidazole
Fusobacterium spp.		Metronidazole

v) Complications

Meningitis is associated with a range of complications, most notable of which are:

- Deafness (most common, associated with *Hemophilus influenzae* infection and *Streptococcus pneumoniae*).
- SIADH (Syndrome of Inappropriate ADH)
- Seizures
- **Encephalitis (=*signs & symptoms of meningitis + mental status changes)***
- Cranial nerve palsies
- Spasticity
- Subdural effusions: Most effusions are sterile and asymptomatic (detected by CT scan or MRI) and do not necessitate drainage unless associated with increased intracranial pressure or focal neurologic signs.
- Hydrocephalus
- Reoccurance:

- A parameningeal focus or resistant organisms may lead to **relapse** 3 to 14 days after treatment.
- Recurrance suggests an underlying predisposing immunologic or anatomic defect.

vi) Prevention

- Vaccinations against *H. influenzae, S. pneumoniae,* and *N. meningitidis* have been developed.
- Chemoprophylaxis for close contacts is recommended with Rifampicin (children) or ciprofloxacin (adults), except in cases of *S. pneumoniae* infections.

(V) Encephalitis

There is high suspicion for a diagnosis of encephalitis with signs & symptoms of meningitis in combination with mental status changes.

Table. Some important causes of encephalitis	
Infectious	**Post-infectious**
Herpes simplex.	Measles (SSPE)
Enterovirus (Coxsackie, echovirus)	Varicella zoster
Mumps.	

- Herpes simplex is the most common cause of severe encephalitis. Mortality is high and neurological sequelae in the survivors are common.
  - The CSF shows a raised white count, and the EEG and CT scan may show characteristic changes in the temporal lobes.
- Acute self-limiting encephalitis may follow chickenpox, resulting in cerebellar ataxia.
- Encephalitis may also follow measles in two broad forms.
  - Early onset encephalitis with irritability and seizures a few days after the rash. There may be complete recovery or it can progress to severe neurological impairment or death.
  - Late onset complication of measles includes Subacute Sclerosing Panencephalitis (SSPE). Degeneration of the brain occurs several years after the initial infection. It is thought to occur due to persistence of the virus in the brain.

(VI) Acute flaccid paralysis

Acute flaccid paralysis (AFP) is defined as paralysis of acute onset (<4 weeks), and the affected limb or limbs are flaccid, i.e., floppy or limp. Muscle tone is **diminished** and *sensations are not affected*.

AIP can be classified into four groups based on the levels of affected motor unit (muscle, neuromuscular junction, motor fibers, and anterior horn cells).

Anatomically, AFP can be classified into four groups based on the levels of affected motor unit (muscle, neuromuscular junction, motor fibers, and anterior horn cells).

Common causes of AFP include poliomyelitis, Guillain-Barre syndrome, transverse myelitis, and traumatic neuritis.

i) Poliomyelitis

Introduction: Poliovirus is an enterovirus spread through fecal or pharyngeal secretions and is the cause of paralytic poliomyelitis.

The incubation period is 7-14 days following exposure to the virus.

Typically, enterovirus infections are asymptomatic or minor febrile illnesses. Only about 1% of polio infections result in clinically apparent neurologic disease.

It has been eradicated from developed countries, except for rare imported cases and rare cases of vaccine associated paralytic poliomyelitis (VAPP), a rare consequence of the live-attenuated oral polio vaccine.

a) Clinical features

- Malaise, headache, nausea, vomiting, and sore throat; uneventful recovery within several days— *abortive poliomyelitis*. This occurs most commonly.
- 10-20% of symptomatic infections progress with severe muscle spasms, neck and back stiffness, and muscle tenderness lasling about 10 days with complete recovery— *non-paralytic poliomyelitis*
- Very few cases develop **paralytic poliomyelitis**— ***asymmetric*** weakness or acute flaccid paralysis.
- Asymmetric flaccid paralysis from lower motor neuron damage— spinal poliomyelitis.
- Bulbar paralysis involves 9th, 10th, 11th, and 12th cranial nerves leading to paralysis of pharynx, larynx and tongue. **Rope sign— acute angulation between chin and larynx due to weakness of hyoid muscles** may be seen in addition signs and symptoms produced by cranial nerve dysfunction, (e.g. inability to swallow, deviated tongue and uvula, etc.)
- Cranial nerve palsies without sensory loss or dysphagia; deep tendon reflexes diminished or lost asymmetrically.
- Poliomyelitis is an important diagnosis to consider in acute flaccid limb paralysis, especially if asymmetric, after acute febrile illness in a child or young adult.

b) Investigations

- CSF analysis
- Viral cultures of spinal fluid

c) Differential diagnosis

- **Acute Guillain-Barre syndrome** (post-infectious polyneuritis)**:** May be clinically similar in presentation, but usually has an afebrile, **symmetric paralysis**, often assodated with sensory loss. *Important to differentiate due to potential for intervention (immunoglobulin, plasmapheresis)*

Table. Clinical features to distinguish causes of acute flaccid paralysis

	Polio	**Guillain-Barre syndrome**
Paralysis onset	During (or after) febrile illness	Several weeks after febrile illness
Pattern of paralysis	Asymmetrical	Symmetrical
Time to peak weakness	Short (e.g. 2-3 days)	Relatively longer (e.g. 7-14 days)
Sensory involvement	No	Often
Cerebrospinal fluid (CSF)	↑ lymphocytes	↑ protein

- Encephalitis
- Brain abscess
- Tuberculous meningitis

d) Treatment and prevention

- Supportive care is indicated, including bed rest antipyretics, and analgesics.
- No specific treatment.
- Physical therapy with early mobilization after illness
- Prevention is by improved hygiene, safe drinking water and immunization. Injectable polio vaccine does not have risk of VAPP.

e) Complications

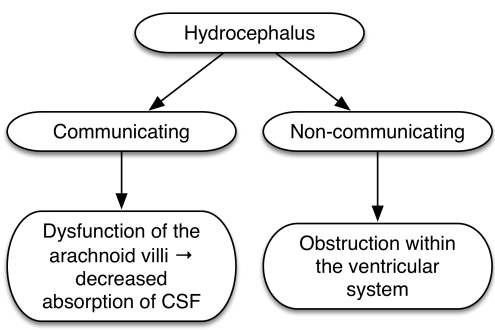
- Myelitis
- Peripheral neuropathy
- Skeletal deformity in affected limbs
- **Post-polio syndrome**: This is a late complicalion characterized by recurrence or worsening of prior paralysis that had resolved, often *along with pain* involving affected limbs several years after resolution of the initial paralytic illness. The weakness is slowly progressive.

ii) Traumatic Neuritis

Intramuscular injection in gluteal region (that site should not be used) may cause trauma to the sciatic nerve. There usually is local pain within a few hours followed by flaccid weakness of the affected limb.

Nerve conduction velocities (NCV) are decreased and the electromyographic studies (EMG) show a normal pattern. Variable degree of residual muscle atrophy and loss of power may be observed.

(VII) Hydrocephalus



In Children:

- Most common cause of communicating hydrocephalus (non-obstructive) is subarachnoid hemorrhage (which may be due to intraventricular hemorrhage in a premature infant). Tuberculous and pneumococcal meningitis can also cause it.
- Most common cause of non-communicating (obstructive) hydrocephalus is aqueductal

stenosis

Idiopathic intracranial hypertension

Also known as pseudotumor cerebri, it is a cause of increased ICP with normal brain imaging.

Clinical Features

- Patients exhibit a daily debilitating headache associated with diplopia, sixth nerve palsy, transient visual obscurations, and papilledema.
- If untreated, permanent visual field loss may develop.
- The syndrome has been associated with ingestion of medications (tetracycline, vitamin A, oral contraceptive agents) and endocrine disturbances (thyroid disease, Addison disease).
- Most commonly, this condition is idiopathic and affects children who are otherwise well except for being overweight, with rapid weight gain being a predisposing factor.

Treatment

- Weight loss and cessation of triggering medications are mainstays of treatment.
- Acetazolamide,
- Topiramate,
- Corticosteroids
- Optic nerve fenestration may be needed to preserve vision.

(VIII) Seizures

i) Classification of seizures

- Partial seizures: abnormal electrical discharge originates from discrete regions of the brain; they can be simple (patient fully conscious) or complex (decreased awareness)
- Generalized seizures: abnormal electrical discharge involves the entire brain
- Absence seizures: 'petit mal'; sudden brief lapses of consciousness without loss of postural control
- Tonic–clonic seizures: 'grand mal', involving jerking movements
- Atonic seizures: sudden loss of postural muscle tone; lasts 1–2 s
- Myoclonic seizures: sudden contractions of the limbs ± unconsciousness.

ii) Febile seizures

These are most common cause of seizures among children 6 months to 6 years of age.

Simple benign febrile fits	Atypical febrile fits
• Fits occur: - Within 24 hours of onset of fever, - Lasting < 10 minutes, and are - Usually single per febrile episode • Convulsions are generalized • No post-ictal neurological deficit • Family history may be present.	Anything different from features of simple febrile convulsions are **atypical fits.** Presence of family history of epilepsy, neurodevelopmental retardation and atypical episodes increase risk of febrile episodes and subsequent epilepsy.

a) Treatment

- Antipyretics (paracetamol, ibuprofen avoid aspirin due to risk of Reye's syndrome).
- Hydrotherapy, tepid sponging, oxygen.
- IV diazepam or phenobarbitone for control of seizures,

b) Prophylaxis

It is indicated for atypical febrile fits:

- Diazepam is used at the onset of fever and continued for the duration of febrile illness.
- Phenobarbitone may be indicated for complicated cases.

iii) Status Epilepticus

- Status epilepticus is defined as persistence of a seizure for more than 10 minutes or recurrent seizures without gain of consciousness.
- Prompt medical treatment is required to reduce mortality and limit cerebral damage.

a) Etiology

- Status epilepticus may occur as in a seizure disorder or neurologically ill patients, drug withdrawal, or due to intercurrent illnesses like inflammatory, traumatic, hypoxic, and metabolic causes.

b) Clinical features

- Persistent and prolonged seizure activity causes cerebral edema, hypoxia, hyperthermia, hypoglycemia and vasomotor instability.
- Respiratory depression may occur either due to involvement of the respiratory center, or as a result of drugs used for seizure control.
- Vomiting and aspiration of secretions also increase morbidity.

c) Management

- Prompt treatment is more important than investigation of cause in emergency situations:
    - ABCDE approach
    - Intravenous line established with 10 percent dextrose and IV diazepam
    - The half-life is short and seizures may recur.
    - If seizures do not stop within 5 minutes, a second dose may be repeated.
- *The benzodiazepines should be followed by intravenous phenytoin to maintain prolonged seizure control.* Rate of administration should not exceed 1 mg/kg/minute.
- If seizures remain uncontrolled, phenobarbitone 20 mg/kg/intravenous may be used at a rate of 1 mg/kg/minute.
- Maintain a seizure-free state for 10–12 hours following which the dose may be tapered.
    - Midazolam infusion or thiopental may be also be used.
    - 4 mg/kg intravenously or as a slow infusion may be used till seizure control.
    - Ventilatory support, respiratory and hemodynamic monitoring is essential.
    - Mortality and sequelae are determined by etiology of status epilepticus, ade-

quacy and promptness of therapy and presence of secondary complications.

- Mannitol (to reduce brain edema), careful monitoring of body temperature and prevention of aspiration and injury should be provisioned.

iv) Epilepsy syndromes

Epilepsy is neurological disorder of recurrent seizures.

- Causes:
    - Idiopathic,
    - Cerebral palsy,
    - Brain insult (head injury/meningitis),
    - Metabolic,
    - Genetic
- Focal/partial seizures involving various parts of the brain show some characteristic manifestations during the seizure, e.g.
    - Frontal lobe – simple partial seizures (e.g. Jacksonian march/todd's paresis)
    - Temporal lobe – automatisms, sensory phenomena, déjà vu
    - Parietal lobe – vertigo, sensory symptoms, distorted body image
    - Occipital lobe – visual symptoms

Table. Common Pediatric Epilepsy Syndromes

Syndrome	Symptoms	Diagnosis	Treatment
Absence	Multiple brief seizures staring episodes	Generalized 3-Hz spike & wave pattern on EEG	Ethosuximide
Infantile spasms (West Syndrome)	Affects infants spasms <1 year, 'jackknife spasms', developmental regression	***Hypsarrythmia**** on EEG, associated with Tuberous sclerosis	ACTH
Lennox Gastaut syndrome	Multiple progressive difficult to treat type seizures with GTCSand drop attacks	Atypical spike and wave pattern in frontal region on EEG.	No effective treatment
Juvenile mycolonic epilepsy	Affects healthy adolescents as myoclonic jerks occurring early mornings after waking up	Positive family history	Treatable with antiepileptic medications
Benign partial epilepsy	Partial vocal or oral seizures during wakefulness	Classic interictal spikes from the centrotemporal rolandic region.	Seizures stop by adolescence usually.
Landau Klefner syndrome	Children loose language 3-6 years, associated with autism	Bilateral temporal spike and sharp waves on EEG	Antiepileptic medications

**Hypsarrhythmia consists of chaotic high-voltage slow waves, spikes, and polyspikes.*

(IX) Cerebral palsy

It is a non-progressive neuromotor disorder of cerebral origin associated with a prenatal, perinatal or postnatal insult (ischaemia, congenital infection, neonatal meningitis, prematurity, IVH, kernicterus, etc).

i) Risk factors

Table. Risk Factors for Cerebral Palsy
PREGNANCY
Low socioeconomic status
Pregnancy complications (incl. abnormal fetal presentation and eclampsia)
Third-trimester bleeding (incl. threatened abortion and placenta previa)
Multiple births
BIRTH
Prematurity
Low birth weight (<1500 g at birth)
Congenital malformations/syndromes
Newborn hypoxic-ischemic encephalopathy
Bilirubin (kernicterus)
AFTER THE NEWBORN PERIOD
Meningitis
Head injury
Near-drowning
Stroke

ii) Classification

Table. Classification of Cerebral Palsy (CP) according to type of motor disorder		
Type		**Features**
Spastic cerebral palsy (most common, 70-80%, due to injury of UMNs of corticospinal tract).		It is characterized by ≥ 2 of: ○ Abnormal movement pattern, ○ Increased tone, or ○ Pathologic reflexes (e.g. babinski, hyperreflexia).
Atonic/ataxic CP (uncommon)		Atonic diplegia → hypotonia, babinski's, and cognitive delay is seen. Cerebellar injury → abnormal posture or movement and loss of orderly muscle coordination or both.
Extrapyramidal CP	**Dyskinetic CP (10-15%)**	It is dominated by abnormal patterns of movement and involuntary, uncontrolled, recurring movements.
	Dystonic CP (uncommon)	It is characterized by reduced activity and stiff movement (hypokinesia) and hypotonia.
	Choreoathetotic CP (associated with kernicterus hx)	This form is dominated by increased and stormy movements (hyperkinesia) and hypotonia.
Mixed CP (10%–15%, more than one type of motor pattern is present and neither pattern dominates the other)		It typically is associated with more complications, including sensory deficits, seizures, and cognitive-perceptual impairments.

iii) Diagnosis

- Mostly clinical
- Other labs include:

- Radiology, e.g. CT or MRI
- Electroencephalogram (EEG)

iv) Treatment

- Multidisciplinary –
- Medical/physiotherapy/occupational therapy (OT)
- Speech and language therapy (SALT)
- Special needs teachers)
- Cerebral palsy is manageable with intensive rehabilitative efforts centered on the type and extent of motor disease.

(X) Reye's Syndrome

It is a syndrome of acute encephalopathy characterized by cerebral edema and fatty degeneration of the liver. It carries a high mortality rate.

There is mitochondrial injury of unknown etiology with resulting dysfunction of oxidative phosphorylation and fatty-acid oxidation.

i) Associations

- Aspirin therapy
- Viral infections (influenza B, varicella)
- Congenital mitochondrial pathologies causing reye-like illnesses.

ii) Clinical Features

- Prodromal viral infection (e.g. chicken pox) or drug (e.g. aspirin) exposure history.
- 4–7 days later:
    - Vomiting
    - Encephalopathy
    - Moderate hepatomegaly, no jaundice usually
    - Hypoglycaemia is common

Staging of Reye's syndrome	
Stage 1	Vomiting, lethargy, drowsiness, extensor plantar responses with evidence of liver dysfunction.
Stage 2	Disorientation and combativeness, semicoma, hyperventilation, marked increase in liver dysfunction.
Stage 3	Come, hyperventilation, upper midbrain dysfunction with deceleration continued liver function abnormalities
Stage 4	Deepening coma, lower midbrain dysfunction with decreleration, continued liver function abnormalities
Stage 5	Coma, medullary involvement with respiratory arrest, even though improvement of liver function may occur.

iii) Differential diagnoses

- CNS infections (incl. cerebral malaria)
- Drug ingestion
- Metabolic disease, e.g. fatty acid oxidation defects, organic acidurias, urea cycle defects

iv) Investigations

Avoid lumbar puncture in Reye syndrome as ICP is raised.

- Bloods testing reveals
    - High ammonia levels (levels > 300 µg carries a poor prognosis)
    - Liver enzymes, i.e. AST, ALT, LDH, CK increased
    - Glucose decreased (in young children especially)
    - Clotting deranged (PT increased)
- Liver biopsy shows fatty infiltration without inflammatory cells.

v) Management

- Mainly supportive, with correction of hypoglycaemia and coagulation defects, and intensive care as needed.
- It is important to ensure correct diagnosis and control raised ICP.

CHAPTER 31 NEURO-MUSCULAR DISEASES

(I) Duchenne muscular dystrophy

It is also known as 'pseudohypertrophic muscular dystrophy', so called because of fibrous tissue and fat replacing atrophied muscles (typically calf muscles). It is an X-linked recessive disease that manifests early between 3-5 years of life. By 12-14 years of age, the child is bedridden.

Child is bed-bound by 12-14 years age. Gower's sign, gluteal muscle weakness (trendelenberg waddling gait), cardiomyopathy and intellectual impairment is common.

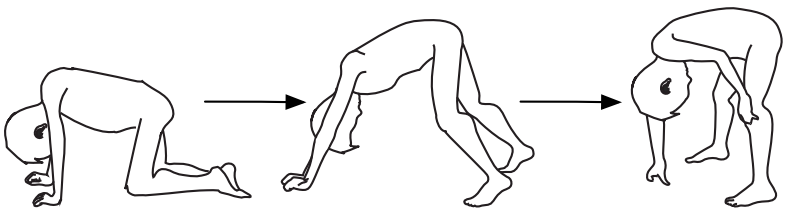


Figure. Gower's sign. It is a characteristic sequence of movements performed by the child to lift him from the floor; usually seen around 5-6 years of age.

i) Diagnosis

- Clinical examination-gower's maneuver
- Serum CPK, aldolase and AST
- EMG
- DNA analysis for mutations

ii) Treatment

- Physiotherapy to prevent contractures
- Steroids to delay progression
- Digoxin for cardiac failure
- Myoblast transfer therapy

Fatality in DMD is due to respiratory infections, acute gastric dilatation, and cardiac failure.

(II) Other muscular dystrophies

Table. Other muscular dystrophies (MDs).

Limb girdle MD	Fascioscapulohumeral MD	Emery-dreifuss MD
Weakness and wasting develops in the ***pelvic and shoulder girdle muscles***. Progression is slower than Duchenne's as a distinguishing feature. It can be inherited in both autosomal recessive and dominant fashion.	It is a group of diseases with identical clinical features. Inheritance is predominantly autosomal dominant. There is wasting and weakness of proximal upper limbs, scapular, and facial muscles. The child is unable to lift his arms above the head.	Contractures in humeral and peroneal muscles and cardiomyopathies.

CHAPTER 32 SELECT PEDIATRIC MALIGNANCIES

(I) Cancer associations

Table. Hereditary conditions with associated tumors
Klinefelter syndrome- Teratoma, Breast cancers
Neurofibromatosis - Glioma,
Von hippel landau syndrome – Renal cell carcinoma
WAGR syndrome - Wilms tumor
Li-fraumeni syndrome-Sarcoma, CNS, Breast tumors
Beckwith - Wiedemann syndrome - Wilm's tumor, hepatoblastoma, Rhabdomyosarcoma

(II) Neuroblastoma

- It is the most common tumour in infants.
- It is most commonly seen in adrenal medulla but can occur anywhere along sympathetic chain; affects children <5 years.
- Presents after metastasis to other organs in upto 60% cases. Clinically, abdominal mass, leg edema, bulging eyes, periorbital bruising, hepatomegaly (metastasis) may sbe seen in the abdominal tumor.
- Radiological imaging, tumor markers [Homovanillic acid (HVA), and vinylmandelic acid (VMA)] in urine HVA in urine, metaiodobenzylguanidine (MIBG) scan (helps identify neural tissue tumors) and biopsy can be used.
- Treatment localized tumours cured with **excision**; chemotherapy and radiotherapy can be used as adjunct. Good prognosis if diagnosed <1 year of age.

(III) Wilms Tumour

- It is renal malignancy of early childhood (< 5 years) mostly.
- Presents with large palpable flank mass, hematuria, hypertension.

Syndromic associations of Wilm's tumor
WAGR syndrome - Wilms tumour, *Ariiridia*, Genital anomalies, mental Retardation.
Beckwith-Wideman syndrome (Enlargement of body organs: *hemihypertrophy*, renal medullary cysts, adrenal cytomegaly).

- Diagnosis is made by abdominal ultrasound and/or CT scans and confirmed by excisional biopsy.
- Treatment transabdominal nephrectomy followed by chemotherapy (vincristine, actinomycin D); prognosis is usually good.

Features	Wilm's tumor	Neuroblastoma
Age	< 5 years	< 2 years usually
Health	Well	Ill-looking, lethargy
Clinical	Swollen abdomen	Pale, weight loss, diffuse bone pain
Mass	Lobulated	Irregular edge, craggy hard
Crosses midline	Rarely	Common
Renal pelvis on U/S	Grossly distorted	Pushed down by mass above
Metastases	Lungs	Retro-orbital and orbital infiltrateon, liver.

(IV) Retinoblastoma

- It is a neoplastic growth usually in posterior portion of the retina.
- Both hereditary and sporadic forms exist.
- Hereditary form shows following characteristics:
    - Autosomal dominant
    - Mutation of **tumor-suppressor retinoblastoma (Rb) gene** on chromosome 13.
    - Most bilateral in both eyes (unlike sporadic form)
    - Increased risk of secondary tumors and other malignancies.

i) Clinical features

- Leucocoria (white pupillary reflex)
- Strabismus
- Decreased vision
- With more advanced disease—
    - Orbital pain
    - Irregular pupils
    - Proptosis
    - Raised ICP

ii) Investigations

- Fundoscopy
- Orbital radiology
    - Ultrasound of orbits
    - CT
    - MRI

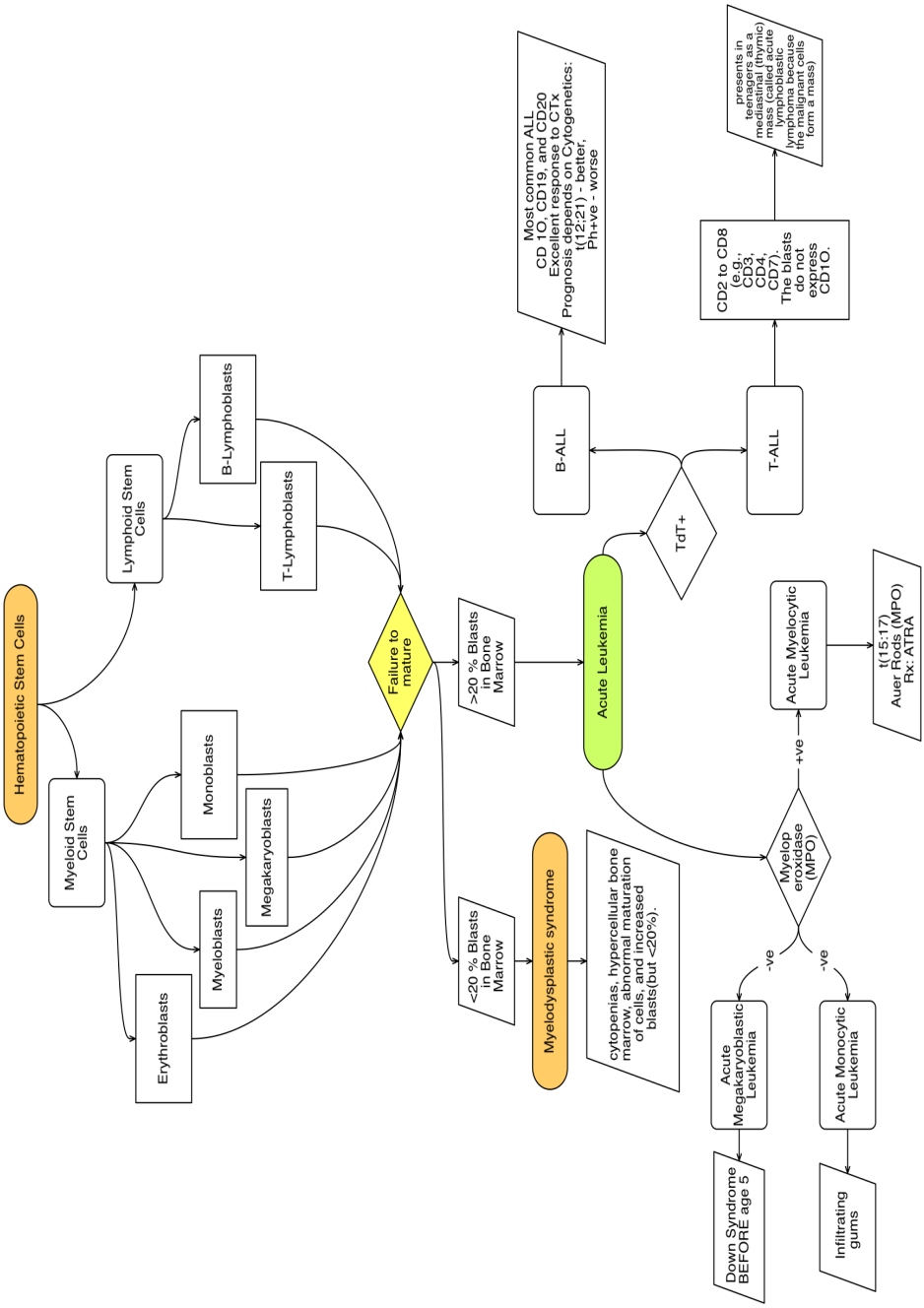
iii) Management

- Enucleation— removal of the entire globe, including cornea, sclera, and a portion of the optic nerve.
- Other options:
    - Radiotherapy
    - Photocoagulation,
    - Cryotherapy can also be used.
- Chemotherapy if metastatic disease.

iv) Prognosis

- Overall survival 90%.
- Poor survival for extensive and metastatic disease.

(V) Leukemias and lymphomas



i) Acute lymphoblastic leukemia

This is the most common form of childhood leukaemia. It arises when lymphoid precursors cell fail to mature.

a) Investigations

- CBC and peripheral film may show a normocytic, normochromic anaemia, and immature cells (blasts).
- CXR: Mediastinal mass (in T-ALL)

- Bone marrow (aspirate or biopsy): > 20% leukaemic blast cells
- CSF: Immature cells (blasts) may be observed in CSF involvement
- Specialized testing
    - Terminal deoxynucleotidyl transferase (TdT)— positive
    - Myeloperoxidase (MPO)— negative
    - Testing for chromosomal translocations— give prognostically helpful information. ***Philadelphia chromosome translocations [t(9:22)] is a poor prognostic sign.***

b) Management

- Chemotherapeutic agents – methotrexate, vincristine, danorubicin, mercaptopurine
- Steroids
- Prophylaxis for CNS involvement: intrathecal chemotherapy, localized may be considered.
- Bone marrow transplant- can be curative

c) Prognosis

- Prognosis is good but also depends on factors like age of occurrence, metastasis etc.

CHAPTER 33 IMNCI

With collaborative efforts, World Health Organization (WHO), United Nations Children's Fund (UNICEF, previously United Nations International Children Emergency Fund), and Ministry of Health Pakistan released Integrated Management Guidelines For Neonatal And Childhood Illness (IMNCI). As of first quarter of 2015, the latest guidelines released were in February 2010, and are accepted throughout the country, and is cited here.

The guidelines are standardized for two age groups:

- Newborn to 2 months of age infant
- Child from the age of 2 months to 5 years

The IMNCI guidelines for Pakistan provide basic level knowledge for standardized practice in cases of problems such as:

- Cough or difficult breathing
- Diarrhea
- Sore throat
- Ear problem
- Fever
- Malnutrition
- Anaemia

These guidelines are subdivided into following sections for these problems:

- Assessment
- Treatment
- Followup
- Counselling the caretaker

ASSESS AND CLASSIFY THE SICK CHILD AGE 2 MONTHS UP TO 5 YEARS

ASSESS

ASK THE MOTHER WHAT THE CHILD'S PROBLEMS ARE

- Determine if this is an initial or follow-up visit for this problem.
  - if follow-up visit, use the follow-up instructions on FOLLOW-UP chart.
  - if initial visit, assess the child as follows:

CLASSIFY

USE ALL BOXES THAT MATCH THE CHILD'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS.

IDENTIFY TREATMENT

CHECK FOR GENERAL DANGER SIGNS

ASK:
- Is the child not able to drink or breastfeed?
- Does the child vomit everything?
- Has the child had convulsions?

LOOK:
- See if the child is lethargic or unconscious.
- See if the child is convulsing now

SIGNS	CLASSIFY AS	TREATMENT (Urgent pre-referral treatments are in bold and italic print.)
• Any general danger sign	VERY SEVERE DISEASE	▸ Treat convulsions if present now. ▸ Complete assessment immediately ▸ Give first dose of an appropriate antibiotic. ▸ Treat the child to prevent low blood sugar. ▸ Refer URGENTLY to hospital.

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
- Look and listen for wheeze.

} CHILD MUST BE CALM

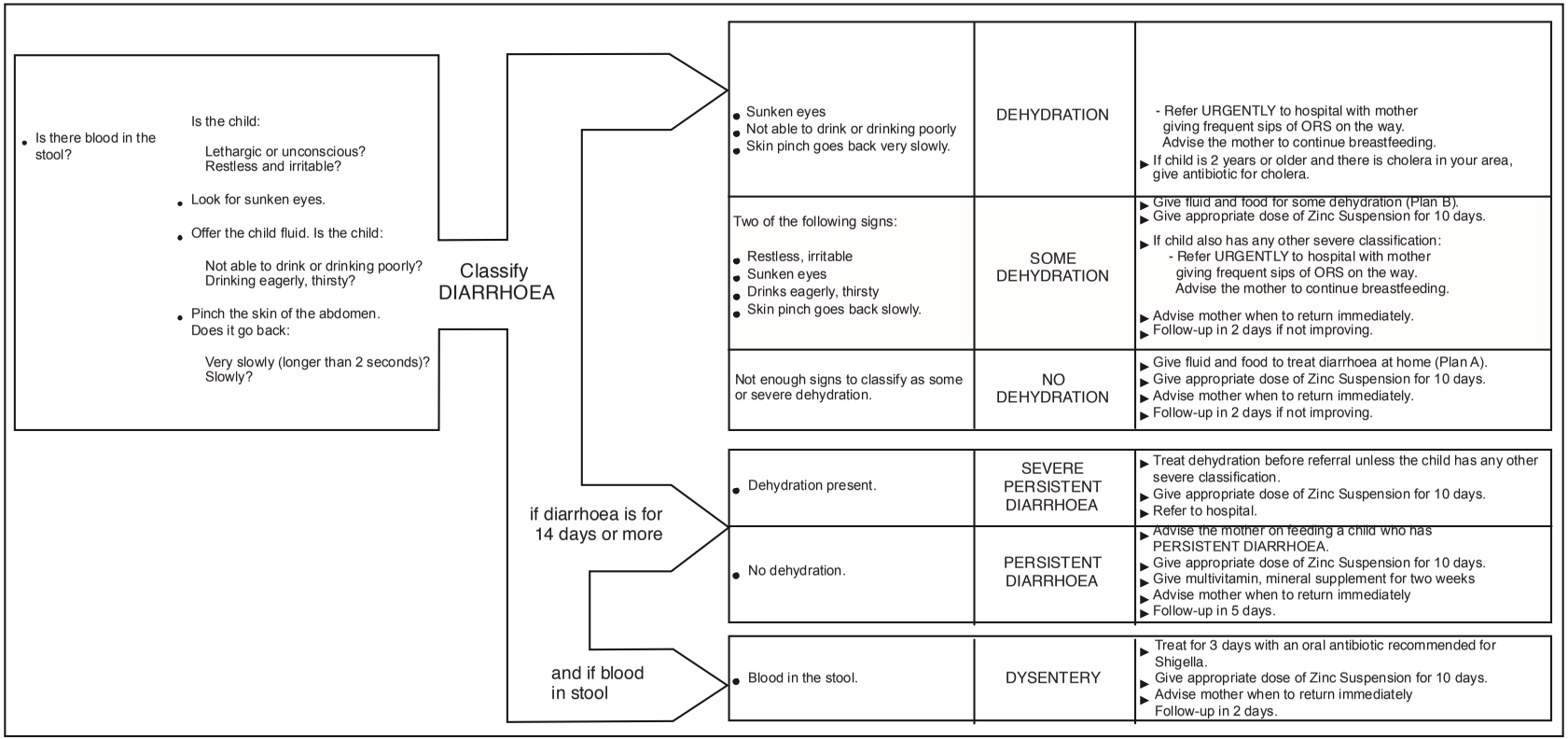
Classify COUGH or DIFFICULT BREATHING

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

If wheezing and either fast breathing or chest indrawing:

Give a trial of rapid acting inhaled bronchodilator for up to three times 15-20 minutes apart. Count the breaths and look for chest indrawing again, and then classify.

• Any general danger sign or • Stridor in calm child	VERY SEVERE DISEASE	▸ Give first dose of an appropriate antibiotic. ▸ Treat wheezing if present ▸ Treat the child to prevent low blood sugar. ▸ Refer URGENTLY to hospital.*
• Fast Breathing and / or Lower Chest Indrawing	PNEUMONIA	▸ Give an appropriate Oral antibiotic for 5 days ▸ If wheezing (even if it disappeared after rapidly acting bronchodilator) give oral bronchodilator for 5 days ▸ Soothe the throat and relieve the cough with a safe remedy ▸ If coughing for more than 3 weeks or if having recurrent wheezing, refer for assessment for TB or Asthma ▸ Advise mother when to return immediately. ▸ Follow-up in 3 days.
• No signs of pneumonia or very severe disease. (if wheeze go directly to treat wheezing)	NO PNEUMONIA: COUGH OR COLD	▸ If wheezing (even if it disappeared after rapidly acting bronchodilator) give a oral bronchodilator for 5 days. ▸ If coughing more than 3 weeks or if having recurrent wheezing refer for assessment for TB or Asthma. ▸ Soothe the throat and relieve the cough with a safe remedy. ▸ Advise mother when to return immediately. ▸ Follow up in 3 days if not improving.



*If referral is not possible, manage the child as described in Integrated Management of Childhood Illness, Treat the Child, Annex: Where Referral Is Not Possible, and WHO guidelines for inpatient care.

Does the child have throat problem:

IF YES, ASK:	LOOK AND FEEL:
• Does the child have sore throat? • Is the child not able to drink? • Does the child have fever?	• Fever (temperature 37.5℃ or above) • Feel the front of the neck for tender enlarged lymph nodes. • Look for red, enlarged tonsils • Look for exudate on the throat.

Classify SORE THROAT

• Sore throat AND not able to drink	THROAT ABSCESS	▸ Give first does of an appropriate antibiotic. ▸ Treat the child to prevent low blood sugar. ▸ Give first dose of paracetamol for high fever or pain. ▸ Refer URGENTLY to hospital.
Fever and/ or sore throat AND at least two of the following signs. • Tender, enlarged lymph nodes on neck. • Red, enlarged tonsils. • White exudate on throat.	STREPTOCOCCAL SORE THROAT	▸ Give benzathine penicillin or Amoxycillin. ▸ Give paracetamol for high fever or pain. ▸ Give safe, soothing remedy for sore throat. ▸ Advice mother when to return immediately ▸ Follow-up in 5 days if not improving
• Not enough signs to classify as throat abscess or streptococcal sore throat.	VIRAL SORE THROAT	▸ Give safe, soothing remedy for sore throat. ▸ Give paracetamol for high fever or pain. ▸ Advice mother when to return immediately ▸ Follow-up in 5 days, if not improving.
• No signs present (with or without fever)	NO THROAT PROBLESM	▸ No additional treatment.

Does the child have an ear problem?

IF YES, ASK:	LOOK AND FEEL:
• Is there severe ear pain? • Is there ear discharge? If yes, for how long?	• 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 an appropriate antibiotic. ▸ Treat the child to prevent low blood sugar. ▸ Give first dose of paracetamol for high fever or pain. ▸ Refer URGENTLY to hospital.
• Pus is seen draining from the ear and/or discharge is reported for less than 14 days, OR • Severe ear pain.	ACUTE EAR INFECTION	▸ Give an appropriate oral antibiotic for 5 days. ▸ Give paracetamol for high fever or pain. ▸ Dry the ear by wicking. ▸ Advise mother when to return immediately. ▸ Follow-up in 5 days.
• Discharge is reported for 14 or more days (pus is seen or not seen draining from the ear).	CHRONIC EAR INFECTION	▸ Dry the ear by wicking if pus seen draining from the ear ▸ Give appropriate topical quinolone ear drops for 2 weeks ▸ Give paracetamol for high fever or pain ▸ Refer to Ear Nose & Throat specialist. ▸ Follow-up in 5 days.
• No ear pain and No pus draining from the ear.	NO EAR INFECTION	▸ If any other ear problem present give appropriate treatment or refer to Ear Nose & Throat specialist.

Does the child have fever?

(by history or feels hot or temperature 37.5℃ *** or above)

A patient presenting with fever (continuous or intermittent) (temp=or >more then 37.5 ℃) or history of fever with in the last 3 days associated with rigors, with no features of other diseases and have one or more of the following: headache, nausea vomiting.

IF YES:
Malaria transmission in the area = Yes
Transmission season = Yes
In non or low endemic areas travel history within the last 15-days to an area where malaria transmission occurs = Yes
Yes_____ No_____
(if yes, use the treatment instructions for the relevant malaria risk area)

THEN ASK:

- Fever For how long?
- If more than 7 days, has fever been present every day?
- Has the child had measles within the last 3 months?

LOOK AND FEEL

- Look or feel for stiff neck.
- Look for runny nose.

Look for signs of MEASLES

- Generalized rash of measles 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

IF YES		
• Any general danger sign or • Stiff neck.	VERY SEVERE FEBRILE DISEASE	▸ Take the slide (thick and thin) immediately before giving IM artimether or quinine and send it with the patient. ▸ Give first dose of IM artimether or quinine for suspected severe or complicated malaria. ▸ Give first dose of an appropriate antibiotic. ▸ Treat the child to prevent low blood sugar. ▸ Give one dose of paracetamol in clinic for high fever (38.5C or°above). ▸ Refer URGENTLY to hospital.
• Fever (by history or feels hot or temperature 37.5℃*** or above).	SUSPECTED (CLINICAL) MALARIA****	▸ Confirm through RDTs or Microscopy if available. ▸ Treat the child with appropriate antimalarial. ▸ Give one dose of paracetamol in clinic for high fever (38.5 C or above). ▸ Advise mother when to return immediately. ▸ Follow-up in 3 days if fever persists. ▸ If fever is present every day for more than 7 days, refer for assessment.
IF NO		
• Any general danger sign or • Stiff neck.	VERY SEVERE FEBRILE DISEASE	▸ Take the slide (thick and thin) immediately before giving IM artimether or quinine and send it with the patient. ▸ Give first dose of IM artimether or quinine for suspected severe or complicated malaria. ▸ Give first dose of an appropriate antibiotic. ▸ Treat the child to prevent low blood sugar. ▸ Give one dose of paracetamol in clinic for high fever (38.5C or°above). ▸ Refer URGENTLY to hospital.
• Fever for more than two days. AND - 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 (38.5 C or above). ▸ Treat other cause of fever accordingly. ▸ Advise mother when to return immediately. ▸ Follow-up in 3 days if fever persists. ▸ If fever is present every day for more than 7 days, refer for assessment.
MEASLES NOW OR WITH IN THE LAST 3 MONTHS		
• Any general danger sign or • Clouding of cornea or • Deep or extensive mouth ulcers.	SEVERE COMPLICATED MEASLES*****	▸ Give first dose of an appropriate antibiotic. ▸ Give one dose of paracetamol in clinic for high fever (38.5 C or above). ▸ If clouding of the cornea or pus draining from the eye, apply chloramphenicol eye ointment. ▸ Treat the child to prevent low blood sugar. ▸ Give Vitamin A. Refer URGENTLY to hospital.
• Pus draining from the eye or • Mouth ulcers.	MEASLES WITH EYE AND / OR MOUTH COMPLICATIONS ****	▸ Give one dose of paracetamol in clinic for high fever (38.5 C or above). ▸ If pus draining from the eye, treat eye infection with chloramphenicol eye ointment. If mouth ulcers, treat with gentain violet ▸ Give Vitamin A. ▸ Advice mother when to return immediately. ▸ Follow-up in 2 days.
• Measles now or within the last 3 months.	MEASLES	▸ Give one dose of paracetamol in clinic for high fever (38.5 C or above). ▸ Give Vitamin A. ▸ Advice mother when to return immediately. ▸ Follow-up in 2 days if not improving or if measles now follow-up in 2 days

* ACT Artemesinine based Combination Therapy.
*** These temperatures are based on axillary temperature.
***** Other important complications of measles - pneumonia, stridor, diarrhoea, ear infection, and malnutrition - are classified in other tables.

** RDT is Rapid Diagnostic Test.
**** All Suspected (Clinical) Malaria cases may be confirmed through RDTs or Microscopy for determining wether it is a Vivax or Falciparum Malaria and then treat appropriately (Give Chloroquine for Vivax Malaria and ACT for Falciparum Malaria).

THEN CHECK FOR MALNUTRITION

LOOK AND FEEL:

- Look for visible severe wasting.
- Look and feel for oedema of both feet.
- Determine weight for age.

Classify NUTRITIONAL STATUS

• Visible severe wasting or • Oedema of both feet.	SEVERE MALNUTRITION	▸ Give Vitamin A. ▸ Treat the child to prevent low blood sugar ▸ Refer URGENTLY to hospital.
• Very low weight for age.	VERY LOW WEIGHT	▸ Assess the child's feeding and counsel the mother on feeding according to the FOOD box on the COUNSEL THE MOTHER chart. ▸ Advise mother when to return immediately. ▸ If feeding problem, follow-up in 5 days. ▸ Follow-up 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 years old, assess the child's feeding and counsel the mother on feeding according to the FOOD box on the COUNSEL THE MOTHER chart. ▸ Advise mother when to return immediately. ▸ If feeding problem, follow-up in 5 days.

THEN CHECK FOR ANAEMIA

LOOK

- Look for palmar pallor. Is it:

  Severe palmar pallor?
  Some palmar pallor?

Classify ANAEMIA

• Severe palmar pallor	SEVERE ANAEMIA	▸ Treat the child to prevent low blood sugar ▸ Refer URGENTLY to hospital.
• Some palmar pallor	ANAEMIA	▸ Assess the child's feeding and counsel the mother on feeding according to the FOOD box on the COUNSEL THE MOTHER chart. ▸ Give iron. ▸ Give oral antimalarial if high malaria risk. ▸ Deworm if child is two years or older & has not had a dose in previous six months, or has evidence or worm infestation ▸ Advise mother when to return immediately.
• No palmar pallor	NO ANAEMIA	▸ No additional treatment.

THEN CHECK CHILD'S IMMUNIZATION, VITAMIN A SUPPLEMENTATION, AND DEWORMING STATUS

IMMUNIZATION SCHEDULE:

AGE	VACCINE	
Birth	BCG	OPV-0
6 weeks	PENTAVLENT-1	OPV-1
10 weeks	PENTAVLENT-2	OPV-2
14 weeks	PENTAVLENT-3	OPV-3
9 months	MEASLES-1	
15 months of age	MEASLES-2	

VITAMIN A SUPPLEMENTATION STATUS:

- if child is 6 months or older and has not received a dose in the last 6 months, give a dose of vitamin A in the clinic

DEWORMING STATUS:

- if child is 1 year or older and has not received deworming dose in the last 6 months, give a dose of Mebendazole 500mg (single dose)

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.

TEACH THE MOTHER TO GIVE ORAL DRUGS AT HOME

Follow the instructions below for every oral drug to be given at home. Also follow the instructions listed with each drug's dosage table.

- Determine the appropriate drugs and dosage for the child's age or weight.
- Tell the mother the reason for giving the drug to the child.
- Demonstrate how to measure a dose.
- Watch the mother practice measuring a dose by herself.
- Ask the mother to give the first dose to her child.
- Explain carefully how to give the drug, then label and package the drug.
- If more than one drug will be given, collect, count and package each drug separately.
- Explain that all the oral drug tablets or syrups must be used to finish the course of treatment, even if the child gets better.
- Check the mother's understanding before she leaves the clinic.

▶ Give an Appropriate Oral Antibiotic

▶ FOR PNEUMONIA AND ACUTE EAR INFECTION:

FIRST-LINE ANTIBIOTIC: AMOXYCILLIN
SECOND-LINE ANTIBIOTIC: CEPHRADINE

	AMOXYCILLIN ▶ Give two times daily for 5 days		CEPHRADINE ▶ Give three times daily for 5 days	
AGE or WEIGHT	SYRUP 125 mg per 5 ml	SYRUP 250 mg per 5 ml	SYRUP 125 mg per 5 ml	SYRUP 250 mg per 5 ml
2 months up to 12 months (4 - <10 kg)	5 ml	2.5 ml	5 ml	2.5 ml
12 months up to 5 years (10 - 19 kg)	10 ml	5 ml	10 ml	5 ml

▶ FOR DYSENTERY AND CHOLERA:
Give recommended antibiotic for 5 days.
FIRTS-LINE ANTIBIOTIC CIPROFLOXCIN
SECOND-LINE DRUG METRONIDAZOLE (REFER TO FOLLOW UP BOX)

	CIPROFLOXCIN ▶ Give two times daily for 3 days		METRONIDAZOLE ▶ Give three times daily for 5 days	
AGE or WEIGHT	TABLET 500 mg	SYRUP 250 mg per 5 ml	TABLET 200 mg	SYRUP 200 mg per 5 ml
2 months up to 4 months (4 - <6 kg)				
4 months up to 12 months (6 - <10 kg)	1/5	1.5ml		
12 months up to 3 years (10 -< 14 kg)	1/3	3.5 ml	1/2	2.5 ml
3 years up to 5 years (14 - 19 kg)	1/2	5 ml	1	5 ml

TEACH THE MOTHER TO GIVE ORAL DRUGS AT HOME

Follow the instructions below for every oral drug to be given at home.
Also follow the instructions listed with each drug's dosage table.

Give an Oral Antimalarial

ANTIMALARIAL FOR FALCIPARUM MALARIA : ACT (Artemesinine based Combination Therapy) ,
ANTIMALARIAL FOR VIVAX MALARIA: CHLOROQUINE

- IF Artemesinine based Combination Therapy (ACT), which is Artesunate + SULFADOXINE - PYRIMETHAMINE:
  - Give the first dose as directly observed therapy in the clinic.
  - If the child vomits the drug with in 30 minutes of intake, repeat the dose.
- IF CHLOROQUINE:
  - Explain to the mother that she should watch her child carefully for 30 minutes after giving a dose of chloroquine. If the child vomits within 30 minutes, she should repeat the dose and return to the clinic for additional tablets.
  - Explain that itching is a possible side effect of the drug, but is not dangerous.

Dose in mg (No. of tablets)						
AGE	Artesunate (50 mg)			Sulfadoxine-Pyrimethamine (500/25 mg)		
	DAY 1	DAY 2	DAY 3	DAY 1	DAY 2	DAY 3
5 months up to 12 months	25 (!)	25 (!)	25 (!)	250 / 12.5 (!)		
1 year to 5 years	50 (1)	50 (1)	50 (1)	500/25 (1)		

CHLOROQUINE Give for 3 days									
AGE or WEIGHT	TABLET (150 mg base)			TABLET (100 mg base)			SYRUP (50 mg base per 5 ml)		
	DAY 1	DAY 2	DAY 3	DAY 1	DAY 2	DAY 3	DAY 1	DAY 2	DAY 3
2 months up to 12 months (4 - <10 kg)	1/2	1/2	1/2	1	1	1/2	7.5 ml	7.5 ml	5.0 ml
12 months up to 3 years (10 - <14 kg)	1	1	1/2	1 1/2	1 1/2	1/2	15.0 ml	15.0 ml	5.0 ml
3 years up to 5 years (14 - 19 kg)	1 1/2	1 1/2	1 1/2	2	2	1			

Give Paracetamol for High Fever (> 38.5C) or Sore Throat or Ear Pain

- Give paracetamol every 6 hours until high fever or sore throat or ear pain is relieved.

	PARACETAMOL	
AGE or WEIGHT	TABLET (500 mg)	SYRUP (120 mg per 5 ml)
2 months up to 6 months (4- <7 kg)		2.5 ml
6 months up to 3 years (7- <14 kg)	1/4	5 ml
3 years up to 5 years (14 - 19 kg)	1/2	10 ml

Give Zinc Suspension

- Along with increased fluids and continued feeding, all children with diarrhoea should be given Zinc Suspension for 10 days

AGE	Zinc Sulphate (20mg / 5ml)
Up to 6 months	2.5ml
6 months up to 5 years	5ml

Give Multivitamin / Mineral Supplement

- For persistent diarrhoea, give 5 ml (one tea spoon) once daily of multivitamin minerals for 2 weeks each 5 ml contains

Vitamin-A:	8000 IU (800 micrograms)
Folate:	100 micrograms
Magnesium:	150 mg
Iron:	20 mg
Zinc:	20 mg
Copper:	2 mg

Give Vitamin A

- Give two doses.
  - Give first dose in clinic.
  - Give mother one dose to give at home the next day.

AGE	VITAMIN A CAPSULES	
	200 000 IU	100 000 IU
Up to 6 months		50 000 IU
6 months up to 12 months	1/2 capsule	1 capsule
12 months up to 5 years	1 capsule	2 capsules

Give Iron

- Give one dose daily for 14 days.

AGE or WEIGHT	IRON/FOLATE TABLET Ferrous sulfate 200 mg + 250 mcg Folate (60 mg elemental iron)	IRON SYRUP Ferrous Fumarate 100 mg per 5 ml (20 mg elemental iron per ml)
2 months up to 4 months (4 - <6 kg)		1.00 ml
4 months up to 12 months (6 - <10 kg)		1.25 ml
12 months up to 3 years (10 - <14 kg)	1/2	2.00 ml
3 years up to 5 years (14 - 19 kg)	1/2	2.5 ml

Give Mebendazole

- FOR TREATMENT OF ANEMIA AND IF STOOLS POSITIVE FOR WORMS OR:
  If the child is 1 year or older and has not had a dose in the previous 6 months or
  If child is less then 12 months of age and has evidence of worm infestation, such cases should be referred and managed on case by case basis.

GIVE MEBENDAZOLE AS A SINGLE DOSE IN CLINIC.

AGE or WEIGHT	MEBENDAZOLE (500 mg)	ALBENDAZOLE (200 mg)
Above 12 months (10 - <19 kg)	1	1

TEACH THE MOTHER TO TREAT LOCAL INFECTIONS AT HOME

- Explain to the mother what the treatment is and why it should be given.
- Describe the treatment steps listed in the appropriate box.
- Watch the mother as she doses the first treatment in the clinic (except remedy for cough or sore throat).
- Tell her how often to do the treatment at home.
- If needed for treatment at home, give mother the tube of chloramphenicol ointment or a small bottle of gentian violet.
- Check the mother's understanding before she leaves the clinic.

Treat Eye Infection with Chloramphenicol Eye Ointment

- Clean both eyes 3 times daily.
  - Wash hands
  - Ask child to close the eye.
  - Use clean cloth and water to gently wipe away pus.
- Then apply Chloramphenicol eye ointment in both eyes 3 times daily.
  - Ask the child to look up.
  - Squirt a small amount of ointment on the inside of the lower lid.
  - Wash hands again.

Treat until redness is gone.
Do not use other eye ointments or drops, or put anything else in the eye.
Return to clinic immediately, if infection becomes worse.

Dry the Ear by Wicking

- Dry the ear at least 3 times daily.
  - Roll clean absorbent cloth or soft, strong tissue paper into a wick.
  - Place the wick in the child's ear.
  - Remove the wick when wet.
  - Replace the wick with a clean one and repeat these steps until the ear is dry.

Treat Mouth Ulcers with Gentian Violet

- Treat the mouth ulcers twice daily.
  - Wash hands.
  - Wash the child's mouth with clean soft cloth wrapped around the finger and wet with salt water.
  - Paint the mouth with half-strength gentian violet (0.25 %).
  - Wash hands again.

Soothe the Throat, Relieve the Cough with a Safe Remedy

- Safe remedies to recommend:
  Breast milk for exclusively breastfed infant.
  Honey with water : one tea spoon honey in half cup of luke warm water.
  Green tea, Soup etc.
- Harmful remedies to discourage:
  Cough syrup containing codeine, antihistamines, alcohol, atropine and expectorants.
  Oral and nasal decongestants
  Do not massage or bind the chest
  Do not give opium, alcohol etc.

GIVE THESE TREATMENTS IN CLINIC ONLY

- Explain to the mother why the drug is given.
- Determine the dose appropriate for the child's weight (or age).
- Use a sterile needle and sterile syringe. Measure the dose accurately.
- Give the drug as an Intramuscular injection.
- If child cannot be referred, follow the instructions provided.

Treat the convulsing Child with Diazepam

Manage the Airway:

Turn the child on the side to avoid aspiration

- Do not insert any thing in the mouth
- If lips and tongue are blue, open the mouth and make sure the airway is clear.
- If necessary remove secretions from the throat through a catheter inserted through the nose

Give Diazepam Rectally:

- Draw up the dose of diazepam into a small syringe
- Add 2-3 ml water Then remove the needle
- Attach a piece of nasogastric tube to the syringe if possible.
- Insert 4 to 5 cm of the tube or tip of the syringe into the rectum and inject the diazepam solution.
- Hold buttocks together for a few minutes

AGE or WEIGHT	Diazepam Given Rectally (10 mg= 2ml) Dose 0.5mg/kg
Less then 7 days (If weight < 2.5 kg)	0.25 ml
Less then 7 days (If weight > 2.5 kg)	0.5 ml
7 days up to 4 months (3 - < 6 kg)	0.5 ml
4 months up to 12 months (6- < 10 kg)	1 ml
12 months up to 3 years (10- < 14 kg)	1.25 ml
3 years up to 5 years (14 - 19 kg)	1.5 ml

If High Fever, Lower the Fever:

- Sponge the child with tap water
- Give antipyretic

Treat the child to prevent low blood suger.

Give Intramuscular Antibiotics

FOR CHILDREN BEING REFERRED URGENTLY:

- Give first dose of Intramuscular Ampicillin and Gentamicin and refer child urgently to hospital.

IF REFERRAL IS NOT POSSIBLE:

- Repeat the Ampicillin and Gentamicin or Chloramphenicol injection in divided doses every 12 hours for 7 and 5 days respectively.
- Then change to an appropriate oral antibiotic to complete 10 days of treatment.

AGE or WEIGHT	AMPICILLIN Dose: 50 mg per kg Add 3 ml sterile water to vial containing 500 mg = 3.5ml at 143 mg/ml	GENTAMICIN Dose: 7.5 mg per kg 1 vial = 40mg/2ml	CHLORAMPHENICOL Dose: 40 mg per kg Add 5.0 ml sterile water to vial containing 1000 mg = 5.6 ml at 180 mg/ml
2 months up to 4 months (4 - < 6 kg)	1.5 ml = 214 mg	1.5 ml = 30 mg	1.0 ml = 180 mg
4 months up to 9 months (6 - < 8 kg)	2 ml = 286 mg	2.5 ml = 50 mg	1.5 ml = 270 mg
9 months up to 12 months (8 - < 10 kg)	3 ml = 429 mg	3 ml = 60 mg	2.0 ml = 360 mg
12 months up to 3 years (10 - < 14 kg)	3.5 ml = 500 mg	4 ml = 80 mg	2.5 ml = 450 mg
3 years up to 5 years (14 - 19 kg)	5 ml = 715 mg	5 ml = 100 mg	3.5 ml = 630 mg

Give Quinine HCL/ARTEMETHER INJ. for Severe Malaria

FOR CHILDREN BEING REFERRED WITH VERY SEVERE FEBRILE DISEASE:

- Check which quinine*/artemether formulation is available in your clinic.
- Give first dose of intramuscular quinine/artemether and refer child urgently to hospital.
- If low risk of malaria, do not give quinine/artemether to a child less than 4 months of age.

IF REFERRAL IS NOT POSSIBLE:

- Give first dose of intramuscular quinine/artemether.
- The child should remain lying down for one hour.
- Repeat the quinine injection at 4 and 8 hours later, and then every 12 hours until the child is able to take and oral antimalarial. Do not continue quinine injections for more than 1 week.
- In case of intramuscular artemether injection give 1.6mg/kg body weight every day for 7 days.
- If low risk of malaria, do not give quinine to a child less than 4 months of age.

AGE or WEIGHT	INTRAMUSCULAR QUININE HCL (in 2 ml ampoules) AMPOULES (300 mg/ml)			INTRAMUSCULAR ARTEMETHER (1ml ampoules) AMPOULES (40 & 80 mg/ml)	
	Draw up this dose of undiluted quinine in syringe	Add this amount of normal saline	Total diluted solution to administer (60 mg/ml)	40 mg/ml	80 mg/ml
2 months up to 4 months (4 - < 6 kg)	0.2 ml	0.8 ml	1.0 ml	0.2 ml	0.1 ml
4 months up to 12 months (6 - < 10 kg)	0.3 ml	1.2 ml	1.5 ml	0.4 ml	0.2 ml
12 months up to 2 years (10 - < 12 kg)	0.4 ml	1.6 ml	2.0 ml	0.5 ml	0.25 ml
2 years up to 3 years (12 - < 14 kg)	0.5 ml	2.0 ml	2.5 ml	0.5 ml	0.25 ml
3 years up to 5 years (14 - 19 kg)	0.6 ml	2.4 ml	3.0 ml	0.5 ml	0.3 ml

* In Pakistan Quinine HCL is available in ampoules of 300mg / ml.

Treat Wheezing:

- CHILDREN WITH WHEEZING AND GENERAL DANGER SIGN OR STRIDOR
  - Give one dose of rapid acting bronchodilator and REFER immediately
- CHILDREN WITH WHEEZING AND CHEST INDRAWING AND/OR FAST BREATHING
  - Give a rapid acting bronchodilator and reassess the child 30 minutes later

IF:		THEN:
CHEST INDRAWING OR FAST BREATHING PERSISTS	→	Treat for PNEUMONIA Give oral salbutamol for 5 days.
NO FAST BREATHING	→	Treat for NO PNEUMONIA COUGH OR COLD Give oral salbutamol for 5 dats,

CHILDREN WITH WHEEZING AND NO DANGER SIGNS, NO STRIDOR,NO CHEST INDRAWING NO FAST BREATHING

- Treat for no pneumonia: cough or cold
- Give oral salbutamol for 5 days

RAPID ACTING BRONCHODILATOR

AGE or WEIGHT	Nebulized Salbutamol (5mg/ml)	Metered dose inhaler with spacer device (100mcg/dose)
2 months up to 6 months (4- <7 kg)	0.25 ml (plus 2.0 ml sterile water)	1 puff
6 months up to 12 months (7- <10 kg)	0.5 ml (plus 2.0 ml sterile water)	1 to 2 puffs
12 months up to 5 years (10- 19 kg)	0.5 ml (plus 2.0 ml sterile water)	2 to 3 puffs

ORAL SALBUTAMOL

- Three times daily for five days

AGE or WEIGHT	TABLETS (2 mg)	SYRUP (2 mg/5ml)
2 months up to 6 months (4- <7 kg)	1/4	1.25 ml
6 months up to 12 months (7- <10 kg)	1/2	2.5 ml
12 months up to 5 years (10- 19 kg)	1	5 ml

Treat the Child to Prevent Low Blood Sugar

- If the child is able to breastfeed:

  Ask the mother to breastfeed the child.

- If the child is not able to breastfeed but is able to swallow:

  Give expressed breast milk or a breast milk substitute.
  If neither of these is available, give sugar water.
  Give 30-50 ml of milk or sugar water before departure.

  To make sugar water: Dissolve 4 level teaspoons of sugar (20 grams) in a 200-ml cup of clean water.

- If the child is not able to swallow:

  Give 50 ml of milk or sugar water by nasogastric tube.

Give An Antibiotic for Streptococcal Sore Throat

- Give a single dose of Intramuscular Benzathine Penicillin

Age	Benzathine Penicillin (600,000 units add 5 ml sterile water)
< 5 years	600,000 unit

OR

- Give Amoxycillin for 10 days (see "Appropriate Oral Antibiotic" box for dose of Amoxycillin)

GIVE EXTRA FLUID FOR DIARRHOEA AND CONTINUE FEEDING

(See FOOD advice on COUNSEL THE MOTHER chart)

Plan A: Treat Diarrhoea at Home

Counsel the mother on the 3 Rules of Home Treatment:
Give Extra Fluid, Continue Feeding, When to Return

1. GIVE EXTRA FLUID (as much as the child will take)

▸ TELL THE MOTHER:
- Breastfeed frequently and for longer time at each feed.
- If the child is exclusively breastfed, give ORS or clean water in addition to breast milk
- If the child is not exclusively breastfed, give one or more of the following: ORS solution, food-based fluids (such as soup, rice water, and yoghurt drinks), or clean water.

It is especially important to give ORS at home when:
- the child has been treated with Plan B or Plan C during this visit.
- the child cannot return to a clinic if the diarrhoea gets worse.

▸ TEACH THE MOTHER HOW TO MIX AND GIVE ORS, GIVE THE MOTHER 2 PACKETS OF ORS (1000 ml) TO USE AT HOME.

▸ SHOW THE MOTHER HOW MUCH FLUID TO GIVE IN ADDITION TO THE USUAL FLUID INTAKE:

Up to 2 years	50 to 100 ml after each loose stool
2 years or more	100 to 200 ml after each loose stool

Tell the mother to:
- Give frequent small sips from a cup.
- If the child vomits, wait 10 minutes. Then continue, but more slowly.
- Continue giving extra fluid until the diarrhoea stops.

▸ GIVE ZINC SUSPENSION
- Along with increased fluids and continued feeding, all children with diarrhoea should be given Zinc Suspension for 10 days

AGE	Zinc Suspension (20mg / 5ml)
Up to 6 months	2.5ml
6 months up to 5 years	5ml

2. CONTINUE FEEDING
3. WHEN TO RETURN

} See COUNSEL THE MOTHER chart

Plan B: Treat Some Dehydration with ORS

Give in clinic recommended amount of ORS over 4-hour period

▸ DETERMINE AMOUNT OF ORS TO GIVE DURING FIRST 4 HOURS.

AGE*	Up to 4 months	4 months up to 12 months	12 months up to 2 years	2 yearsup to 5 years
WEIGHT	< 6 kg	6 - < 10 kg	10 - < 12 kg	12 - 19 kg
In ml	200 - 400	400 - 700	700 - 900	900 - 1400

* Use the child's age only when you do not know the weight. The approximate amount of ORS required (in ml) can also be caluclated by multiplying the child's weight (in kg) times 75.

- If the child wants more ORS than shown, give more.
- For infants under 6 months who are not breastfed, also give 100-200 ml clean water during this period.

▸ SHOW THE MOTHER HOW TO GIVE ORS SOLUTION.
- Give frequent small sips from a cup.
- If the child vomits, wait 10 minutes. Then continue, but more slowly.
- Continue breastfeeding whenever the child wants.

▸ AFTER 4 HOURS:
- Reassess the child and classify the child for dehydration.
- Select the appropriate plan to continue treatment.
- Begin feeding the child in clinic.

▸ IF THE MOTHER MUST LEAVE BEFORE COMPLETING TREATMENT:
- Show her how to prepare ORS solution at home.
- Show her how much ORS to give to finish 4-hour treatment at home.
- Give her enough ORS packets to complete rehydration. Also give her 2 packets as recommended in Plan A.
- Explain the 3 Rules of Home Treatment:

▸ GIVE ZINC SUSPENSION
- Along with increased fluids and continued feeding, all children with diarrhoea should be given Zinc Suspension for 10 days

AGE	Zinc Suspension (20mg / 5ml)
Up to 6 months	2.5ml
6 months up to 5 years	5ml

1. GIVE EXTRA FLUID
2. CONTINUE FEEDING
3. WHEN TO RETURN

} See Plan A for recommended fluids and See COUNSEL THE MOTHER chart

GIVE EXTRA FLUID FOR DIARRHOEA AND CONTINUE FEEDING

(See FOOD advice on COUNSEL THE MOTHER chart)

Plan C: Treat Severe Dehydration Quickly

FOLLOW THE ARROWS. IF ANSWER IS "YES", GO ACROSS. IF "NO", GO DOWN.

START HERE

Can you give intravenous (IV) fluid immediately? — YES →

Start IV fluid immediately. If the child can drink, give ORS by mouth while the drip is set up. Give 100 ml/kg Ringer's Lactate Solution (or, if not available, normal saline), divided as follows:

AGE	First give 30 ml/kg in:	Then give 70 ml/kg in:
Infants (under 12 months)	1 hour*	5 hours
Children (12 months up to 5 years)	30 minutes*	2 1/2 hours

* Repeat once if radial pulse is still very weak or not detectable.

- Reassess the child every 1- 2 hours. If hydration status is not improving, give the IV drip more rapidly.
- Also give ORS (about 5 ml/kg/hour) as soon as the child can drink: usually after 3-4 hours (infants) or 1-2 hours (children).
- Reassess an infant after 6 hours and a child after 3 hours. Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment.

NO ↓

Is IV treatment available nearby (within 30 minutes)? — YES →

- Refer URGENTLY to hospital for IV treatment.
- If the child can drink, provide the mother with ORS solution and show her how to give frequent sips during the trip.

NO ↓

Are you trained to use a naso-gastric (NG) tube for rehydration? — YES →

- Start rehydration by tube (or mouth) with ORS solution: give 20 ml/kg/hour for 6 hours (total of 120 ml/kg).
- Reassess the child every 1-2 hours:
  - If there is repeated vomiting or increasing abdominal distension, give the fluid move slowly.
  - If hydration status is not improving after 3 hours, send the child for IV therapy.
- After 6 hours, reassess the child. Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment.

NO ↓

Can the child drink? — YES →

NOTE:

- If possible, observe the child at least 6 hours after rehydration to be sure the mother can maintain hydration giving the child ORS solution by mouth.

NO ↓

Refer URGENTLY to hospital for IV or NG treatment

▸ GIVE ZINC SUSPENSION

- Along with increased fluids and continued feeding, all children with diarrhoea should be given Zinc Suspension for 10 days

AGE	Zinc Suspension (20mg / 5ml)
Up to 6 months	2.5ml
6 months up to 5 years	5ml

GIVE VITAMIN-A SUPPLEMENTATION, AS NEEDED

GIVE MEBENDAZOLE, AS NEEDED

IMMUNIZE EVERY SICK CHILD, AS NEEDED

GIVE FOLLOW-UP CARE

- Care for the child who returns for follow-up using all the boxes that match the child's previous classifications.
- If the child has any new problem, assess, classify and treat the new problem as on the ASSESS AND CLASSIFY chart.

PNEUMONIA

After 3 days:

Check the child for general danger signs.
Assess the child for cough or difficult breathing. } See ASSESS & CLASSIFY chart.
Ask:
- Is the child breathing slower?
- Is there less fever?
- Is the child eating better?
- Is the child wheezing?

Treatment:

- If child has chest indrawing or has fast breathing and with or without wheeze, give a dose of intramuscular Ampicillin and Gentamicin. If wheezing also give three cycles of rapidly acting bronchodilator.
- If breathing rate, fever and eating are the same, with or without wheeze, change to the second-line antibiotic and advise the mother to return in 3 days. If wheezing now or had wheezing on first visit give/continue oral salbutamol. (If this child had measles within the last 3 months, refer).
- If breathing rate slower, less fever, or eating better, with or without wheezing, complete the 5 days of antibiotic. If wheezing now or had wheezing on first visit give/continue oral salbutamol for five days.
- If child had no wheeze on the first visit but has wheeze now and had no general danger signs or stridor, or chest indrawing or fast breathing, treat as in "No Pneumonia: Cough or Cold - Wheeze" box.

NO PNEUMONIA: COUGH OR COLD- WHEEZE

After 3 days:

Check the child for general danger signs.
Assess the child for cough or difficult breathing. } See ASSESS & CLASSIFY chart.

Treatment:

- If any general danger sign or stridor -, treat as VERY SEVERE DISEASE, give a dose of pre-referral intramuscular antibiotics. If wheezing now, give one dose of rapid acting bronchodilator and refer URGENTLY to hospital.
- If fast breathing or chest indrawing, with wheeze also give a dose of rapid acting bronchodilator and reassess according to "treat wheezing" box.
- If child is wheezing but has no general danger signs, no stridor, no chest indrawing or no fast breathing
  - if this is the first episode of wheezing or if the child had previous episodes but has not been referred, give salbutamol and refer for assessment.
  - If the child has already been referred for a previous episode of wheezing advise the mother to continue with treatment prescribed by the referral hospital. Advise the mother to return if the child's breathing becomes more difficult. If this child returns because condition has worsened, refer URGENTLY to hospital for further treatment.
- If had wheeze and now no wheezing- complete 5 days of oral salbutamol.

DYSENTERY

After 2 days:

Assess the child for diarrhoea. > See ASSESS & CLASSIFY chart.
Ask:
- Are there fewer stools?
- Is there less blood in the stool?
- Is there less fever?
- Is there less abdominal pain?
- Is the child eating better?

Treatment:

- If the child is dehydrated, treat dehydration.
- If number of stools, amount of blood in stools, fever, abdominal pain, or eating is worse-refer to hospital.
- If number of stools, amount of blood in stools, fever, abdominal pain, or eating is the same: Add metronidazole. Give for 5 days. Advise the mother to return in 2 days.
  Exceptions - if the child:
  - is less than 12 months old, or
  - was dehydrated on the first visit, or
  - had measles within the last 3 months

  } Refer to hospital.
- If fewer stools, less blood in the stools, less fever, less abdominal pain, and eating better, continue giving the same antibiotic until finished.

GIVE FOLLOW-UP CARE

- Care for the child who returns for follow-up using all the boxes that match the child's previous classifications.
- If the child has any new problem, assess, classify and treat the new problem as on the ASSESS AND CLASSIFY chart.

PERSISTENT DIARRHOEA

After 5 days:

Ask:
- Has the diarrhoea stopped?
- How many loose stools is the child having per day?

Treatment:
- If the diarrhoea has not stopped (child is still having 3 or more loose stools per day), do a full reassessment of the child. Give any treatment needed. Then refer to hospital.
- If the diarrhoea has stopped (child having less than 3 loose stools per day), tell the mother to follow the usual feeding recommendations for the child's age.
- Tell the mother to continue giving multivitamin minerals supplement for two weeks.

EAR INFECTION

After 5 days:
Reassess for ear problem. > See ASSESS & CLASSIFY chart.
Measure the child's temperature.

Treatment:
- If there is tender swelling behind the ear or high fever (38.5C or above), refer URGENTLY to hospital.
- Acute ear infection: if ear pain or discharge persists, treat for 5 more days with the same antibiotic. Continue wicking to dry the ear. Follow-up in 5 days.
- Chronic ear infection: Check that the mother is wicking the ear correctly, encourage her to continue. Check for compliance of treatment prescribed by the Ear Nose & Throat specialist
- If no ear pain or discharge, praise the mother for her careful treatment. If she has not yet finished the 5 days of antibiotic, tell her to use all of it before stopping.

MALARIA (Low or High Malaria Endemic Area)

If fever persists after 3 days, or returns immediately if the same symptoms reappear within 28 days:
Do a full reassessment of the child. Assess for other causes of fever. > See ASSESS & CLASSIFY chart.

Treatment:
- If the child has any general danger sign or stiff neck, treat as VERY SEVERE FEBRILE DISEASE.
- If the child has any cause of fever other than malaria, provide treatment.
- If malaria is the only apparent cause of fever:
  - Treat with the second-line oral antimalarial. (If no second-line antimalarial is available, refer to hospital.) Advise the mother to return again in 2 days if the fever persists
  - If fever has been present for 7 days, refer for assessment.

FEVER-MALARIA UNLIKELY (Malaria non endemic Area)

If fever persists after 2 days:
Do a full reassessment of the child. Assess for other causes of fever. > See ASSESS & CLASSIFY chart.

Treatment:
- If the child has any general danger sign or stiff neck, treat as VERY SEVERE FEBRILE DISEASE.
- If the child has any cause of fever other than malaria, provide treatment.
- If malaria is the only apparent cause of fever:
  - Treat with the first-line oral antimalarial. Advise the mother to return again in 2 days if the fever persists.
  - If fever has been present for 7 days, refer for assessment.

GIVE FOLLOW-UP CARE

- Care for the child who returns for follow-up using all the boxes that match the child's previous classifications.
- If the child has any new problem, assess, classify and treat the new problem as on the ASSESS AND CLASSIFY chart.

MEASLES WITH EYE OR MOUTH COMPLICATIONS

After 2 days:

Look for red eyes and pus draining from the eyes.
Look at mouth ulcers.
Smell the mouth.

Treatment for Eye Infection:

- If pus is draining from the eye, ask the mother to describe how she has treated the eye infection.
  If treatment has been correct, refer to hospital. If treatment has not been correct, teach mother correct treatment.
- If the pus is gone but redness remains, continue the treatment.
- If no pus or redness, stop the treatment.

Treatment for Mouth Ulcers:

- If mouth ulcers are worse, or there is a very foul smell from the mouth, refer to hospital.
- If mouth ulcers are the same or better, continue using half-strength gentian violet (0.25 %) for a total of 5 days.

MEASLES

After 2 days:

Do a full reassessment of the child. > See ASSESS & CLASSIFY Chart.

Treatment:

- If general danger sign or clouding of the cornea or deep extensive mouth ulcers or pneumonia, treat as SEVERE COMPLICATED MEASLES.
- If pus draining from the eye or mouth ulcers, treat as MEASLES WITH EYE OR MOUTH COMPLICATIONS.
- If none of the above signs, advise the mother when to return immediately.
- Follow up in two days if not improving.
  If the child received already the dose of vitamin A in the previous visit, do not repeat.

FEEDING PROBLEM

After 5 days:
Reassess feeding. > See questions at the top of the COUNSEL Chart
Ask about any feeding problems found on the initial visit.

- Counsel the mother about any new or continuing feeding problems. If you counsel the mother to make significant changes in feeding, ask her to bring the child back again.
- If the child is very low weight for age, ask the mother to return 30 days after the initial visit to measure the child's weight gain.

ANAEMIA

After 14 days:

- Give iron. Advise mother to return in 14 days for more iron.
- Continue giving iron every 14 days for 2 months.
- If the child has palmar pallor after 2 months, refer for assessment.

VERY LOW WEIGHT

After 30 days:

Weigh the child and determine if the child is still very low weight for age.
Reassess feeding. > See questions at the top of the COUNSEL chart

Treatment:

- If the child is no longer very low weight for age, praise the mother and encourage her to continue.
- If the child is still very low weight for age, counsel the mother about any feeding problem found. Ask the mother to return again in one mouth. Continue to see the child monthly until the child is feeding well and gaining weight regularly or is no longer very low weight for age.

  Exception:
  If you do not think that feeding will improve, or if the child has lost weight, refer the child.

IF ANY MORE FOLLOW-UP VISITS ARE NEEDED BASED ON THE INITIAL VISIT OR THIS VISIT, ADVISE THE MOTHER FOR THE NEXT FOLLOW-UP VISIT

ALSO, ADVISE THE MOTHER WHEN TO RETURN IMMEDIATELY.
(SEE COUNSEL CHART.)

FOOD

Assess the Child's Feeding

Ask questions about the child's usual feeding and feeding during this illness, Compare the mother's answers to the Feeding Recommendations for the child's age in the box below.

ASK

- Do you breastfeed your child?
  - How many times during the day?
  - Do you also breastfeed during the night?
- Does the child take any other food or fluids?
  - What food or fluids?
  - How many times per day?
  - What do you use to feed the child?
  - If very low weight for age: How large are servings?
- During this illness, has the child's feeding changed? If yes, how?

Feeding Recommendations During Sickness and Health

Up to 6 Months of Age

- Breast feed as often as the child wants, day and night, at least 8 times in 24 hours.
- Breast feed at least for 10 minutes on each breast every time
- Do not give other foods water.
- Do not use bottles or pacifiers

6 Months up to 12 Months

Breastfeed as often as the child wants.

Give adequate servings of:
Khichri*, Rice (Bhatt)* with seasonal vegetables (Carrot, Spinach, Potatoes etc.), or Minced Meat. Rice Kheer, Suji ka Halwa or Kheer*, Dalia*, Vermicelli's*, Choori*, Mashed Potato or vegetables*, Egg, Banana, Seasonal Fruit and any foods listed for 4 to 6 month child.
(upto 9 months food should be mashed)

- 3 times per day if breastfed;
- 5 times per day if not breastfed.
- Each serving should be equivalent to 1/2-3/4 or a cup.

12 Months up to 2 Years

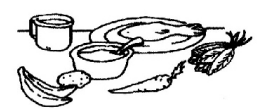
- Breastfeed as often as the child wants.
- Give adequate servings of: Roti, Parattha, Khichri or Rice, Curry, Minced Meat, Chicken, Egg, Seasonal Vegetables, Choori, Vermicelli's, and/or any foods listed for 6-12 months child
- Give food at least 3 times per day

AND

- Give also snacks 2 times per day between meals such as seasonal fruit (Banana, Apple, Mango, Orange etc.) Biscuit, Rusk, Chips, Pakora or Samosa, Lassi, Yoghurt, Bread with Egg, Halwa etc.

OR

Family foods 5 times per day.



2 Years and Older

- Give family foods at 3 meals each day. Also, twice daily, give nutritious food between meals, such as:
- Seasonal fruit (Banana, Apple, Mango, Orange etc.) Biscuit, Rusk, Chips, Pakora, Samosa, Lassi, Yoghurt, Bread with Eggs, Halwa etc.

Wash your hands before preparing the child's food and use clean cooking utensils.

* A good daily diet should be adequate in quantity and include an energy-rich food (for example, thick cereal with added oil / Ghee / Butter); meat, fish, eggs, or pulses; and fruits and vegetables.

Feeding Recommendations For a Child Who Has PERSISTENT DIARRHOEA

- If still breastfeeding, give more frequent, longer breastfeeds, day and night.
- If taking other milk:
  - replace with increased breastfeeding OR
  - replace with fermented milk products, such as yoghurt OR
  - replace half the milk with nutrient-rich semisolid food.
- For other foods, follow feeding recommendations for the child's age.

Counsel the Mother About Feeding Problems

If the child is not being fed as described in the above recommendations, counsel the mother accordingly. In addition:

- If the mother reports difficulty with breastfeeding, assess breastfeeding. (See YOUNG INFANT chart.)
  As needed, show the mother correct positioning and attachment for breastfeeding.
- If the child is less than 6 months old and is taking other milk or foods OR:
- If the mother thinks she does not have enough milk:

  - Build mother's confidence that she can produce all the breast milk that the child needs.
  - Suggest giving more frequent, longer breastfeeds day or night, and gradually reducing other milk or foods.

  If other milk needs to be continued, counsel the mother to:

  - Breastfeed as much as possible, including at night.
  - Make sure that other milk is a locally appropriate breast milk substitute.
  - Make sure other milk is correctly and hygienically prepared and given in adequate amounts.
  - Prepare only an amount of milk which child can consume within one hour. If their is some left over milk, discard.

- If the mother is using a bottle to feed the child:

  - Recommend substituting a cup for bottle.
  - Show the mother how to feed the child with a cup.

- If the child is being fed too small amounts
  - Recommend increasing the frequency and portion size for each meal day by day. until recommended portion size achieved.
  - Recommend that the mother encourages the child to eat more.
- If the child is not being fed actively, counsel the mother to:

  - Sit with the child and encourage eating.
  - Give the child an adequate serving in a separate plate or bowl.
  - Observe what the child likes and consider these for preparing the food.(consider energy rich, high density food).

- If the child is not feeding well during illness, counsel the mother to:

  - Breastfeed more frequently and for longer if possible.
  - Use soft, varied, appetizing, favorite foods to encourage the child to eat as much as possible, and offer frequent small feedings.
  - Add oil/ghee/butter to prepare foods. Also give green leafy and yellow vegetables and fruits to the child.
  - Clear a blocked nose if it interferes with feeding.
  - Expect that appetite will improve as child gets better.
  - Give expressed breast milk if necessary.

- Follow-up any feeding problem in 5 days.
- Advise mother not to give her child, harmful, contaminated and unhygienicaly prepared junk foods from vendors e.g. kulfi, ice cream, sodas/ sherbet/drinks etc., paparrs, pakoras, samosas, nimkos etc.

FLUID AND FOOD

▶ Advise the Mother to Increase Fluid and Continue Feeding During Illness

FOR ANY SICK CHILD:

- ▶ Breastfeed more frequently and for longer at each feed.
- ▶ Increase fluid. For example, give soup, rice water, yoghurt drinks or clean water.
- ▶ Give small frequent meals of energy rich food.

FOR CHILD WITH DIARRHOEA:

- ▶ Giving extra fluid can be lifesaving. Give fluid according to Plan A or Plan B on TREAT THE CHILD chart.

WHEN TO RETURN

▶ Advise the Mother When to Return to Health Worker

FOLLOW-UP VISIT
Advise the mother to come for follow-up at the earliest time listed for the child's problems.

If the child has:	Return for follow-up in:
PNEUMONIA NO PNEUMONIA WITH WHEEZE if no improvement MALARIA, if fever persists FEVER-MALARIA UNLIKELY, if fever persists	3 days
DYSENTERY MEASLES WITH EYE OR MOUTH COMPLICATIONS MEASLES (if measles now)	2 days
PERSISTENT DIARRHOEA ACUTE EAR INFECTION CHRONIC EAR INFECTION FEEDING PROBLEM ANY OTHER ILLNESS, if not improving	5 days
ANAEMIA	14 days
VERY LOW WEIGHT FOR AGE	30 days

NEXT WELL-CHILD VISIT
Advise mother when to return for next immunization according to immunization schedule.

WHEN TO RETURN IMMEDIATELY

Advise mother to return immediately if the child has any of these signs:	
Any sick child	• Not able to drink or breastfeed • Becomes sicker • Develops a fever
If child has NO PNEUMONIA: COUGH OR COLD, also return if:	• Chest indrawing • Fast breathing • Difficult breathing
If child has Diarrhoea, also return if:	• Blood in stool • Drinking poorly

Counsel the Mother About Her Own Health

- If the mother is sick, provide care for her, or refer her for help.

  If she has a breast problem (such as engorgement, sore nipples, breast infection), provide care for her or refer for help.

  Advise her to eat well to keep up her own strength and health.

  Check the mother's immunization status and give her tetanus toxoid if needed.

  Make sure she has access to:

  - Family planning
  - Counseling on STD and AIDS prevention

ASSESS, CLASSIFY AND TREAT THE SICK YOUNG INFANT AGE LESS THEN 2 MONTHS

ASSESS | CLASSIFY | IDENTIFY TREATMENT

ASSESS

ASK THE MOTHER WHAT THE YOUNG INFANT'S PROBLEMS ARE

- Determine if this is an initial or follow-up visit for this problem.
  - if follow-up visit, use the follow-up instructions on the FOLLOW-UP chart.
  - if initial visit, assess the young infant as follows:

CLASSIFY

USE ALL BOXES THAT MATCH INFANT'S SYMPTOMS AND PROBLEMS TO CLASSIFY THE ILLNESS.

CHECK FOR POSSIBLE INFECTION

ASK:

- Has the infant had convulsions (fits)?
- Is the infant having difficulty in feeding?

LOOK, LISTEN, FEEL:

- Count the breaths in one minute. Repeat the count if elevated.
- Look for severe chest indrawing.
- Look and listen for grunting.

} YOUNG INFANT MUST BE CALM

- Measure axillary temperature.
- Look at the umbilicus. Is it red or draining pus?
- Look for skin pustules.
- Look at the young infant's movements.
  Does the infant move only when stimulated?
  Does the infant not move even when stimulated?

Classify ALL YOUNG INFANTS

SIGNS	CLASSIFY AS	TREATMENT (Urgent pre-referral treatments are in bold)
Any one of the following signs • Convulsions OR • Not feeding well OR • Fast breathing (60 breaths per minute or more) OR • Severe chest indrawing OR • Grunting OR • Fever (37.5℃* or above) OR • low body temperature (less than 35.5℃*) OR • Movements only when stimulated or no movements even when stimulated	VERY SEVERE DISEASE	▶ Give first dose of Intramuscular antibiotics. ▶ Treat to prevent low blood sugar. ▶ Advise mother how to keep the infant warm on the way to the hospital. ▶ Refer URGENTLY to hospital.**
• Umbilicus red or draining pus • Skin pustules	LOCAL BACTERIAL INFECTION	▶ Give an appropriate oral antibiotic. ▶ Teach the mother to treat local infections at home. ▶ Advise mother to give home care for the young infant. ▶ Follow-up in 2 days.
• None of the signs of ver severe disease or local bacterial infection	BACTERIAL INFECTION UNLIKELY	▶ Advise mother to give home care for young infant.

THEN CHECK FOR JAUNDICE

ASK

LOOK, LISTEN, FEEL:

- Look for jaundice
- Look at the young infants plams and soles. Are they yellow?

Classify JAUNDICE

• Any jaundice if age less than 24 hours or • Yellow palms and soles at any age	SEVERE JAUNDICE	▶ Treat to prevent low blood sugar. ▶ Refer URGENTLY to hospital. ▶ Advise the mother how to keep the young infant warm on the way to the hospital.
• Jaundice appearing after 24 hours of age and • Palms and soles not yellow	JAUNDICE	▶ Advise the mother to give home care for the young infant ▶ Advise mother to return immediately if palms and soles appear yellow. ▶ Follow-up in 1 day.
• No jaundice	NO JAUNDICE	▶ Advise the mother to give home care for the young infant.

THEN ASK:
Does the young infant have diarrhoea?

IF YES, LOOK AND FEEL:

- Look at the young infant's general condition.

  Does the infant move only when stimulated?
  Does the infant not move even when stimulated?

  Is the infant restless and irritable?

- Look for sunken eyes.

  Offer the child fluid.

- Pinch the skin of the abdomen.
  Does it go back:

  Very slowly (longer than 2 seconds)?
  Slowly?

Classify DIARRHOEA

for DEHYDRATION		
Two of the following signs: • Movement only when stimulated or no movement even when stimulated • Sunken eyes • Skin pinch goes back very slowly.	SEVERE DEHYDRATION	▶If infant does not have VERY SEVERE DISEASE: - Give fluid for severe dehydration (Plan C). OR ▶If infant also has VERY SEVERE DISEASE: - 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 antibiotic for cholera.
Two of the following signs: • Restless, irritable • Sunken eyes • Skin pinch goes back slowly.	SOME DEHYDRATION	▶Give fluid and food for some dehydration (Plan B). ▶If infant also has VERY SEVERE DISEASE: - Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. - Advise mother to continue breastfeeding. ▶Advise mother when to return immediately. ▶Follow-up in 2 days if not improving.
• Not enough signs to classify as some or severe dehydration.	NO DEHYDRATION	▶Give fluids to treat diarrhoea at home (Plan A). ▶Advise mother when to return immediately. ▶Follow-up in 2 days if not improving.
and if diarrhoea 14 days or more		
• Diarrhoea lasting 14 days or more.	SEVERE PERSISTENT DIARRHOEA	▶ If the young infant is dehydrated, treat dehydration before referral unless the infant has also POSSIBLE SERIOUS BACTERIAL INFECTION.OR POSSIBLE NEONATAL TETANUS OR SIGNIFICANT JAUNDICE ▶Refer to hospital.
and if blood in stool		
• Blood in the stool.	BLOOD IN STOOL	▶Treat to prevent low blood sugar ▶Advise mother how to keep the infant warm on the way to hospital ▶Refer URGENTLY to hospital

* These thresholds are based on axillary temperature.

** If referral is not possible, see Integrated Management of Childhood Illness, Treat the Child, Annex: "Where Referral is Not Possible."

THEN CHECK FOR FEEDING PROBLEM OR LOW WEIGHT :

ASK:

- Is the infant breastfeed? If yes, how many times in 24 hours?

  Does the infant usually receive any other foods or drinks? If yes, how often?

LOOK, LISTEN, FEEL:

- Determine weight for age.

If an infant has no indications to refer urgently to hospital:

ASSESS BREASTFEEDING:

- Has the infant breastfeeding 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 attache well?
  not well attached good attachment

TO CHECK ATTACHMENT, LOOK FOR:
- More areola visible above than below the mouth
- Mouth wide open
- Lower lip turned outward
- Chin touching breast

(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 effectively suckling effectively

  Clear a blocked nose if it interferes with breastfeeding.

- Look for ulcers or white patches in the mouth (thrush).

Classify FEEDING

• Not well attached to breast or not suckling effectively, OR • Less than 8 breatfeeds in 24 hours, OR • Receive other foods or drinks, OR • Low weight for age, OR • Thrush (Ulcers or white patches in month)	FEEDING PROBLEM OR LOW WEIGHT	▶ If not well attached or not suckling effectively, teach correct positioning and attachment. . If not able to attach well immediately, teach the mother to express breast milk and feed by a cup. ▶ If breastfeeding less than 8 times in 24 hours, advise to increase frequency of feeding. Advise her to breastfeed as often and for as long as the infant wants, day and night. ▶ If receiving other foods or drinks, counsel mother about breastfeeding more, reducing other foods or drinks, and using a cup. . If not breastfeeding at all: - Refer for breastfeeding counseling and possible relactation - Advise about correctly preparing breastmilk substitutes and using a cup. ▶ Advise the mother how to feed and keep the low weight young infant warm at home. ▶ If thrush, teach the mother to treat thrush at home ▶ Advise mother to give home care for the young infant. ▶ Fellow-up any feeding problems or thrush in 2 days.
• Not low weight and no other signs of inadequate feeding.	NO FEEDING PROBLEM	▶ Advise mother to give home care for the young infant. ▶ Praise the mother for feeding the infant well.

TREAT THE YOUNG INFANT AND COUNSEL THE MOTHER

▶ TO TREAT CONVULSIONS, SEE TREAT THE CHILD CHART

▶ Give First Dose of Intramuscular Antibiotics

- Give first dose of Ampicillin or benzylpenicillin intramuscularly.
- Give first dose of Gentamicin intramuscularly.

WEIGHT	AMPICILLIN Dose: 50 mg per kg To a vial of 250 mg Add 1.3 ml sterile water = 250 mg / 1.5 ml	BENZYLPENICILLIN Dose: 50.000 mg per kg To a vial of 600 mg (1000000 units) Add 1.6 ml sterile water = 500000 units / ml	GENTAMICIN		
			Undiluted 2 ml vial containing 20 mg = 2 ml at 10 mg/ml	OR	Add 6 ml sterile water to 2 ml vial containing 80 mg* = 8 ml at 10 mg/ml
			Age < 7 days Dose: 5 mg per kg		Age > 7 days Dose: 7.5 mg per kg
1 - 1.5 kg	0.4 ml	0.2 ml	0.6 ml		0.9 ml
1.5 - 2 kg	0.5 ml	0.2 ml	0.9 ml		1.3 ml
2 - 2.5 kg	0.7 ml	0.3 ml	1.1 ml		1.7 ml
2.5 - 3 kg	0.8 ml	0.5 ml	1.4 ml		2.0 ml
3 - 3.5 kg	1.0 ml	0.5 ml	1.6 ml		2.4 ml
3.5 - 4 kg	1.1 ml	0.6 ml	1.9 ml		2.8 ml
4 - 4.5 kg	1.3 ml	0.7 ml	2.1 ml		3.2 ml

* Avoid using undiluted 40 mg/ml gentamicin. The dose is 1/4 of that listed.

- Referral is the best option for a young infant classified with VERY SEVERE DISEASE. If referral is not possible, give ampicillin and gentamicin for at least 5 days. Give ampicillin every 2 times daily to infants less than one week of age and 3 times daily to infants one week or older. Give gentamicin ones daily.

▶ Give an Appropriate Oral Antibiotic for local infection

FIRST-LINE ANTIBIOTIC: AMOXYCILLIN
SECOND-LINE ANTIBIOTIC: CEPHRADINE

AGE or WEIGHT	AMOXYCILLIN SYRUP (125 mg / 5 ml) ▶ Give two times daily for 5 days	CEPHRADINE SYRUP (125 mg / 5 ml) ▶ Give three times daily for 5 days
Birth up to 1 month (<3 kg)	1.25 ml	5 ml
1 month up to 2 months (3 - 4 kg)	2.5 ml	10 ml

TREAT THE YOUNG INFANT AND COUNSEL THE MOTHER

To Treat Diarrhoea, See TREAT THE CHILD Chart.

Immunize Every Sick Young Infant, as Needed.

Teach the Mother to Treat Local Infections at Home

- Explain how the treatment is given.
- Watch her as she does the first treatment in the clinic.
- Tell her to do the treatment twice daily. She should return to the clinic if the infection worsens.

To Treat Skin Pustules or Umbilical Infection

The mother should:

- Wash hands
- Gently wash off pus and crusts with soap and water
- Dry the area
- Paint with gentian violet
- Wash hands

To Treat Thrush (ulcers or white patches in mouth)

The mother should:

- Wash hands
- Wash mouth with clean soft cloth wrapped around the finger and wet with salt water
- Paint the mouth with half-strength gentain violet (0.25 %)
- Wash hands

To Treat Eye Infection, See Treat the Child Chart

TREAT THE YOUNG INFANT AND COUNSEL THE MOTHER

▶ Teach Correct Positioning and Attachment for Breastfeeding

- Show the mother how to hold her infant
  - with the infant's head and body straight
  - facing her breast, with infant's nose opposite her nipple
  - with infant's body close to her body
  - supporting infant's whole body, not just neck and shoulders.
- Show her how to help the infant to attach. She should:
  - touch her infant's lips with her nipple
  - wait until her infant's mouth is opening wide
  - move her infant quickly onto her breast, aiming the infant's lower lip well below the nipple.
- Look for signs of good attachment and effective suckling. If the attachment or suckling is not good, try again.

▶ Advise Mother to Give Home Care for the Young Infant

- EXCLUSIVELY BREATFEED THE YOUNG INFANT.

  Give only breastfeeds to the young infant.

  Breastfeed frequently, as often and for as long as the infant wants, day or night, during sickness and health.
- MAKE SURE THE YOUNG INFANT STAYS WARM AT ALL TIMES.

  In cool weather cover the infant's head and feet and dress the infant with extra clothing.
- WHEN TO RETURNED

  Follow-up Visit

If the infant has:	Return for follow-up in:
LOCAL BACTERIAL INFECTION DIARRHOEA ANY FEEDING PROBLEM THRUSH	2 days
LOW WEIGHT FOR AGE LOW BIRTH WEIGHT	14 days

When to Return Immediately:

Advise the mother to return immediately if the young infant has any of these signs:
Breastfeeding or drinking poorly Becomes sicker Develops a fever Fast breathing Difficult breathing Depressed breathing

GIVE FOLLOW-UP CARE FOR THE SICK YOUNG INFANT

LOCAL BACTERIAL INFECTION

After 2 days:
Look at the umbilicus. Is it red or draining pus?
Look at the skin pustules.

Treatment:

- If umbilical pus or redness remains or is worse, refer to hospital. If pus and redness are improved, tell the mother to continue giving the 5 days of antibiotic and continue treating the local infection at home.
- If skin pustules are same or worse, refer to hospital. If improved, tell the mother to continue giving the 5 days of antibiotic and continue treating the local infection at home.

DIARRHOEA

After 2 days:
Ask: Has the diarrhoea stopped?

Treatment:

- If the diarrhoea has not stopped, assess and treat the young infant for diarrhoea. >SEE “Does the Young Infant Have Diarrhoea?”
- If the diarrhoea has stopped, tell the mother to continue exclusive breastfeeding.

GIVE FOLLOW-UP CARE FOR THE SICK YOUNG INFANT

FEEDING PROBLEM

After 2 days:
Reassess feeding. > See "Then Check for Feeding Problem or low birth weight" above.
Ask about any feeding problems found on the initial visit.

- Counsel the mother about any new or continuing feeding problems. If you counsel the mother to make significant changes in feeding, ask her to bring the young infant back again.
- If the young infant is low weight for age, ask the mother to return 14 days after the initial visit to measure the young infant's weight gain.

Exception:
if you do not think that feeding will improve, or if the young infant has lost weight, refer the child.

LOW WEIGHT

After 14 days:
Weigh the young infant and determine if the infant is still low weight for age.
Reassess feeding. > See "Then Check for Feeding Problem or low weight" above.

- If the infant is no longer low weight for age, praise the mother and encourage her to continue.
- If the infant is still low weight for age, but is feeding well, praise the mother. Ask her to have her infant weighed again within a month or when she returns for immunization.
- If the infant is still low weight for age and still has a feeding problem, counsel the mother about the feeding problem. Ask the mother to return again in 14 days (or when she returns for immunization, if this is within 2 weeks). Continue to see the young infant every few weeks until the infant is feeding well and gaining weight regularly or is no longer low weight for age.

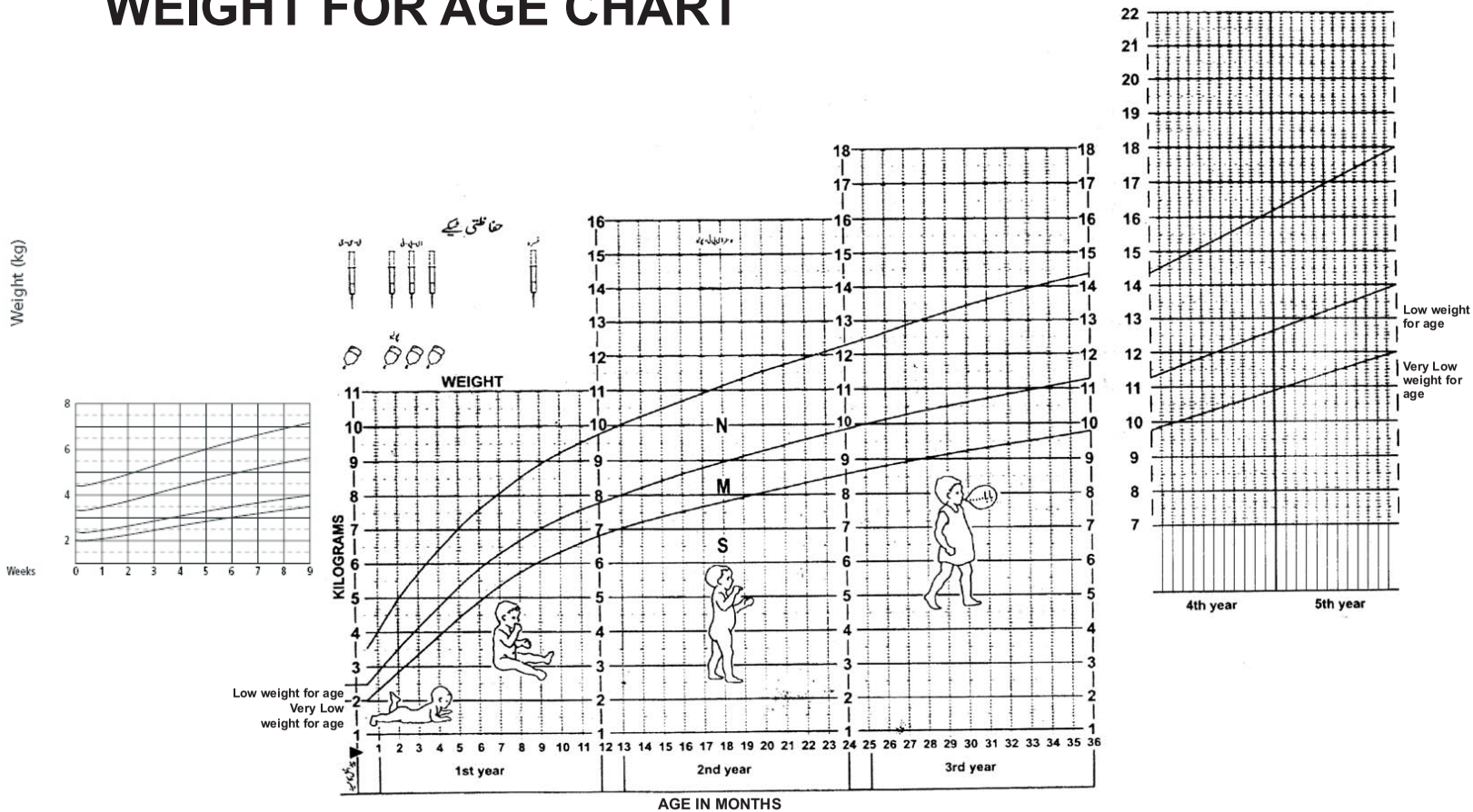
Exception:
if you do not think that feeding will improve, or if the young infant has lost weight, refer to hospital.

THRUSH

After 2 days:
Look for ulcers or white patches in the mouth (thrush).
Reassess feeding. > See "Then Check for Feeding Problem or low birth weight or Low Weight" above.

- If thrush is worse, or the infant has problems with attachment or suckling, refer to hospital.
- If thrush is the same or better, and if the infant is feeding well, continue half-strength gentian violet for a total of 5 days.

WEIGHT FOR AGE CHART



CHAPTER 34 PRACTICAL PEDIATRICS

(I) History taking proforma

- Biodata
- Presenting complains
- History of presenting illness/complains (HOPI)
    - When and how did it start?
    - Was he/she well before?
    - How did it develop
    - What aggravates/alleviates it?
    - Has there been any contact with infections?
- Special questions for infants
    - Feeding habits
    - Urinary and bowel habits
    - Alertness
    - Weight gain
- Systemic review
    - General Systemic Review
        - *Aide mémoire*: WAFFLE
        - Weight
        - Apetite
        - Fever
        - Fatigue
        - Lumps
        - Everything else
    - Cardiorespiratory review
        - Tachypnoea
        - Grunts, wheeze
        - Cyanosis
        - Exertional dyspnoea
        - Sputum
        - Chest pain
    - Gastrointestinal review
        - Apetite
        - Diarrhea
        - Vomiting
        - Feeding problems
        - Stool frequency

        - Jaundice
        - Abdominal pain
    - Genitourinary review
        - Wet napies
        - Hematuria
        - Dysuria
        - Sexual development (for older children)
    - Neuromuscular review
        - Seizures
        - Drowsiness
        - Hyperactivity
        - Vision problems
        - Gait problems
        - Headache
        - Coordination
    - Otorhinolaryngology review
        - Noisy breathing
        - Ear discharge
        - Ear ache
        - Sore throat
- Birth history
    - Prenatal
    - Natal/At birth
        - Duration of gestation
        - Duration of labor
        - Mode of delivery
        - Birth weight
        - Resuscitation required
        - Birth Injury
        - Congenital malformations
    - Post natal
        - Jaundice
        - Fits
        - Fever
        - Bleeding
        - Feeding Problems
        - Surgeries
        - Accidents
        - Screening tests

- Drugs

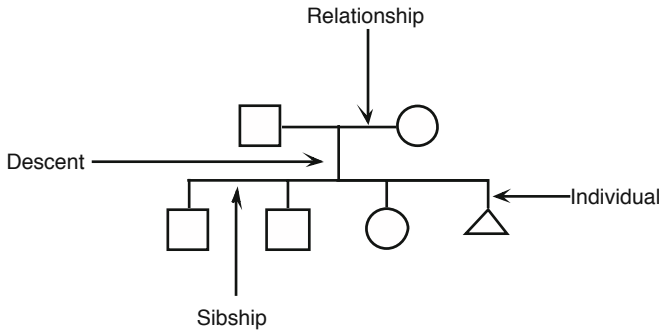
- Immunizations history
  - Ask questions before looking at immunizations card?
  - Check for BCG scar?
- Nutritional history
  - Upto 6 months of age
    - Breast-feed as often as the child wants, atleast 8 times a day and night (24 hours) for >10 minutes.
  - 6 months - 12 months of age
    - Breast-feed as often as the child wants, atleast 8 times a day and night (24 hours) for >10 minutes.
    - Khichri, bhatt (rice), seasonal vegetables, seasonal fruits (upto 9 months of age, food should be mashed).
    - Each serving should be equivalent to ½ - ¾ of a cup.
    - 3 times/day if breast fed
    - 5 times/day if not breast fed
  - 12 months - 2 years of age
    - Breast feed on demand
    - 3 times a day: Roti, paratha, khichri, chicken, egg, seasonal vegetables + snacks 2 times a day between meals: banana, apple, mango, orange, biscuit, chips, pakora, samosa, lassi, OR
    - Family foods 5 times/day
- Developmental milestones history
  - Neonate
    - Gross motor
      - Tonic neck reflex (fencing posture)
      - Pulled to sit—Marked head lag
      - Turns head side to side
    - Hearing/Speech: Eye corners reflexly in the direction of sound
    - Social behavior
      - Baby recognizes parents, drops toys
      - Moro, Rooting, sucking and swallowing reflexes are positive
  - 3 months of age
    - Gross motor
      - Lifts head and chest above the couch using forearm as support
      - Pulled to sit—No head lag
      - Back is straight except lumbar region
      - Ventral suspension—Head extended
      - Palmar grasp fading

        - Fine motor--Follows light through an arc of 180° (6 weeks)
        - Hearing/Speech: Turns head to nearby voice
        - Social behavior: Happy response to mothers face
    - 6 months of age
        - Gross motor
            - Lifts leg to vertical
            - Lifts head and chest well up supporting weight on extended arms
            - Back is straight (incl. lumbar region)
            - Held standing—bears weight
            - Parachute reflex appears
        - Fine motor
            - Reaches for objects with one hand
            - Eyes move in unison
        - Hearing/Speech
            - Shouts to attract attention
            - Turns head towards sound
        - Social behavior
            - Still friendly with strangers (negative stranger anxiety)
            - Inhibited by the word "No!"
            - Puts everything into mouth
    - 1 year of age
        - Can say "mama, papa"
        - Able to stand
    - 18 months
        - Able to speak 2-4 words
        - Can walk backwards
        - Important: Drooling ± throwing items on the floor is abnormal by now and is a sign of developmental delay at this stage.

- Past History
    - Past Medical History
    - Past Surgical History
    - Drugs and Transfusion History
    - Allergies
- Family History
    - Stillbirths
    - Tuberculosis
    - Diabetes
    - Renal Disease

- Seizures
- Jaundice
- Malformations

- Socioeconomic History
- Family Tree



(II) Physical examinations pearls

Table. Normal vital signs in children			
Age	**Heart rate**	**Respiratory rate**	**Blood pressure**
Newborn	120-170	30–60	75/40
1-6 months	85-160	30-40	96/60
6-12 months	75-160	24-39	100/60

i) 180° Flip Test

The subject is put in the following positions and observed for various findings in this sequence.

- Lying supine—
- Pulled to sit— check for neck holding that develops at 3 months of age.
- Sitting posture— rouded back (at 3 months) or straight back (at ~ 6 months of age)
- Attemped weight bearing—
  - Flexion at hip and knee
  - Scissoring (seen in cerebral palsy
- Vertical suspension—
  - Back rounded,
  - Head and limbs hang down
- Prone
  - Failure of neck extension

This sequence of maneuvres is a quick way of assessing developmental milestones in an infant.

ii) Examination of skull fontanelles

The *anterior fontanelle* is diamond shaped. It is closed by 12–18 months' age.

The *posterior fontanelle* is triangle-shaped. It is closing by 2–3 months of age.

iii) Observing the breathing

- Kussmaul's **breathing** is a regular, deep, and rapid breathing pattern seen in severe metabolic acidosis, e.g.
    - Diabetic ketoacidosis
    - Renal failure
    - *Do not confuse with* Kussmaul's **sign,** which refers to an inspiratory rise in jugular venous pulse (***Aide mémoire: I R JVP: I****nspiratory* ***R****ise* ***JVP)*** seen pericardial effusion, constrictive pericarditis, etc.
- Cheyne-stoke's breathing is an alternating pattern of hyperventilation and hypoventilation with periods of apnoea. It is seen in:
    - LV failure
    - ↑ ICP
    - Brainstem lesion
    - Narcotic Overdose

iv) Examining the pulse

- For every 1° rise in temperature, pulse rate rises by 10.
    - If the pulse rate is less than expected for given temperature in cases of fever, it is called **relative bradycardia.**
    - Enteric Fever and Viral infections are two causes for relative bradycardia.
- Pulsus Plateau (Slow rising pulse)— aortic stenosis
- Collapsing Pulse (Water-hammer pulse)— aortic regurgitation
- Pulsus Bisferiens (=two systolic peaks in one pulse)— Combined Aortic Stenosis & Regurgitation.
- Pulsus Paradoxus: ***Exaggeration of Normal*** Inspiratory drop in SBP > 10 mm Hg— Massive pericardial effusion (pericardial tamponade), Constrictive pericarditis, and Acute Severe Bronchial Asthma.
- Pulsus Alternans (strong beat with a weak beat, constant interval in between)— Left ventricular failure, and SVTs.
- Pulsus Bigeminus (strong beat with a weak beat, short interval between two, followed by pause) — Digoxin Toxicity.
- Jerky Pulse may be seen in Hypertrophic Obstructive Cardiomyopathy (HOCM)

v) Grading the murmurs

Table. Grades of Murmurs*	
Grade-1	Murmur barely audible in a quiet room
Grade-2	Easily audible but not loud
Grade 3	Loud -ve thrill
Grade 4	Loud +ve thrill
Grade 5	Very loud murmur, audible outside precordium/ Stethoscope partially off the chest wall
Grade 6	Murmur audible without stethoscope
**Diastolic murmurs are only graded till grade 4.*	

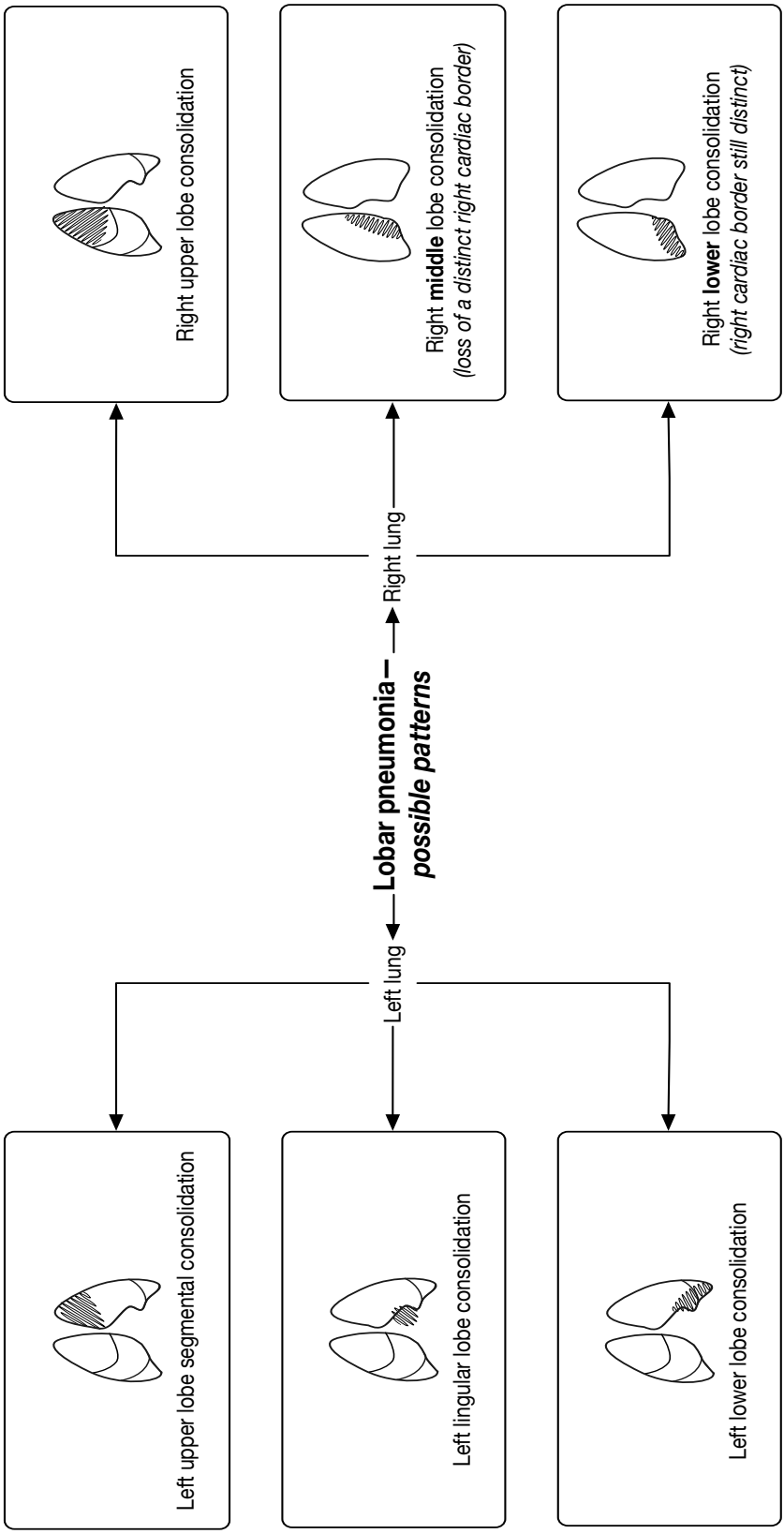
vi) Grading the Reflexes

Table. Grading of deep tendon reflexes	
Grade 0	No reflex
Grade I	Slight response
Grade 2	Normal reflex
Grade 3	Hyperactive
Grade 4	Hyperactive with clonus

vii) Grading of muscle power

Table. Grading of muscle power		
Grade 0	No reflex	
Grade I	Trace	Palpable or visual contraction without joint motion.
Grade 2	Poor	Complete range of motion of joint with gravity eliminated.
Grade 3	Fair	Complete range of motion of joint against gravity
Grade 4	Good	Complete range of motion of joint against gravity + some resistance
Grade 5	Normal	Complete range of motion of joint against gravity + resistance

(III) Where is the consolidation?



Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Abacavir							
Adrenaline							
For wheeze	0.01 ml/kg (up to a maximum of 0.3 ml) of 1:1000 solution (or 0.1 ml/kg of 1:10 000 solution) given subcutaneously with a 1-ml syringe		Calculateexact dose based on body weight (as rapid-acting bronchodilator)				
For severe viral croup	0.5 ml/kg of 1:1000 solution (maximum dose: 5 ml)		–	3 ml	5 ml	5 ml	5 ml
For anaphylaxis	0.15 ml of 1:1000 solution IM (0.3 ml for children > 6 years)						
Note: Make up a 1:10 000 solution by adding 1 ml of 1:1000 solution to 9 ml of normal saline or 5% glucose							
Aminophylline							
For asthma	Oral: 6 mg/kg	Tablets: 100 mg	¼	½	¾	1	1½
		Tablets: 200 mg	–	¼	½	½	¾
	IV: Calculate exact dose based on body weight when possible; use the doses below only when this is not possible.						
	Loading dose: IV: 5–6 mg/kg (max. 300 mg) slowly over 20–60 min	250 g/10-ml vial	1 ml	1.5 ml	2.5 ml	3.5 ml	5 ml

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Aminophylline For asthma (continued)	Maintenance dose: IV: 5 mg/kg up to every 6 h		1 ml	1.5 ml	2.5 ml	3.5 ml	5 ml
	or by continuous infusion at 0.9 mg/kg per h		Calculate exact dose				
Give IV loading dose only if the child has not taken aminophylline or theophylline within 24 h.							
Amoxicillin	25 mg/kg twice a day	250 mg tablet (chewable or dispersible)	½	1	1½	2	2½
		Syrup (containing 250 mg/5 ml)	2.5 ml	5 ml	7.5 ml	10 ml	–
For pneumonia	40 mg/kg twice a day		1 2.5 ml	1½ 7.5 ml	2 10 ml	3 –	4 –
Amphotericin B For oesophageal candidiasis	0.25 mg/kg per day increasing to 1 mg/kg per day, as tolerated, by IV infusion over 6 h/day for 10–14 days	50 mg vial	–	2–8 mg	3–12 mg	4.5–18 mg	6–24 mg
Ampicillin	IM/IV: 50 mg/kg every 6 h	Vial of 500 mg mixed with 2.1 ml sterile water to give 500 mg/2.5 ml	1 ml	2 ml	3 ml	5 ml	6 ml
Note: These oral doses are for mild disease. If oral ampicillin is required after a course of injectable ampicillin for severe disease, the oral dose must be two to four times higher than that given here.							

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Antituberculosis antibiotics(see p. 370)							
Artemether For severe malaria	Loading dose: IM: 3.2 mg/kg	40 mg/1-ml ampoule 80 mg/1-ml ampoule	0.4 ml 0.2 ml	0.8 ml 0.4 ml	1.2 ml 0.6 ml	1.6 ml 0.8 ml	2.4 ml 1.2 ml
	Maintenance dose: IM: 1.6 mg/kg	40 mg/1-ml ampoule 80 mg/1-ml ampoule	0.2 ml 0.1 ml	0.4 ml 0.2 ml	0.6 ml 0.3 ml	0.8 ml 0.4 ml	1.2 ml 0.6 ml
Give the maintenance dose daily for a minimum of 24 h until the patient can take oral artemisinin-based combination therapy.							
Artemether/ lumefantrine	Oral: 2 mg/kg artemether – 12 mg/kg lumefantrine twice per day	Tablet: 20 mg artemether–120 mg lumefantrine	1	1	1	2	2
Artesunate For severe malaria	IV or IM: 2.4 mg/kg	60 mg artesumic acid (already dissolved in 0.6 ml of saline and sodium bicarbonate) in 3.4 ml of saline and glucose	0.8 ml	1.4 ml	2.4 ml	3.0 ml	5.0 ml
The IV solution should be prepared just before use. Dilute by dissolving 60 mg artesunic acid (which is already dissolved in 0.6 ml of 5% sodium bicarbonate) in 3.4 ml of 5% glucose. Give a dose at 0, 12 and 24 h and then daily until child is able to take it orally. If the patient is able to swallow, give the recommended full dose of artemisinin-based combination therapy.							
Artesunate– mefloquine	Oral: 4 mg/kg artesunate–8.3 mg/kg mefloquine once a day	Tablet: 25 mg artesunate–55 mg mefloquine	–	1	2	2	3
Not recommended for children < 5 months of age owing to limited information.							
Aspirin	Oral: 10–20 mg/kg every 4–6 h	300 mg tablet	–	¼	½	¾	1
Note: Avoid in young children, if possible, because of the risk of Reye syndrome.							

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Benzathine penicillin – see Penicillin							
Cefotaxime	IV: 50 mg/kg every 6 h	Vial of 500 mg mixed with 2 ml sterile water or vial of 1 g mixed with 4 ml sterile water or vial of 2 g mixed with 8 ml sterile water	0.8 ml	1.5 ml	2.5 ml	3.5 ml	5 ml
Ceftriaxone	IV: 80 mg/kg per day as a single dose given over 30 min as infusion or 3 min as IV injection	Vial of 1 g mixed with 9.6 ml sterile water to give 1 g/10 ml or vial of 2 g mixed with 19 ml of sterile water to give 2 g/20 ml	3 ml	6 ml	10 ml	14 ml	20 ml
For meningitis	IM/IV: 50 mg/kg every 12 h (max single dose, 4 g)		2 ml	4 ml	6 ml	9 ml	12.5 ml
	or IM/IV: 100 mg/kg		4 ml	8 ml	12 ml	18 ml	25 ml
Cefalexin	12.5 mg/kg four times a day	250 mg tablet	¼	½	¾	1	1¼

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Chloramphenicol	Calculate exact dose based on body weight. Use the doses below only if this is not possible.						
For meningitis	IV: 25 mg/kg every 6 h (max, 1 g per dose)	Vial of 1 g mixed with 9.2 ml sterile water to give 1 g/10 ml	0.75–1.25 ml	1.5–2.25 ml	2.5–3.5 ml	3.75–4.75 ml	5–7.25 ml
For cholera	IM: 20 mg/kg every 6 h for 3 days	Vial of 1 g mixed with 3.2 ml sterile water to give 1 g/4 ml	0.3–0.5 ml	0.6–0.9 ml	1–1.4 ml	1.5–1.9 ml	2–2.9 ml
For other conditions	Oral: 25 mg/kg every 8 h	125 mg/5 ml suspension (palmitate)	3–5 ml	6–9 ml	10–14 ml	15–19 ml	–
	(maximum 1 g per dose)	250 mg capsule	–	–	1	1½	2
Phenobarbital reduces and phenytoin increases chloramphenicol levels when given together.							
Chloramphenicol, oily (for treatment of meningococcal meningitis during epidemics)	100 mg/kg single dose; max, 3 g	IM: vial of 0.5 g in 2 ml	1.2–2 ml	2.4–3.6 ml	4–5.6 ml	6–7.6 ml	8–11.6 ml
Chlorphenamine	IM/IV or SC:	10 mg in 1 ml	0.1 ml	0.2 ml	0.3 ml	0.5 ml	0.6 ml
	0.25 mg/kg once (can be repeated up to four times in 24 h	IV solution					
	Oral: two or three times daily	Tablet: 4 mg	–	–	–	–	½

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Ciprofloxacin	Oral: 10-20 mg/kg per dose given twice a day for 5 days (max, 500 mg per dose)	100 mg tablet	½	1	1½	2	3
		250 mg tablet	¼	½	½	1	1½
Cloxacillin or flucloxacillin or oxacillin	IV: 25–50 mg/kg every 6 h	Vial of 500 mg mixed with 8-ml dose in sterile water to give 500 mg/10 ml	2–(4) ml	4–(8) ml	6–(12) ml	8–(16) ml	12–(24) ml
	IM: 25–50 mg/kg every 6 h	Vial of 250 mg mixed with 1.3 ml sterile water to give 250 mg/1.5 ml	0.6 (1.2) ml	1 (2) ml	1.8 (3.6) ml	2.5 (5) ml	3.75 (7.5) ml
		250 mg capsule	half (1)	1 (2)	1 (2)	2 (3)	2 (4)
For treating abscesses	15 mg/kg every 6 h	250-mg capsule	¼	½	1	1½	2½
Co-trimoxazole (trimethoprim-sulfamethoxazole)	4 mg/kg trimethoprim and 20 mg/kg sulfamethoxazole twice a day	Oral: adult tablet (80 mg trimethoprim + 400 mg sulfamethoxazole)	¼	½	1	1	1
		Oral: paediatric tablet (20 mg trimethoprim + 100 mg sulfamethoxazole)	1	2	3	3	4

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Co-trimoxazole (trimethoprim-sulfamethoxazole (continued)		Oral: syrup (40 mg trimethoprim + 200 mg sulfamethoxazole per 5 ml)	2 ml	3.5 ml	6 ml	8.5 ml	—
Note: For interstitial pneumonia in children with HIV, give 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole three times a day for 21 days. For an infant < 1 month, give co-trimoxazole (half paediatric tablet or 1.25 ml syrup) twice a day. Avoid co-trimoxazole in neonates who are premature or jaundiced.							
Deferoxamine For iron poisoning	15 mg/kg per h IV to max of 80 mg/kg in 24 h, or IM: 50 mg/kg every 6 h. Maximum dose, 6 g/day	500-mg ampoule	2	2	2	2	2
Dexamethasone For severe viral croup	Oral: 0.6 mg/kg single dose	0.5-mg tablets					
		IM: 5 mg/ml	0.5 ml	0.9 ml	1.4 ml	2 ml	3 ml
For meningitis	IV: 0.15 mg/kg/dose every 6 h for the first 2–4 days						
Diazepam For convulsions	Rectal: 0.5 mg/kg	10 mg/2 ml solution	0.4 ml	0.75 ml	1.2 ml	1.7 ml	2.5 ml
	IV: 0.2–0.3 mg/kg		0.25 ml	0.4 ml	0.6 ml	0.75 ml	1.25 ml
For sedation before procedures	0.1–0.2 mg/kg IV						
Give phenobarbital (20 mg/kg IV or IM) instead of diazepam to neonates. If convulsions continue, give 10 mg/kg IV or IM after 1–3 h. The maintenance dose of oral phenobarbital is 2.5–5 mg/kg.							

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–< 15 kg	15–< 20 kg	20–29 kg
Digoxin	These doses are for oral digoxin. Give as an initial loading dose followed by twice daily maintenance doses, starting 6 h after the loading dose:						
	Loading dose: 15 µg/kg, once only	62.5-µg tablets	¾–1	1½–2	2½–3½	3½–4½	–
		125-µg tablets	–	–	1-1½	1¾–2	2½–3
	Maintenance dose: (Start 6 h after loading dose) 5 µg/kg every 12 h (max, 250 µg per dose)	62.5-µg tablets	¼–½	½–¾	¾–1	1¼–1½	1½–2¼
Dobutamine For treatment of shock that is unresponsive to fluids	2–20 µg/kg per min	250 mg/20 ml ampoule Dilute to 250 mg in 250 ml of 0.9% sodium chloride with 5% glucose to 1000 µg/ml	Calculateexact dose based on body weight and required rate of infusion.				
Diluted solutions may be stored for a maximum of 24 h.							
Dopamine For treatment of shock that is unresponsive to fluids	2–20 µg/kg per min	200 mg/5 ml ampoule Dilute to 250 mg in 250 ml of 0.9% sodium chloride with 5% glucose to 1000 µg/ml	Calculateexact dose based on body weight and required rate of infusion.				
Efavirenz (see separate table for antiretrovirals, p. 372)							
Erythromycin (estolate)	Oral: 12.5 mg/kg four times a day for 3 days	250-mg tablet	¼	½	1	1	1½
Must not be given with theophylline (aminophylline) because of risk of serious adverse reactions.							

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Fentanyl	IV injection: 1-4 µg/kg every 2–4 h	Injection: 50 µg/ml	–	Calculateexact dose based on body weight, and tailor dose to relieve pain.			
	Infusion: initial IV dose 1–2 µg/kg, then 0.5–1 µg/kg per h		–	Calculateexact dose based on body weight and required rate of infusion.			
Fluconazole	3–6 mg/kg once a day	50 mg/5 ml oral suspension	–	–	5 ml	7.5 ml	12.5 ml
For cryptococcal meningitis	6–12 mg/kg once a day	50-mg capsule	–	–	1	1–2	2–3
Flucloxacillin (see Cloxacillin)							
Furazolidone	1.25 mg/kg 4 times a day for 3 days	Oral: 100-mg tablet	–	–	¼	¼	¼
Furosemide (frusemide) For cardiac failure	Oral or IV: 1–2 mg/kg every 12 h	20-mg tablets IV 10 mg/ml	¼–½	½–1	½–1	1–2	1¼–2½
			0.4–0.8 ml	0.8–1.6 ml	1.2–2.4 ml	1.7–3.4 ml	2.5–5 ml
Gentamicin	Calculateexact dose based on body weight, and use the doses below only when this is not possible.						
	7.5 mg/kg once a day	IM/IV: vial containing 20 mg (2 ml at 10 mg/ml) undiluted	2.25–3.75 ml	4.5–6.75 ml	7.5–10.5 ml	–	–
		IM/IV: vial containing 80 mg (2 ml at 40 mg/ml) mixed with 6 ml sterile water	2.25–3.75 ml	4.5–6.75 ml	7.5–10.5 ml	–	–

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Gentamicin (continued)		IM/IV: vial containing 80 mg (2 ml at 40 mg/ml) undiluted	0.5–0.9 ml	1.1–1.7 ml	1.9–2.6 ml	2.8–3.5 ml	3.75–5.4 ml
Risk for adverse effects when given with theophylline. In administering an aminoglycoside (gentamicin, kanamycin), it is preferable to avoid use of undiluted 40 mg/ml gentamicin.							
Gentian violet: Topical application to skin							
Hydromorphone	0.1–0.2 mg/kg every 4 h for two or three doses, then every 6–12 h	Tablet: 2 or 4 mg	–	Calculate exact dose based on body weight, and tailor dose to relieve pain.			
		Oral liquid: 1 mg/ml	–				
	0.015–0.02 mg/kg every 3–6 h	IV: 1 or 2 or 4 mg/ml	–	Calculate exact dose based on body weight and required rate of infusion.			
Ibuprofen	5–10 mg/kg orally every 6–8 h to a max total daily dose of 40 mg/kg	200-mg tablet	–	¼	¼	½	¾
		400-mg tablet	–	–	–	¼	½
Iron	Once a day for 14 days	Iron–folate tablet (ferrous sulfate 200 mg + 250 µg folate = 60 mg elemental iron	–	–	½	½	1
		Iron syrup (ferrous fumarate, 100 mg per 5 ml = 20 mg/ml elemental iron)	1 ml	1.25 ml	2 ml	2.5 ml	4 ml

Drug	Dosage	Form	Dose according to body weight 3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Kanamycin	Calculateexact dose based on body weight. Use the doses below only if this is not possible.						
	IM/IV: 20 mg/kg once a day	250 mg vial (2 ml at 125 mg/ml)	0.5–0.8 ml	1–1.5 ml	1.6–2.2 ml	2.4–3.0 ml	3.2–4.6 ml
Ketamine For anaesthesia in major procedures	Calculateexact dose based on body weight.						
	IM: Loading dose: 5–8 mg/kg		20–35 mg	40–60 mg	60–100 mg	80–140 mg	125–200 mg
	IM: Further dose: 1–2 mg/kg (if required)		5–10 mg	8–15 mg	12–25 mg	15–35 mg	25–50 mg
	IV: Loading dose: 1–2 mg/kg		5–10 mg	8–15 mg	12–25 mg	15–35 mg	25–50 mg
	IV: Further dose: 0.5–1 mg/kg(if required)		2.5–5 mg	4–8 mg	6–12 mg	8–15 mg	12–25 mg
For light anaesthesia in minor procedures	IM: 2–4 mg/kg IV: 0.5–1 mg/kg						
Lamivudine							
Lidocaine	Apply topically Local injection: 4–5 mg/kg per dose as local anaesthetic						
Mebendazole	100 mg twice a day for 3 days	100-mg tablet	–	–	1	1	1
	500 mg once only	500-mg tablet	–	–	1	1	1

Not recommended for children < 5 months of age owing to limited information.

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Metoclopramide For nausea and vomiting	0.1–0.2 mg/kg every	10-mg tablets	–	–	¼	¼	½
	8 h as required (maximum dose: 10 mg/dose)	Injection: 5 mg/ml	–	–	0.5 ml	0.7 ml	1 ml
Metronidazole	Oral: 7.5 mg/kg three times a day for 7 days	200-mg tablet	–	¼	½	½	1
		400-mg tablet	–	–	¼	¼	½
For the treatment of giardiasis, and for amoebiasis, 10 mg/kg.							
Morphine	Calculateexact dose based on weight of the child. Oral: 0.2–0.4 mg/kg every 4–6 h; increase if necessary for severe pain IM: 0.1–0.2 mg/kg every 4–6 h IV: 0.05–0.1 mg/kg every 4–6 h, or 0.005–0.01 mg/kg per h by IV infusion						
Nevirapine							
Nystatin	Oral: 100 000–200 000 U into the mouth	Oral suspension 100 000 units/ml	1–2 ml	1–2 ml	1–2 ml	1–2 ml	1–2 ml
Oxacillin (see Cloxacillin)							
Paracetamol	10–15 mg/kg, up to six times a day	100-mg tablet	–	1	1	2	3
		500-mg tablet	–	¼	¼	½	½

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
PENICILLIN							
Benzathine benzylpenicillin	50 000 U/kg once a day	IM: vial of 1 200 000 U mixed with 4 ml sterile water	0.5 ml	1 ml	2 ml	3 ml	4 ml
Benzylpenicillin (penicillin G) General dosage	IV: 50 000 U/kg every 6 h	Vial of 600 mg mixed with 9.6 ml sterile water to give 1 000 000 U/10 ml	2 ml	3.75 ml	6 ml	8.5 ml	12.5 ml
	IM:	Vial of 600 mg (1 000 000 U) mixed with 1.6 ml sterile water to give 1 000 000 U/2 ml	0.4 ml	0.75 ml	1.2 ml	1.7 ml	2.5 ml
For meningitis	100 000 U/kg every 6 h	IV	4 ml	7.5 ml	12 ml l	17 ml	25 ml
		IM	0.8 ml	1.5 ml	2.5 ml	3.5 ml l	5 m
Procaine benzylpenicillin	IM: 50 000 U/kg once a day	3-g vial (3 000 000 U) mixed with 4 ml sterile water	0.25 ml	0.5 ml	0.8 ml	1.2 ml	1.7 ml
Phenobarbital	IM: Loading dose: 15 mg/kg	200 mg/ml solution	0.4 ml	0.6 ml	1.0 ml	1.5 ml	2.0 ml
	Oral or IM: Maintenance dose: 2.5–5 mg/kg		0.1 ml	0.15 ml	0.25 ml	0.35 ml	0.5 ml
Give phenobarbital (20 mg/kg IV or IM) instead of diazepam to neonates. If convulsions continue, give 10 mg/kg IV or IM after 1 to 3 h.							

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Potassium Chloride	2–4 mmol/kg per day		Calculateexact dose				
Prednisolone	Oral: 1 mg/kg twice a day for 3 days	5-mg tablet	1	1	2	3	5
1 mg prednisolone is equivalent to 5 mg hydrocortisone or 0.15 mg dexamethasone.							
Quinine (mg/kg expressed as mg of quinine hydrochloride salt)	IV: Loading dose: 20 mg salt/kg given slowly over 2–4 h after dilution in 10 ml/kg of IV fluid		Loading dose is double the maintenance dose given below. Infusion rate should not exceed a total of 5 mg quinine dihydrochloride salt/kg per h.				
	IV: Maintenance dose: 10 mg salt/kg given slowly over 2 h after dilution in 10 ml/kg of IV fluid	IV (undiluted): quinine dihydrochloride injection 150 mg/ml (in 2-ml ampoules)	0.3 ml	0.6 ml	1 ml	1.2 ml	2 ml
		IV (undiluted): quinine dihydrochloride injection 300 mg/ml (in 2-ml ampoules)	0.2 ml	0.3 ml	0.5 ml	0.6 ml	1 ml
	If IV infusion is not possible, quinine dihydrochloride can be given at the same dosages IM	IM quinine dihydrochloride (diluted): in normal saline to a concentration of 60 mg salt/ml	1 ml	1.5 ml	2.5 ml	3 ml	5 ml
		Oral: quinine sulfate 200-mg tablet	¼	½	¾	1	1½

Drug	Dosage	Form	Dose according to body weight				
			3–< 6 kg	6–< 10 kg	10–<15 kg	15–<20 kg	20–29 kg
Quinine (continued)		Oral: quinine sulfate 300-mg tablet	–	–	½	½	1
Note: At 8 h after the start of the loading dose, give the maintenance dose listed here over 2 h. Repeat every 8 h. Give a full dose of oral artemisinin combination therapy treatment when the child is able to take orally to complete treatment.							
Ritonavir (see Lopinavir/ritonavir in separate table for antiretrovirals, p. 373)							
Salbutamol	Inhaler with spacer: two doses contain 200 µg	Metered dose inhaler containing 200 doses					
	Nebulizer: 2.5 mg/dose	5 mg/ml solution, 2.5 mg in 2.5 ml single-dose units					
Silver sulfadiazine: apply topically to area of affected skin							
Spectinomycin For neonatal ophthalmia	IM: 25 mg/kg single dose (max, 75 mg)	2-g vial in 5 ml diluent	0.25 ml	–	–	–	–
Tetracaine, adrenaline, cocaine: Apply topically before painful procedures.							
Tetracycline	12.5 mg/kg four times a day for 3 days	250-mg tablet	–	½	½	1	1
Give to children only for treatment of cholera, because permanently stains teeth.							
Vitamin A	Once a day for 2 days	200 000 IU capsule	–	½	1	1	1
		100 000 IU capsule	½	1	2	2	2
		50 000 IU capsule	1	2	4	4	4
Zidovudine							

Antituberculous antibiotics		
		Calculateexact dose based on body weight
Essential anti-TB drug (abbreviation)	Mode of action	Daily dose: mg/kg (range)
Isoniazid (H)	Bactericidal	10 (10–15)
Rifampicin (R)	Bactericidal	15 (10–20)
Pyrazinamide (Z)	Bactericidal	35 (30–40)
Ethambutol (E)	Bacteriostatic	20 (15–25)
Streptomycin (S): use only for MDR TB treatment	Bactericidal	15 (12–18)

Antiretrovirals								
			Dose according to surface area or body weight (morning and evening)					
Drug	Dosage	Form	3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
Fixed-dose combinations								
Zidovudine/ lamivudine (AZT/3TC)	AZT: 180–240 mg/ m^2 twice a day 3TC: 4 mg/kg twice a day	AZT 60 mg + 3TC 30 mg	1	1.5	2	2.5	3	–
		AZT 300 mg + 3TC 150 mg	–	–	–	–	–	1
Zidovudine/ lamivudine /nevirapine (AZT/3TC/ NVP)	AZT: 180–240 mg/ m^2 twice a day 3TC: 4 mg/kg twice a day NVP: 160–200 mg/m^2	AZT 60 mg + 3TC 30 mg + NVP 50 mg	1	1.5	2	2.5	3	–
		AZT 300 mg + 3TC 150 mg + NVP 200 mg	–	–	–	–	–	1

Drug	Dosage	Form	Dose according to surface area or body weight (morning and evening) 3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
Abacavir/ zidovudine / lamivudine (ABC/ AZT/3TC)	ABC: 8 mg/kg twice a day AZT: 180–240 mg/ m^2 twice a day 3TC: 4 mg/kg twice a day	ABC 60 mg + AZT 60 mg + 3TC 30 mg	1	1.5	2	2.5	3	–
		ABC 300 mg + AZT 300 mg + 3TC 150 mg	–	–	–	–	–	1
Abacavir/ lamivudine (ABC/3TC)	Abacavir: 8 mg/kg twice a day Lamivudine: 4 mg/kg twice a day	Paediatric: ABC 60 mg + 3TC 30 mg	1	1.5	2	2.5	3	–
		Adult: ABC 600 mg + 3TC 300 mg	–	–	–	–	–	½
Adult ABC/3TC fixed-dose combination tablets are not scored; a tablet cutter would be required to divide these tablets. Consider giving one tablet daily.								
Stavudine/ lamivudine (d4T/3TC)	d4T: 1 mg/kg twice a day 3TC: 4 mg/kg twice a day	d4T 6 mg + 3TC 30 mg	1	1.5	2	2.5	3	–
		or d4T 30 mg + 3TC 150 mg	–	–	–	–	–	1
Stavudine/ lamivudine/ nevirapine (d4T/3TC/ NVP)	d4T: 1 mg/kg twice a day 3TC: 4 mg/kg twice a day NVP: 160–200 mg/m^2	d4T 6 mg + 3TC 30 mg + NVP 50 mg	1	1.5	2	2.5	3	–
		or d4T 30 mg + 3TC 150 mg + NVP 200 mg	–	–	–	–	–	1
NVP, maximum dose of 200 mg twice a day								
Lopinavir/ritonavir (LPV/RTV)								

Drug	Dosage	Form	Dose according to surface area or body weight (morning and evening)					
			3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
Nucleoside reverse transcriptase Inhibitors (NRTIs)								
Abacavir (ABC)	8 mg/kg per dose twice a day	Liquid: 20 mg/ml	3 ml	4 ml	6 ml	–	–	–
		Tablet: 60 mg	1	1½	2	2½	3	–
		Tablet: 300 mg	–	–	–	½	1	1
Lamivudine (3TC)	4 mg/kg per dose twice a day	Liquid: 10 mg/ml	3 ml	4 ml	6 ml	–	–	–
		Tablet: 150 mg	–	–	–	½	1	1
Tenofovir (TDF)	8 mg/kg once a day (max 300 mg)	Oral powder scoops	–	–	2.5	3.5	4.5	6.0
		Tablet: 150 mg	–	–	–	1	–	–
		Tablet: 200 mg	–	–	–	–	1	–
		Tablet: 250 mg	–	–	–	–	–	1
Zidovudine (AZT or ZDV)	Oral: 180–240 mg/m^2 per dose given twice a day (total daily dose 360–480 mg/m^2)	Liquid: 10 mg/ml	6 ml	9 ml	–	–	–	–
		Tablet: 60 mg	1	1½	2	2½	3	–
Non-nucleoside reverse transcriptase Inhibitors (NNRTIs)								
Efavirenz	15 mg/kg per day once a day	Tablet: 200 mg	Insufficient data on dosing for children < 3 years or weighing < 10 kg		1 daily	1.5 daily	1.5 daily	2 daily

Higher doses of LPV/RTV may be required when co-administered with enzyme-inducing drugs such as nevirapine, efavirenz, fosamprenavir and rifampicin.

Drug	Dosage	Form	Dose according to surface area or body weight (morning and evening) 3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
Nevirapine	160–200 mg/m² to maximum of 200 mg twice a day	Liquid: 10 mg/ml	5 ml	8 ml	10 ml	–	–	–
		Tablet: 50 mg	1	1½	2	2½	3	
		Tablet: 200 mg	–	–	–	½	1 & ½	1

Divided into unequal doses, give one dose in the morning and the other in the evening.

Drug	Dosage	Form	Dose according to surface area or body weight (morning and evening) 3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg	25–34.9 kg
Protease inhibitors								
Lopinavir/ ritonavir (LPV/RTV)	230–350 mg/m² twice a day	Liquid: (LPV 80 mg + RTV 20 mg)/ml	1 or 1.5 ml	1.5 ml	2 ml	2.5 ml	3 ml	–
		Paediatric tablet: LPV 100 mg/RTV 25 mg	–	–	2	2	2	3
		Adult tablet: LPV 200 mg/RTV 50 mg	–	–	1	1	1	1½

Higher doses of LPV/RTV may be required when co-administered with enzyme-inducing drugs such as nevirapine, efavirenz, fosamprenavir and rifampicin.

Index of Contents

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