

*Tanta University
Faculty of Medicine
Pediatric Department*



PEDIATRICS

For medical students

17th Edition
2021-2022



*By Staff Members of
Tanta Pediatric Department*



VISION

"PROVIDING HIGH QUALITY HEALTH CARE FOR CHILDREN AND THEIR FAMILIES IN OUR COMMUNITY- REGARDLESS OF THE ABILITY TO PAY- THROUGH THE STAFF OF ACADEMIC PROFESSORS, PROFESSIONAL NURSES AND TRAINED RESIDENTS USING THE AVAILABLE RESOURCES TO HELP DIAGNOSE, TREAT AND PREVENT PEDIATRIC ILLNESS CONTINUING TO BE AN EDUCATIONAL HOSPITAL TO TRAIN NEW SPECIALISTS AND A RESEARCH CENTER FOR PEDIATRIC HEALTH CARE NEEDS IN OUR COMMUNITY".

DEPARTMENT OF PEDIATRICS

Tanta University

MISSION

- **Improving our educational role through continuous improvement of our programs for undergraduate students' education, post graduate residencies training and the staff research.**
- **Improve the quality and quantity of research in our hospital to serve the specific needs in our community.**
- **Providing the best medical care for our community children through hospital departments, clinics, and emergency unit.**
- **Using the hospital resources to bring the upmost recent affordable medical equipment to improve services quality.**
- **Work with the concerned organizations and authorities to spread awareness of children health care in our community.**

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Chapter 1

Growth and Development

Objectives:

1. Define the difference between growth and development
2. Understand factors affecting growth and development.
3. Describe stages of human growth and development.
4. Enumerate anthropometric measures to assess growth.
5. Understand the major fields to assess development.

Contents:

1. **Factors influencing growth and development.**
2. **Stages of human growth and development:**
 - Prenatal
 - Postnatal
3. **Assessment of growth:**
 - Anthropometry
 - Teething
 - Skeletal (osseous) maturation
4. **Assessment of development:**
 - Growth motor
 - Fine motor
 - Social
 - Language

GROWTH AND DEVELOPMENT

Although the processes of growth and development are not separable, it is convenient, for teaching purposes to deal with them separately.

Growth is the natural increase of size of the body as a whole and of its separate parts. It results from Multiplication of cells and Increase in size of cells.

Development means maturation of organs and systems, acquisition of new skills and functions as well as ability of adaptation and assuming responsibilities.

Factors influencing growth and development

I- Premarital:

- Genetic Factors: If one parent has a dominant genetic disease or if 2 parents have recessive diseases.

II-Pre-conceptional:

- Maternal age
- Past obstetric history of still birth.

III- Prenatal:

- Fetal factors (Fetal diseases).
- Maternal factors (e.g. maternal infection-maternal medication-radiation).
- Obstetric diseases (Placental insufficiency).

IV- Perinatal Factors:

- Perinatal Hypoxia.
- Perinatal birth trauma.
- Immediate after delivery (Respiratory Distress-Jaundice-Cyanosis).

iv- Postnatal:

- Endocrinal factors: Thyroid hormone.
- Nutritional factors: Maternal and child nutrition during pregnancy and lactation.
- Environmental factors and socio-economic status.
- Chronic infections (e.g. tuberculosis) and debilitating diseases.
- Physical activity: bed-ridden children do not grow normally.

Stages of human growth and development

I- Prenatal:

- **Embryonic stage:** first 12 weeks of gestation (1st trimester). It is the period of organogenesis.
- **Fetal stage:** from 12th to 40th week of gestation. It is a period of rapid growth and development.
- **Perinatal:** From 28th week of fetal life to 7th day after delivery.

II- Postnatal:

1- Neonatal period (First 4 weeks after birth):.

It is the most critical period during which the newborn adapts to extra-uterine environment. It is mostly affected by:

- Prematurity
- Birth trauma
- Congenital anomalies
- Cross infections

2- Infancy (From 1-12 month; up to 2 years by some authors):

It is the period of most rapid physical growth and mental development. It is mostly affected by:

- Infectious diseases (immunizations are given during this period).
- Nutritional disorders.

3- Toddlerhood (From 1-3 years. It is the period of weaning):

The curious child is exploring what around him. It is mostly affected by:

- Nutritional disorders
- Infections

- Accidents (getting upstairs, pulling heavy objects above head level)

4- Early childhood (Preschool age 3-6 years):

It is the period of exploring the outside world and starts learning. Child is thus exposed to:

- Accidents and household poisons (insecticides, potash, etc.)
- Nutritional disorders
- Infections

5- Late Childhood (School age 6-12 years):

The School child starts studying and having exams. These children are mostly exposed to:

- Accidents and infections
- Cardiac diseases (e.g. rheumatic fever and bacterial endocarditis)
- Malignancies (leukemia, lymphoma, etc.)
- Psychological and emotional problems.

6- Adolescence (12-20 years):

It is the period of passage from childhood to puberty and adulthood. The timing of start and the velocity of pubertal changes are highly variable from person to person. It includes:

- Early adolescence: 12-14 years old
- Middle adolescence: 15-16 years old
- Late adolescence: 17-20 years old

The adolescent is subjected to tremendous physical growth and maturation exposing him/her to:

- Psychological and behavioural problems.
- Acne, and sex hormones-related problems.
- Rheumatic heart diseases, diabetes mellitus, malignancies.
- accidents.

Assessment Of Growth

Physical Growth in pediatrics can be assessed through:

- I. Anthropometry.
- II. Dental age.
- III. Bone age.

How can you assess anthropometric measures?

- Get an accurate body measurement e.g. weight, height, head circumference, etc.
- Compare this measurement with growth standards obtained from normal individuals of same age, sex, and community. This can be done by one of two methods:
 - I- Comparison of this single measurement with average for age and sex
 - II- Plot this measurement on percentile growth charts.

I. Anthropometry

1- Weight:

- Average weight at birth is 3 - 3.5 kg.
- There is an initial weight loss of 5-10 % during the first 3 to 4 days of life. The loss is usually regained by the 7th –10th day of life.
- Daily weight gain during infancy:
 - 20-30 g / day during the first 3- 4 months then
 - 15-20 g / day for the rest of the first year.
- In other words, *during infancy*, weight increases as follows:
 - 750 g (3/4 kg) / month for the first 4 months (wt = 6 kg at 4 month)
 - 500 g (1/2 kg) / month for the second 4 months (wt = 8 kg at 8 month)
 - 250 g (1/4 kg) / month for the third 4 months (wt = 9 kg at 12 month)
- During early childhood (from 2-6 years):
 - Weight in kg = (Age in years x 2) + 8
- During late childhood (from 7-12 years):
 - Weight in kg = $\frac{(\text{Age in years} \times 7) - 5}{2}$

2



2- Length / Height:



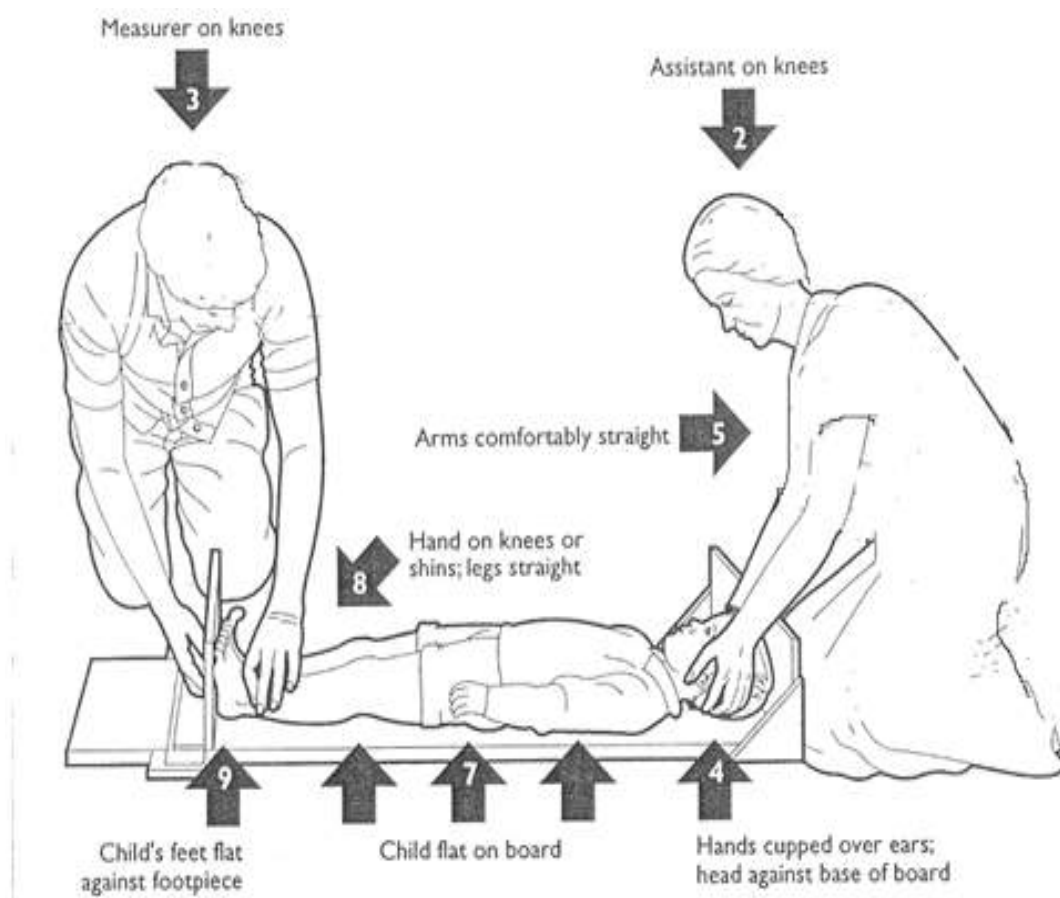
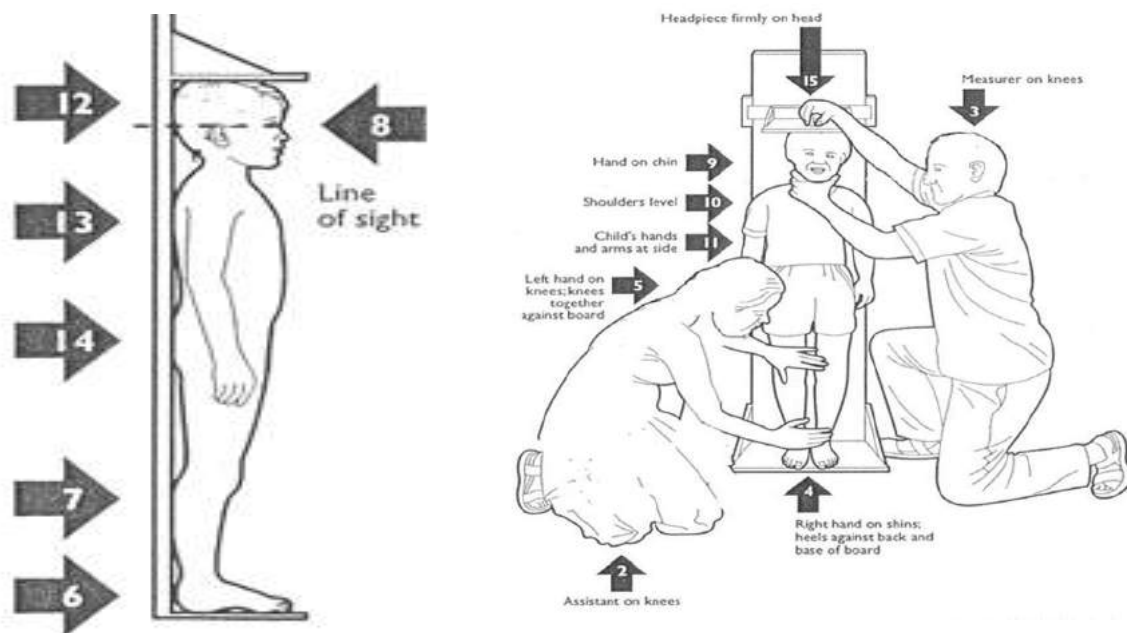
Length (recumbent supine length): is taken from infants and children less than 2 years old.

- Birth length: 50 cm
- First 3 months: increases 3 cm / month (length at 3 months = 59 cm)
- Second 3 months: increases 2 cm / month (length at 6 months = 65 cm)
- From 7- 12 months: increases 1.5 cm / month (length at 12 months = 75cm)
- From 1- 2 years: increases 0.5-1 cm / month (length at 2 years = 87cm)

Height (standing): is measured from children more than 2 years old.

After 2 years use the following formula to calculate height:

- Height in cm = (Age in years x 5) + 80
- Height at 4 years = Birth length X 2
- Height at 12 years = Birth length X 3



3- Body Proportions:

- Upper segment / lower segment ratio (U / L ratio) or crown to symphysis/symphysis to heel, reflects maturation of linear growth.
- In cretinism, children are short and have an infantile U / L segment ratio.

Age	Upper / lower segment ratio (U / L)
Birth	1.7: 1
3 years	1.33: 1
5 years	1.25: 1
Puberty	1: 1

4- Head Circumference:

The size of the skull depends on the growth of the brain. If the brain does not grow adequately, the skull will be small (microcephaly).

To measure the skull the tape is applied firmly over the glabella and supraorbital ridges anteriorly and posteriorly to the posterior occipital protuberance (passing through the widest possible circumference).



Rate of growth of head:

- **During 1st year (average):**
 - First 3 months: 2 cm / month
 - Next 9 months: 0.5 cm / month
- **Rest of life:**
 - From the end of 1st year to adulthood head circumference increases only 10 cm.

Age	Head Circumference
Birth	35 cm
3 months	41 cm
6 months	43 cm
9 months	44 cm
1year	45 cm
5 years	50 cm
12 years	53 cm
Adults	55 cm

- **Anterior fontanel:**
 - At birth 2.5 X 2.5 cm, closes between 6 and 18 months.
- **Posterior fontanel:**
 - At Birth posterior fontanel is nearly closed. It may close during the 1st 3 months after birth.

5- Chest Circumference:

Chest is usually measured at the nipple line, with the subject sitting, in the midway between inspiration and expiration.

- At birth the head circumference is 2 cm larger than chest circumference.
- Between the age of 1 and 2 years both are equal.

- After 2 years the chest is larger than the head.

6- Mid-arm Circumference:

Measured in the non-dominant arm, midway between the acromial and olecranon processes.

- Normally it is between 13.5 and 14.5 cm in children 1-5 years old.
- Those below 12.5 cm are overtly malnourished.
- Those between 12.5 and 13.5 cm have border line malnutrition.



7- Body Mass Index (BMI):

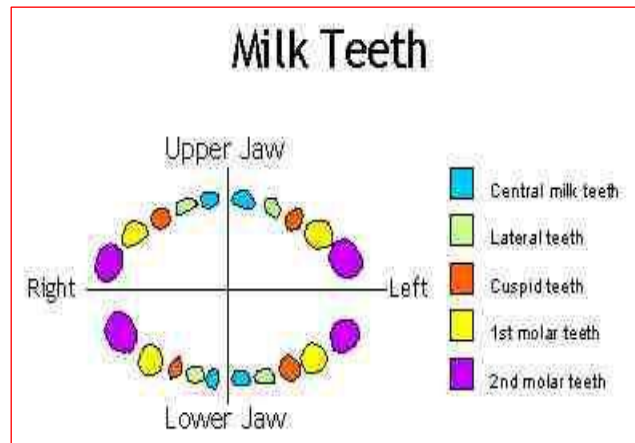
- $BMI = \frac{\text{Weight (in kg)}}{\text{Height}^2 \text{ (in meter)}}$

Weight Status Category	Percentile Range of BMI for age
Underweight	< 5th percentile
Normal or Healthy Weight	5th percentile to < 85th percentile
Overweight	85th to < 95th percentile
Obese	95th percentile or greater

The result should be plotted against standard percentile charts for BMI in different ages (see latter).

II. TEETHING

Eruption of teeth follows a special pattern, and its retardation may indicate retardation in osseous development.



Deciduous (milk) Teeth (20 teeth)

Lower central incisors	5-7 months (2 teeth) at 6m
Upper central incisors	6-8 months (4 teeth) at 7m
Upper lateral incisors	7-10months (6 teeth) at 8m
Lower lateral incisors	8-11months (8 teeth) at 9m
First molars (4 new teeth)	12months (12 teeth at 1 year)
Canines (4 new teeth)	18months (16 teeth at 1.5 years)
Second molars (4 new teeth)	24months (20 teeth at 2 year)

Permanent teeth (28-32 teeth)

First molar (4 new teeth)	6-7 years
Central incisors (changed 4 teeth)	7-8 years
Lateral incisors (changed 4 teeth)	8-9 years
Canines (changed 4 teeth)	9-10 years
First premolars (changed 4 teeth)	10-11 years
Second premolars (changed 4 teeth)	11-12 years
Second molars (4 new teeth)	12-13 years
Third molars (4 new teeth)	17-25 years (32 teeth at adulthood)

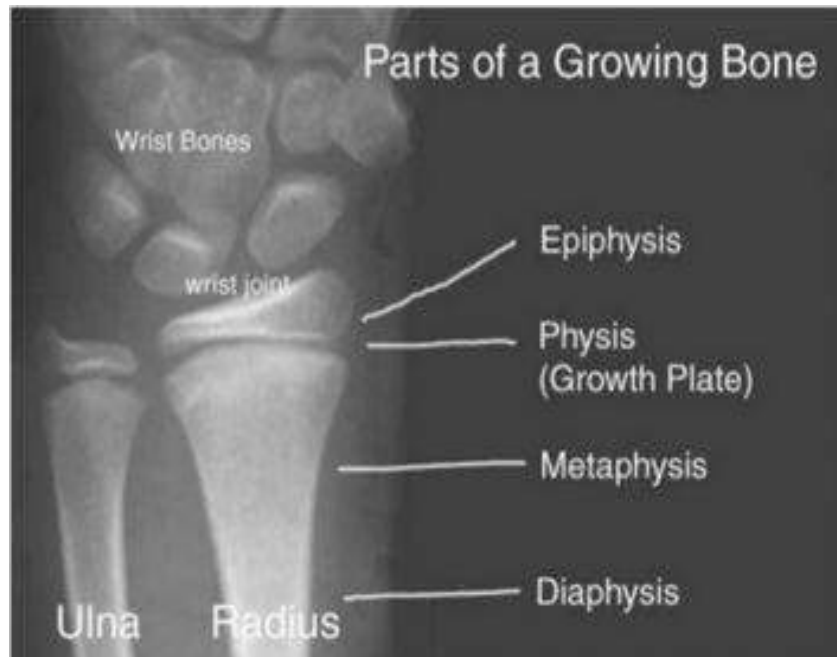
III- Skeletal (osseous) maturation

Bone age, determined radiographically, is the best index for assessment of general growth.

The following data are usually assessed:

- Number and size of epiphyseal centers.
- Size, shape, density and sharpness of outline of the ends of bones.
- Distance separating epiphysis and metaphysis or the degree of fusion between these two elements.

An X-ray of hand and wrist is useful at all ages of childhood, while useful information can also be derived from an X-ray of the lower limb in early infancy.



This can be determined by comparing the radiograph of the child bones with standard atlas of bone maturation radiographs of different ages.

Most important ossification centers:

1- Ossification centers usually present *at birth* in full term infants:

Remember this sentence:

Full Term Infant Has These Centers:

- Distal end of Femur appears at 8th month of fetal life.
- Proximal end of Tibia appears at 9th month of fetal life.
- Calcaneus appears at 5th month of fetal life.
- Talus appears at 7th month of fetal life.
- Cuboid appears at 9th month of fetal life.
- Head of Humerus appears at 7th month of fetal life.

2-Carpal centers are not usually present at birth, but the first one appears about 6 months of age.

3- Two carpal centers are present at one year of age.

4- One additional carpal center appears each year, so that 7 are present at 6 years of age.
(Roughly between 2-6 years bone age = number of carpal centers -1)

5- Distal radial epiphysis is demonstrable radiologically by the first year of life.

6- Metacarpal and phalangeal epiphyseal centers are demonstrable radiologically in 3rd year.

7- Distal ulnar epiphysis appears

- In most girls between 6-8 years.
- In most boys between 7-10 years.

Ossification Centers in Full term Infant:

Assessment of development

- Development is a continuous process from conception to maturity.
- The sequence of development is similar in all children, but its rate varies from child to child.
- The direction of development is cephalo-caudal, i.e. the infant controls his head before he can sit, and crawls before he can walk.
- The developmental process reflects the maturation of the brain and nervous system.
- The newborn cannot do any voluntary activities; all his behavior is reflex in nature.
- As maturation proceeds, this reflex activity is replaced by specific individual responses.

Development is assessed in 4 major fields (see table):

1. **Gross motor:** e.g. head control, sitting, standing, etc.
2. **Fine motor:** e.g. coordination of hands and eyes, using fingers, etc.
3. **Social:** i.e. social reaction of child with his surroundings and relatives.
4. **Language:** all visible and audible forms of communications

Milestones in the first 6 years of life:

Age (mo)	Gross Motor	Fine Motor	Social	Language
1 mo	Prone: Raises up head momentarily,	Primitive Grasp, rooting present	Palmar Moro, still	Spontaneous Smile, face regards alerts to sound
2 mo	Prone: raises chin off couch 45° (sustained)			Reactive smile
3 mo	Supports head & chest on forearms	Open hands spontaneously, Active Palmar Grasp	Appropriate Social smile	Coos, laugh
4 mo	Prone: raises his chest supported on his wrists	Grasps hands together		
5 mo	Supine: rolls from supine to prone position	Reaches to objects & brings to mouth	Looking around, staring	Laughs loudly
6 mo	Sits supported (momentarily)	Transfers objects between hands	Recognizes mother, Shows like/dislike	Babbles with M speech
7 mo	Sits unsupported	Crude radial grasp	Recognizes strangers	
8 mo	Rolls over from prone to supine position			Mono syllable voices (Ma)
9 mo	Crawling on his abdomen Pull to stand	Assisted Pincer Grasp	Waves Bye Bye, plays pat a cake	Imitates sounds
10 mo	Creeps on hands and knees, Stands supported	Tries to retrieve dropped objects		Polysyllable (Mama) speech
11 mo	Stands unsupported	Unassisted Pincer grasp		
12 mo	Walks supported	Releases objects on command	Comes when called, wants and needs	2-4 specific meaningful words

Age	Gross Motor	Fine Motor	Social	Language
15 months	Walks unsupported		Follows commands,	4-5 words
18 mo (1.5 years)	Walks upstairs with assistance	Feeds from spoon, drinks with cup	Mimics actions of others,	At least 6 words (6-10) points to 4 body parts
24 mo (2 years)	Runs	Builds a tower of six blocks	Plays with others	2-3 word sentences, uses I and you, he, she
36 mo (3 years)	Walks downstairs Rides a tricycle, stands on one foot briefly	Draws circle, draws person 3 parts (without neck)	Help in dressing, puts on a shirt	Counts 3 objects, knows 3 colors, all body parts, knows name, age ,sex
4 years		Copies squares and rectangles. draws person 4 parts (with neck)		Counts 4 objects correlated. Identifies some numbers and letters
5 years	Hops on one foot, pedaling, swimming	Dresses without assistance, draws triangles	Full bladder and bowel control	Identifies prepositions and situations, intelligent coherent speech,
6 years	Skips (jumps over a rope) or a distance	Writes first name, some words	Ties shoes, plays competitive games	Counts to 10, (5+5) and multiply (5X5), asks meanings

Practice Questions

(Choose one correct answer)

- 1- The average weight of full-term newborn infant at birth is:
 - a) 2500-3000 gms.
 - b) 3000-3500 gms.
 - c) 3500-4000 gms.
 - d) 2000- 3500 gms.
- 2- During infancy, body weight increases during the first 4 months as follows:
 - a) 500 gm/ month.
 - b) 400 gm/ month.
 - c) 750 gm/ month.
 - d) 600 gm/ month.
- 3- The height of the child at 4 years of age equals:
 - a) birth weight X 2.
 - b) birth weight X 3.
 - c) birth weight X 4.
 - d) birth weight X 2.5.
- 4- In healthy infants, the active palmar grasp appears at the age of:
 - a) 1st mo.
 - b) 3rd mo.
 - c) 6th mo.
 - d) 4- 8th mo.
- 5- Development means the following EXCEPT:
 - a) maturation of organs and systems.
 - b) multiplication of cells.
 - c) acquisition of new skills and functions.
 - d) ability of adaptation and assuming responsibilities.



Chapter 2

Developmental and Behavioral Disorders

Objectives:

1. Recognize normal social and behavioral development at different ages.
2. Enumerate factors Affecting development and behavior.
3. Describe some common developmental and behavioral disorders
4. Discuss the clinical presentations and the special nature of each developmental and behavioral disorder
5. Formulate a management plan for each developmental and behavioral disorder

Contents:

1. Normal social and behavioral development at different ages.
2. Factors Affecting development and behavior.
3. Some common developmental and behavioral disorders.

Normal Social and Behavioral Development at Different Ages

- **At Birth:**

- Primitive Reflexes as Moro (Startling reflex, rooting reflex, suckling and swallowing reflex).

- **At One month:**

- Tight palmar grasp.
- Alerts to sound.
- Regards face {eye-eye conversation}.
- Involuntary Smiles and cries while asleep.

- **At 2 months:**

- Holds and controls head in midline, to 45° from prone.
- Social reactive smile around 40 days
- Coos.
- Recognizes parents.

- **At 3 months:**

- Supports on forearms when prone and starts looking around.
- Holds head steady.
- Hands open at rest. (Less grasp)

- **At 4 months:**

- Rolls front to back, then back to front.
- Supports on wrists when prone.
- Grasps hands together (as supporting himself).

- **At 5 months:**

- Laughs loudly.
- Enjoys looking around(wondering amazing ,starring)

- **At 6 months:**

- Sits well unsupported.
- Transfers objects with Selective grasp.
- Recognizes strangers.
- No head lag.

- **At 9 months:**

- Says Pappa, Mamma, nanna, dadda: nonspecific
- Waves Bye-bye.
- Feeds self by hands and finger, starting some kind of independence.
- Creeps, crawls, pulls to stand.

- **At 12 months:**

- 2-4 words, papa, mama/dada specific.
- Helps turn page of book.
- Indicates wants and needs.

- **At 15 months:**

- 3-5 words.
- Follows commands.
- Walks independently.
- Drinks from cup.
- Imitates others activities.

- **At 18 months:**

- 5-10 words.
- Points to 4 body parts.
- Walks up steps erect and alone.
- Feeds self with spoon, fork or hands.
- Runs.

- **At 2 years:**

- Combines 2 words.
- Uses “I”, “you” and “he/she” appropriately.

- **At 3 years**

- Gives full name, age and sex.
- Names 3 colors, all body parts.
- Walks upstairs and downstairs, and can walk with alternating feet.
- Puts on shirt
- Copies circle
- Draws person with 3 parts.

- **At 4 years:**

- Counts 4 objects correlated.
- Identifies some numbers and letters.
- Copies squares and rectangles.
- Draw person with 4 parts.

- **At 5 years:**

- Hops on one foot, pedaling and swimming.
- Dresses with little or no assistance.

- Understands prepositions and situations.
- Full intelligent coherent speech and Full bladder and bowel control. (the best of childhood era)

- **At 6 years**

- Write first name and some words.
- Counts to 10, (5+5) and multiply 5x5.
- Asks meaning of words.
- Skips (jump over a rope).
- Ties shoes.
- Plays competitive games.

Factors affecting development and behavior:

1. Genetic and Pre-natal: as in ADHD, and Autism.
2. Peri-natal: ADHD.
3. Post-natal and Environmental may induce and or exaggerate the behavioral problems e.g. infectious agents, irradiations, food additives, junk and fast foods (bakeries are exceptionals) and heavy metal exposure.
4. Mass media effects.
5. Death or Traveling of one of parents or both, grandparents or beloved person.
6. Stressors and multiple or sustained psychic traumas as wars, disasters, excessive competitions and exams, child abuse and trafficking.
7. Care-givers influences as in schools& nurseries
8. Drugs specially abused ones, mercury of vaccines.
9. Developmental or maturational defects.
10. Lack or complete absence of family or /and society support.
11. New baby in the family.
12. Idiopathic.

Some Common Developmental and Behavioral Disorders

I. Breath Holding Spells (infantile syncope):

- Involuntary.
- initiated by a noxious stimulus,
- associated with crying,
- consciousness and posture may be lost
- occurs from infancy through age 5,
- Two types: pallid or cyanotic,
- may be associated with convulsive movements

➤ **Etiology:**

- It is due to immaturity or developmental delay of the respiratory center causing it to stop working and hence stoppage of breathing with prolonged and or repetitive expirations during crying. With arrest of breathing, severe hypoxia and/or hypercarbia reach to the high levels needed for the respiratory center to regain work, so a vicious circle commences.

➤ **Management**

EAT the guardians: Explanation, Assurance and Training of the guardians as parents and grand-parents, relatives, neighbors (if needed) as the attacks will stop by age of 5 years.

Some cases may need some investigations as Echocardiography or even CT or MRI to assure the family.

II. Enuresis and Encopresis

➤ Definitions:

- **Enuresis**: Uncontrolled micturition by age of 5.

➤ Types of enureses:

- Primary or secondary,
- Nocturnal, diurnal or mixed

- **Encopresis**: uncontrolled defecation beyond age of 4 years.

➤ Types of encopresis:

- Retentive with overflow, or non-retentive.
- Primary or secondary.

➤ Etiology:

- Maturation or developmental defect.
- A sleep disorder.
- Genetic.
- Psychogenic stressors.
- Organic: as spina bifida, UTI, Constipation....etc
- Hormonal as in ADH deficiency (diabetes insipidus), diabetes mellitus.
- Lack of parental toilet training.
- Severe pelvic trauma
- Child abuse.
- Compulsive water drinking.
- Physical Stressors and illnesses.
- Bad sanitary conditions

➤ **Management:**

- Full history taking and thorough physical examination especially abdomen, pelvis, spine, rectum, blood pressure, and urine analysis should be performed.
- Parents must avoid corporal punishment which causes psychic insult and aggravates the problem (with regards to organic causes), instead try encouragement.
- Use least possible drugs, tools as Enuresis Alarm Devices (EADs) and instructions.

III. Attention-deficit/hyperactivity disorders(ADHD)

➤ **Triad of ADHD:**

- Inattention
- Hyperactivity
- Impulsivity

➤ **2nd Triad of ADHD:** each of above is:

- Pervasive
- Progressive
- Persistent for more than 6 months and occurs in the first decade of life.

➤ **According to DSM-MD IV-TR** (Diagnostic and Statistical Manual of Mental Disorders-fourth edition –Text Revision) is characterized by:

I) INATTENTION DOMAIN OR SIGNS:

- Do not complete assignments.
- Disruptive.
- Often “off task”.
- Impulsive behavior.
- Over curious without satisfaction!
- Finally, it is a “complete mental chaos”!!

- Characteristics Of ADHD

II) HYPERACTIVITY DOMAIN or SIGNS:

- Hyperactive (and Destructive)
- Fidgety (enemy of the chairs)
- Runs around the room (like a bee)
- Overexcited (for nothing)
- Blurts out answers (bizarre)
- Interferes with other's activities
- Struggle with school and rejection by their peers (colleagues).

➤ Some Adaptive Behavior Scales for ADHD:

- Must be done by a licensed mental health professional for medico-legal and ethical issues.
- American Academy of Pediatric Neuropsychiatry (**AAPNP**) Adaptive Behavior Scales
- Vineland Adaptive Behavior Scales(**VABS**)
- Scales of Independent Behavior
- Child Behavior Rating Scale(**CBRS**)

➤ Complications or co-morbidities of ADHD:

1. School failure: 33% held back a year.
2. Poor social skills: 90%.
3. Sleep problems: 50%.
4. Fine motor delay: 90%
5. Accidental injury to self and others: 60%
6. Additional psychiatric diagnosis: 50%.
7. Learning disabilities: 30%.

➤ **Intervention strategy for ADHD:**

- Teamwork is essential! It is not one-man show!! Collaboration by
Parents, general educators, special educators, counselor, psychologist,
and the physician will bring the greatest results.
- Medication: Ritalin or other.
- Dietary changes:
 - 1-More fish & tuna and sea foods,
 - 2-No more sugars and sweets, chocolate,
 - 3-No more junk and fast foods.
- Behavior management.
- Structured teaching.
 - Academic assignments must be clear and manageable.
 - Make sure that the student understands what to do.
 - Smaller, less complex tasks may be required followed by reinforcement.
 - Place students near teacher or in front row, maintain eye contact.
 - Provide work area without distractions for individual work.
 - Require unused materials be stored away
 - Provide verbal and visual directions.
 - Warn about and explain transitions between activities or places.
 - Have a few simple rules and review these rules
 - Reward appropriate behavior, withhold or reinforcement for inappropriate behavior, rank your child higher than expected.
 - Use charts, points, stickers, etc, to make reinforcement visible.
 - Finally, programs of intervention should be affordable for the child and his family.

IV. Autistic Spectrum Disorders (ASD) (Childhood Autism)

- Children who are diagnosed as autistic show problems in three main areas:
- Social interaction
- Communication, and
- Stereotyped behavior problems
- Autism is more common in males than females occurs in about 4-5 out of 10,000 live births(1/2000)
- Autism is explained by altered brain neuro-chemistry resulting in disturbed information processing and weak retrieval memory.
- May resemble a computer infected by a virus deleting most new data and preventing saving them!
- May be exaggerated by deficiency of trace elements specially zinc and selenium.

- **Manifestations of Children with Autism**

- Often show a severe lack of language development.
- Most communicate in a limited, usually showing various abnormal speech and language characteristics.
- A minority (severe cases) may not communicate at all.
- Usually show atypical characteristics in the production, form, and content of their speech. Speech sounds may have inappropriate volume, pitch, rate, rhythm, or tone, be monotonous, have a melody like quality, or be high pitched
- Body language is atypical
- They may not make or sustain eye contact, vary their facial features, or change their body posture when conversing.
- They show little or no emotions.
- Exclude much of the rest of the social world.
- Lack of social reciprocity.

- Do not interact with others with typical emotionalism.
- Some display stereotyped movements or behaviors such as hand flicking, spinning, or complex body movements, produced for escape or self-mutilation. These behaviors are enhanced by excitement, anxiety, boredom and social demands.
- **Investigations**
 1. EEG
 2. Hearing acuity.
 3. MRI
 4. I.Q.
 5. Early diagnosis using some objective measures as Childhood Autism Rating Scale (CARS)
- **Treatment**

NO COMPLETE CURE!! But doctors, therapists, teachers and parents can help.

 - ✓ Behavioral and educational therapy programs like: Treatment and Education of Autistic Children (TEACH) are very helpful. Doctors must be frank and optimistic using simple language and must not leaving the family desperate behind them.
 - ✓ Neuroleptic agents as Haloperidol, Risperidone and some Antidepressants may help with regards to their side effects.
 - ✓ Hyper-baric Oxygen

V.Other Behavioral disorders:

1. Sleep Disorders(BEARS):
 - B: Bedtime Problems.
 - E: Excessive Daytime Sleepiness.
 - A: Awakening During the Night.
 - R: Regularity and Duration of Sleep.
 - S: Snoring
2. Anxiety disorders.

3. Mood disorders as major depression.
4. Childhood psychosis as childhood schizophrenia and Asperger's syndrome.
5. Habit disorders as tics, thumb sucking and teeth grinding.
6. Gender identity disorder (GIDs).
7. Disruptive disorders as aggression and conduct disorders.
8. School phobias (the great imitators).

Practice Questions

(Choose one correct answer)

- 1- Autistic-spectrum disorders (ASD) are caused by interaction of:
 - a) genetic and environmental factors.
 - b) infectious and developmental factors.
 - c) idiopathic factors.
 - d) all of the above.
- 2- Nocturnal enuresis is caused by:
 - a) developmental and organic factors.
 - b) behavioral disturbances.
 - c) nightmares and terrors.
 - d) all of the above.
- 3- Breath Holding Attacks are treated by:
 - a) analeptic drugs and brain stimulants.
 - b) bronchodilators and sedative drugs.
 - c) explanation, assurance and training of the family.
 - d) tonics and calcium supplementation.
- 4- Children with ADHD could be improved by:
 - a) sweetened and junk foods.
 - b) fishes, tuna and sea foods.
 - c) hypnotic and sedative drugs.
 - d) anticonvulsant drugs.
- 5- Causes of behavioural disturbances in children are:
 - a) genetic and familial factors.
 - b) environmental pollution and junk foods.
 - c) mass media and school effects.
 - d) all of the above.



Chapter 3

Preventive Pediatrics

Objectives:

1. Classify different types of Prevention.
2. Enumerate preventable disorders in pediatrics.
3. Understand the process of Immunoprophylaxis and discuss its different types.
4. Formulate the obligatory immunization schedule for children in Egypt.
5. Discuss types, dose, complications, and contraindications of different vaccines.
6. List the special noncompulsory vaccinations.
7. Illustrate the isolation periods for different infectious diseases

Contents:

1. Classification of Prevention
2. Immunoprophylaxis.

General Lines of Prevention

Classification of prevention:

I. Primary prevention: aims at preventing the occurrence of the disease e.g.:

- a) Promotion of general health by adequate nutrition, hygiene etc....
- b) Prevention of specific diseases by immunization and antibiotic prophylaxis.

II. Secondary prevention: aims at early detection of the disease and stopping or reversing its progress.

- c) Neonatal screening for hypothyroidism.
- d) Long-acting penicillin for rheumatic fever.

III. Tertiary prevention: to stop the development of complications in a previously recognized disease and prevention of disability in children with chronic condition i.e. rehabilitation.

- a) Amoxicillin before and after operations in rheumatic valvular heart disease
- b) Physiotherapy in cerebral palsy.

Preventive pediatrics includes:

- 1- Prevention of genetic and congenital diseases: prenatal counseling, prenatal detection of congenital anomalies and intrauterine infection.
- 2- Prevention of endocrine and metabolic disorders e.g. neonatal screening tests for hypothyroidism and phenylketonuria.
- 3- Prevention of nutritional disorders e.g. early supplementation of iron and vitamin D to prevent iron deficiency and rickets.
- 4- Prevention of handicap e.g. antenatal and intrapartum care to prevent medical and physical handicaps e.g. cerebral palsy, mental retardation, early detection of congenital dislocated hip and conductive deafness.

- 5- Prevention of accidents.
- 6- Prevention of psychological and emotional disorders.
- 7- Prevention of infectious diseases through 4 steps:
- 8- Isolation of infected person from those at risk.
- 9- Eradication of vectors that transmit the infection.
- 10- Elimination of infective organisms.
- 11- Increasing the resistance of the host by immunoprophylaxis and antimicrobial prophylaxis.

IMMUNOPROPHYLAXIS

Types of immunity:

I. Passive immunity:

a) Natural (transplacental):

1. Maternal IgG antibodies cross the placenta mainly in later half of last trimester.
2. Preterm baby is not fully protected.
3. IgG protects infants against diphtheria, poliomyelitis, measles, Mumps.
4. Newborn is not protected against pertussis (Its big Ig M cannot cross the placenta).
5. Maternal antibodies disappear from infant's circulation by the 3rd –6th months of age.

b) **Acquired** by administration of antibodies, e.g. antitetanic horse serum or antitoxins e.g. antitoxin.

II. Active immunity:

a) **Natural:** by acquiring the infection either in its subclinical or clinical forms.

It may be life-long as in measles, German measles and chicken pox or transient as in common cold.

b) **Acquired:** by administration of vaccines. Which include dead or live organisms or their antigens or toxoids.

(A) Active immunization (Vaccination)

I - Routine Vaccinations

1- BCG

Type of vaccine:

The immunizing microorganism is a live attenuated strain of *Mycobacterium bovis*.

Preparation:

The vaccine should be stored in the dark and administered immediately following reconstitution.

- The dose is 0.05 ml for neonates and 0.1 for infants; it should be administered intradermally at the insertion of deltoid muscle in the left arm.
- Following successful immunization, a small papule forms at the inoculation site, gradually enlarges, crusts, and disappears in 8-12 wk.



Immunization schedule:

Routine vaccination in Egypt within the 1st month after birth.

Adverse reactions:

1. Cutaneous ulceration,
2. Localized lymphadenopathy, and
3. Less commonly, subcutaneous abscess formation, osteomyelitis, dissemination, and death.

4. A major theoretical disadvantage of BCG is the production of sensitivity to tuberculin.

Contraindications:

- 1 - Skin infections or burns.
- 2- Cellular or combined immunodeficiencies, congenital or acquired.

2- POLIOVIRUS VACCINES

Types:

- 1 - Inactivated polio vaccine (IPV) of Salk.
- 2 - Oral Polio vaccine (OPV) of Sabin.

The vaccines are trivalent, containing a mixture of the three strains of poliovirus.

Preparation:

- 1- The viruses are grown in tissue cultures of monkey kidney cells. The viruses are formalin-inactivated in IPV.
- 2- The viruses used in ORV are Sabin live-attenuated poliovirus strains. The virus is propagated in vitro in sub -cultured monkey kidney cells. Attenuation of the original wild strains is determined by multiple mutations in the genome. The vaccine should be stored in the refrigerator at 4 to 10 0C.

Table (1): Comparison of OPV and IPV

	OPV	IPV
Route of administration	Oral	IM
Protection: - Against disease	98%	98%
- Against enteral infection	+	-
Virus fecal excretion:	+	-
Secondary spread:	+	-
Immunity:		
- Mucosal	+	-
- Systemic	+	+

- Life - long protection	90%	85%
Vaccine - associated poliomyelitis	+	-
Compatibility with other vaccines	+	-
Contraindications:		
- Immunodeficient states	+	-
- Contacts of immunodeficients	+	-
- Adults	+	-
Practical consideration:		
-Cheap	+	-
-Easy administration	+	-



Immunization Schedules:

1-Routine Immunization:

- The primary immunization with trivalent live oral poliovirus vaccine (TVOPV) is three doses (at 2, 4, and 6 months) with an 18 months and 4 to 6 year booster (table).
- An interval of at least 1.5 - 2 months between doses of OPV is required because intestinal carriage of vaccine virus may persist for up to 6 weeks with consequent viral interference.

2-Immunization in special situations (Endemic Areas):

- Frequent administration schedule: The first OPV dose is given at birth. The second dose is given at 6 weeks of age, followed by 2 additional doses 6 weeks apart.
- Combination of OPV and IPV schedule: This schedule is designed to induce an efficient mucosal immune response while avoiding OPV-associated disease.

Side Effects:

- Vaccine-associated poliomyelitis is the major drawback of OPV. The pathogenesis of these side effects is:
- Immunodeficient individuals, as the attenuated strain may invade their CNS.
- The attenuated OPV strains undergo important changes while multiplying in the gut, and neurovirulent mutants (reverts) occasionally arise.

Contraindication:

- OPV should not be given to individuals proven or suspected to be immunocompromised.
- OPV also should not be given to household contacts of immunocompromised individuals.
- Severe acute febrile illness.
- Gastroenteritis.

It is now felt that prematurity, mild cold and concurrent antimicrobial therapy are not reasons to delay immunization.

3- Diphtheria, tetanus, and pertussis

Types:

1. Diphtheria and tetanus toxoids and pertussis vaccine (DPT).
2. Diphtheria and tetanus toxoids for pediatric use (DT).
3. Diphtheria and tetanus toxoids for adult use (Td).



Preparations:

- Conventional pertussis vaccine up to the present time has consisted of chemically inactivated whole bacterial cells. Now available is acellular vaccine to minimize adverse reactions.
- Diphtheria and tetanus vaccines contain modified toxins of both organisms. The three vaccines used with adjuvant substance to retain the antigens at depot site and release them slowly, thus enhancing the response by prolonged contact and reduce the systemic effects observed with fluid antigens, which are rapidly absorbed.

Immunization Schedules:

- Immunization with DPT is usually started at 2 months of age; two additional doses are given at 2 months intervals. A 4th dose is given at 18 months of age, and 5th dose is given at the time of school entry. TD vaccine is recommended at 10-year intervals.

Adverse reactions:

- **Local reactions:** Mild local reactions (redness, tenderness, and swelling) are frequently seen in children within 12 to 24 hours following the injection.

▪ **Systemic:**

	Minor reactions	Major reactions
Fever	<40.5 ⁰ c	>40.5 ⁰ c
Crying	Transient	Persistent > 4hr
Irritable	Mild	Severe
Other	----	Shock-like state

- **Neurological reactions:** These rare reactions may occur within 3 days of DPT and include occasional convulsions and acute encephalopathy resulting in permanent brain damage or death.

Contraindications:

- Acute febrile illness.
- Neurologic illness.
- A severe reaction to a previous dose of DPT:
- Major systemic reactions.
- Neurological reactions.

4- **Hepatitis B vaccine**

Preparation:

- It's a recombinant vaccine composed of a subtype of HbsAg.
- It is prepared by inserting a plasmid containing the gene of HbsAg into yeast cells, which are cultured.
- Then the HbsAg is harvested by lysing these cells. So the vaccine consists of a purified, inactive subunit of virus.

Indications:

- 1) It is now obligatory in Egypt for all infants.

- 2) Newborns to hepatitis B mother should receive the vaccine along with hepatitis B immunoglobulin immediately at birth.
- 3) Staff and patients of hemodialysis.
- 4) Patients receiving frequent blood or blood component transfusion.
- 5) Household contact of chronic hepatitis B.

Immunization with hepatitis B vaccine is usually started at 2 months of age; two additional doses are given at 2-month intervals.

Dosage and administration:

The dose is 0.5 ml for each dose by IM injections at the thigh. In older children over 11 years, one ml of vaccine is injected IM in the deltoid muscle at 0, 1, 6 months.

Complication and side effects:

Only fever and pain at the injection site.

5- Measles, Mumps, and Rubella vaccine (MMR):

- It is a live attenuated vaccine, recommended at 12 months age.
- Mumps vaccine is one of the safest vaccines available, with almost no adverse effects or contraindications.
- The rubella vaccine was primarily developed to prevent cases of congenital rubella syndrome.



Adverse Reactions:

- Transient arthralgia, rarely arthritis, may occur in 1-2% of children.
- Contraindications to rubella vaccine are same as measles vaccine including immunocompromised patients and pregnant women.
- **Mild reactions:** Transient rashes and fever up to 39.40C occurring in a few infants at 6-11 days after immunization.
- **Major:** Encephalitis has been rarely reported after measles vaccine. Epidemiological data have not suggested any relation between measles vaccine and subacute sclerosing panencephalitis.

Contraindications:

- Severe febrile illness.
- Infants recently received immunoglobulins or blood.
- Infants with a history of anaphylactic hypersensitivity to neomycin or eggs.
- Immunocompromised infants.
- Pregnant woman.

6- Haemophilus influenzae B vaccine (Hib):

- It is a killed vaccine using capsular polysaccharide conjugated with a protein carrier.
- It is recommended to be given concurrently with DPT and OPV. Nowadays;
- It has been incorporated in the routine obligatory vaccination in Egypt, given along with DPT and hepatitis B vaccines in a combination called “Penta vaccine” at 2, 4, and 6 months.

Table (2): Recommended Immunization Schedule

Obligatory immunization schedule for children in Egypt from the age of 1 day till the age of 18 months

Age	Vaccine	Dose /Route
At birth	Oral polio vaccine(opv) of sabin	2 drops orally
	BCG	0.5ml intradermally
2months	Oral polio vaccine(opv) of sabin	2 drops orally
	Penta vaccine (Diphtheria- tetanus- pertussis- hepatitis B-haemophilus influenza)	0.5ml intramuscular
	Inactivated polio vaccine (IPV) of Salk.	0.5ml intramuscular
4 months	Oral polio vaccine(opv) of sabin	2 drops orally
	Penta vaccine (Diphtheria- tetanus- pertussis- hepatitis B-haemophilus influenza)	0.5ml intramuscular
	Inactivated polio vaccine (IPV) of Salk.	0.5ml intramuscular
6 months	Oral polio vaccine(opv) of sabin	2 drops orally
	Penta vaccine (Diphtheria- tetanus- pertussis- hepatitis B-haemophilus influenza)	0.5ml intramuscular
	Inactivated polio vaccine (IPV) of Salk.	0.5ml intramuscular
9months	Oral polio vaccine(opv) of sabin	2 drops orally
12months	Oral polio vaccine(opv) of sabin	2 drops orally
	Measles, Mumps, and Rubella vaccine (MMR)	0.5ml subcutaneous
18months	Oral polio vaccine(opv) of sabin	2 drops orally
	Diphtheria, Tetanus and Pertussis (DPT)	0.5ml intramuscular
	Measles, Mumps, and Rubella vaccine (MMR)	0.5ml subcutaneous

- **One capsule of vitamin A is given at the age of 9 months**
- **2 capsule of vitamin A is given at the age of 18 months**

II. Special Vaccinations

1- Influenza viral vaccines:

- Annual immunization against viral influenza disease should be given to children at high risk for infections of the lower respiratory tract.

2- Pneumococcal vaccine:

- A 23-valent pneumococcal polysaccharide vaccine has been recommended in high risk infants for infection at a time of DPT vaccine.

3- Meningococcal vaccine:

- A polysaccharide vaccine provides only short-lived protection (up to 3 years).
- Their use is limited to the control of epidemics, as well as to exposed contact as an adjunct with chemoprophylaxis.
- It is available as: monovalent A, bivalent A and B, and quadrivalent A,B,C, and W 135.

4- Typhoid vaccine:

- The indications of this vaccine are intimate exposure to a carrier or an outbreak of disease.
- Vaccinations are available as: a parental vaccine and an oral vaccine. Immunity lasts for 10 years.

5- Hepatitis A virus vaccine:

- It is a sterile suspension containing formaldehyde inactivated hepatitis A virus adsorbed into aluminium hydroxide.
- The pediatric dose is 0.5 ml, given IM in the deltoid.

- The course of immunization consists of 3 doses, the first administered at the selected date and the second one-month later.
- The booster dose is recommended after 6 months. This vaccine is indicated in subjects at risk of exposure to viral hepatitis A.

6- **Varicella Vaccine:**

- It is a live attenuated vaccine.
- It is given as MMR vaccine subcutaneously.
- The vaccine is recommended after the first year.
- It is safe and effective but an expensive one.

7- **Rota virus Vaccine:**

- It is a recent oral vaccine.
- It is given at the age of 6 weeks and the 2nd dose is given after one month.
- It is safe and effective vaccine for prevention of rotavirus induced diarrheal disorders.
- It is however an expensive vaccine.

(B) Passive Immunization

Passive immunity is the administration of antibodies from an immune subject to provide temporary protection against a microbial agent, poison, or cell.

Three types of preparations are used in passive immunization:

- **Standard human immune serum globulin (HISG)** e.g. ISG for prevention of Rubella during pregnancy.
- **Special human immune serum globulins** with a known antibody content for specific illness e.g. hepatitis B immune globulin (HBIG).
- **Animal serums and antitoxins** as Diphtheria antitoxin, tetanus antiserum.

Table 3: Preparations available for passive immunity

Product	Dose	Indications
A- Standard Human immune Serum Globulin:		
1. For Hepatitis A	0.02 ml/kg.	Household contact
2. For Measles	0.25 ml/kg. exposure	Given within 5 days after
3. For Rubella	20 ml.	Susceptible pregnant women, within 72 hr. after exposure.
B- Special Human immune Serum Globulin:		
1. Hepatitis B immune globulin (HBIG).	0.06ml/kg.	Given immediately after exposure
2. Varicella-zoster immune-globulin (VZIG).	2-4ml.	Use only in high-risk children.

Isolation Measures for Infectious Diseases:

Patients with contagious diseases should be isolated, not only to limit distribution of disease but also to protect them from secondary infection.

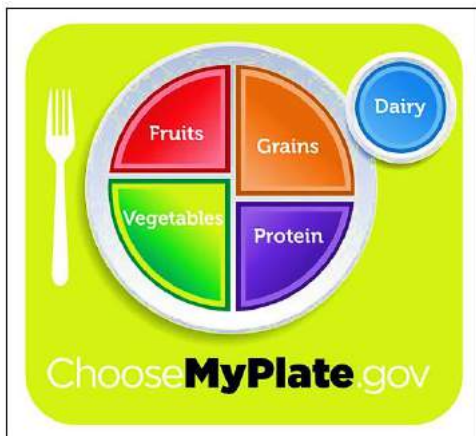
Table (4): Period of recommended isolation

Disease	Recommended Isolation
* Measles rash	From onset of catarrhal stage through 4 th day of
* Rubella	None, except pregnant woman should not be exposed
* Varicella	Until all lesions crusted; usually 5-6 days
* Mumps	Until swelling subsides
* Poliomyelitis	Enteric precautions
* Infective hepatitis	Enteric precautions

Practice Questions

(Choose one correct answer)

- 1- Which of the following are preventive measures for pediatric diseases :
 - a) Immunization.
 - b) antibiotic prophylaxis.
 - c) neonatal screening.
 - d) all of the above.
- 2- Which of the following are Live attenuated vaccines:
 - a) BCG.
 - b) Sabin vaccine.
 - c) measles vaccine.
 - d) all of the above.
- 3- All of the following are true about hepatitis B vaccine EXCEPT:
 - a) it is obligatory vaccine in Egypt.
 - b) it is given intramuscular.
 - c) usually started at 2 months of age.
 - d) the dose is 0.05ml IM.
- 4- Rota virus vaccine is:
 - a) given intramuscular.
 - b) given for school age children.
 - c) safe.
 - d) cheap.
- 5- To which one of the following groups would it be acceptable to give a live attenuated viral vaccine?
 - a) children under 8 years of age.
 - b) patients treated with steroids.
 - c) patients with leukemia.
 - d) pregnant mothers.



Chapter 4

Nutrition

Objectives:

1. Discuss nutritional requirements of infants and children
2. Understand types and techniques of infant feeding.
3. Describe feeding disorders in infants and children.
4. Understand weaning and sequence of food introduction.
5. Understand the major fields to assess development.
6. Classify types of malnutrition and nutritional deficiencies.

Contents:

1. Feeding of infants and children:

- Nutritional requirements of infants and children.
- Vitamins.
- Infant feeding.
- Breast feeding.
- Artificial feeding.
- Feeding of toddlers and children.
- Underfeeding.
- Overfeeding.
- Weaning.

2. Malnutrition:

- Kwashiorkor.
- Marasmus.
- Marasmic Kwashiorkor.
- Obesity.
- Vitamin deficiency & excess.
- Rickets.

Feeding Of Infants and Children

Nutritional requirements of infants and children:

1. Calories:

- In the first year of life 90-110 kcal/kg/day.
- In the second year 70 kcal/kg/day.
- At puberty about 50 kcal/kg/day are needed.

2. Water:

- In the first year the infant requires 120-150 ml/kg/day.
- In second year, 90-100 ml/kg/day.

3. Proteins:

- The child needs 2-3 g/kg/day proteins of high biological value to supply amino acids required for metabolic processes and growth.
- Proteins should provide about 15% of total caloric intake in balanced diet (1 g yields 4 kcal).

4. Fats:

- 30-35% of total energy intake should come from fats. (1 g. yields 9 kcal).
- Poly unsaturated fatty acids such as linoleic and linolenic acids are essential as they cannot be formed by the body, and they are important for skin health and brain development.

5. Carbohydrates:

- They should supply 50-55% of total calories (1 g. yields 4 kcal). They can be synthesized from fats or proteins.

6. Vitamins:

- They are essential to maintain a good health and many of them function as co-enzymes needed in different metabolic processes. (**Table 1**)

1. Minerals: (Table 1)

- They are as important as vitamins for growth and normal health.
- The main extracellular minerals are sodium and chloride, whereas the main intracellular minerals are potassium, magnesium and phosphorus.
- Calcium and phosphorus are the main minerals of the skeleton.

Vitamins/ Minerals	Daily Requirements	
	Infants	Children
A	1000 – 2000 U	1000 – 2000 U
B1	0.5 mg	0.5 mg
B2	0.5 mg	1 mg
B6	0.6 mg	0.6 mg
B7	5 mg	5 mg
FOLIC ACID	50 µg	50 µg
B12	0.5 µg	0.5 µg
Vitamin C	30 mg	50 mg
Vitamin D	400 – 800 U 1500 U for prematures	400 – 800 U
Vitamin E	5 mg	5 mg
Vitamin K	5 µg	15 µg
Calcium	400 – 500 mg	600 – 800 mg
Phosphorous	250 – 350 mg	800 – 900 mg
Iron	8 – 15 mg	8 – 15 mg
Zinc	5 mg	10 mg
Iodine	40 – 50 µg	70 – 150 µg
Selenium	10 µg	20 µg

Table 1: Daily requirements of vitamins and minerals for infants and children.

Infant feeding

- Successful infant feeding is essential for proper growth and contributes greatly to the infant's and mother's emotional well-being.
- It requires cooperation between the mother and her baby and feeding time should be pleasurable for both mother and child.
- The best food for infants is breast milk, but animal milks are used after modifications when breast-feeding fails.

Exclusive breast-feeding means:

- No drinks or food other than breast milk are given to a baby.
- No pacifiers or artificial teats are used.
- It is now recommended that babies should be exclusively breast fed during the first 4 to 6 months and that breast-feeding should continue with other feeds up to 2 years of age.



Initiation:

- Feeding should be initiated as soon after birth as an infant can tolerate it.
- This should occur shortly after birth or within 1- 4 hours in order to:
 - Maintain normal metabolism.
 - Promote maternal-infant bonding.
 - Prevent dehydration fever.
 - Decrease the risk of hypoglycemia, hyperkalemia, hyperbilirubinemia and azotemia.

Types of infant feeding:**1- Breast feeding.****2. Artificial feeding.****3. Mixed feeding (both together). It may be:**

- a) **Complementary feeding:** i.e. the mother completes one or more of the breast feeds by formula given just after the breast particularly in the mid-day feeds.
- b) **Supplementary feeding:** i.e. the mother replaces one or more of the breast feeds by formula for example if breast milk is scanty or the mother is exhausted.

Breast feeding

Breast milk is the natural food for infants during the first months of life.

Advantages:

1. To the infant:

1. Milk from the mother whose diet is sufficient and properly balanced will supply the proper nutrients for the infant.
2. Easily digestible due to low content of casein.
3. Less allergy and intolerance.
4. It is always readily available at the proper temperature.
5. It is fresh and free of contaminating bacteria (less chance of GIT disturbances).
6. Human milk contains bacterial and viral antibodies.
7. It contains secretory IgA antibodies, which prevent microorganisms from adhering to the intestinal mucosa.
8. It contains macrophages that can synthesize complement, lysozyme, and lactoferrin that enhance the immunity of the infant.
9. Breast milk is a source of lactoferrin, which inhibits growth of *E. coli* in the intestine.
10. The lower stool pH of the breast-fed infant than that of the infant fed cow's milk helps to inhibit bacterial growth.
11. It contains bile salt-stimulated lipase that digests fats and kills *Giardia lamblia* and *Entamoeba histolytica*.
12. Transfer of tuberculin responsiveness by breast milk also suggests passive transfer of T-cell immunity.
13. It contains prebiotics: Breast milk contains about 200 different types of oligosaccharides (prebiotics) which are non-digestible food ingredients that may stimulate the growth and/or the activity of good bacteria in the colon.

14. It contains probiotics, (live microorganisms) which, when administered, give a health benefit on the host. These microorganisms are important for colonization of infant's gut and the development of the immune system, and could decrease the risk of allergies, asthma and autoimmune diseases.

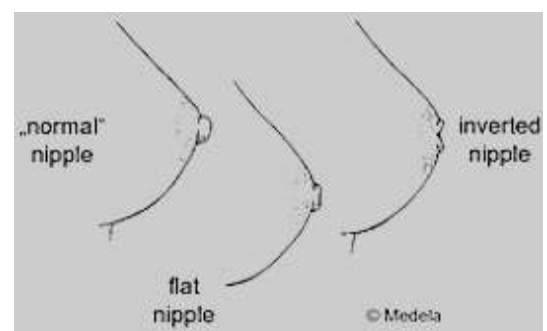
II. For the mother:

1. Helps involution of the uterus.
2. Less effort and needs no time for preparation.
3. Economically, it is the cheapest food.
4. A lower incidence of cancer breast has been reported in women who breast-fed their babies.
5. It helps the mother return to her pre-pregnancy weight sooner.
6. The psychologic advantages of breast-feeding for both mother and infant. The mother gains a feeling of being essential and a sense of accomplishment. The infant is provided with close and comfortable physical and psychological relationships with the mother.

Management of Breast Feeding

I. Instructions to the mother during pregnancy:

1. Wash your breasts with water.
2. Keep the nipple clean.
3. Check for flat or inverted nipples. Retracted nipples usually benefit from daily manual breast-pump or manual traction during the latter weeks of pregnancy; truly inverted nipples may be helped by the use of milk cups, or breast shells starting as early as the 3rd month of pregnancy.



II. After delivery:

1. Breast-feed as soon as possible, in the first hour after birth, if the newborn is alert.
2. Breast-feed every two or three hours, for 20-30 minutes each.
3. Avoid giving bottles or pacifiers in these early weeks, in order the baby not to get confused.
4. Keep your baby with you (rooming in) so you can breast-feed when your baby first seems hungry.
5. Ask for help to make sure you are holding your baby correctly.

Technique of breast feeding

I. Holding your baby

- The mother should sit well supported and comfortable.
- The baby should be semi-upright.
- Turn your baby's whole body toward you.
- Bring your baby's chest close to your chest.
- Your nipple should be right at your baby's mouth.
- A pillow on your lap can support your arm and your baby.



The baby is hungry when:

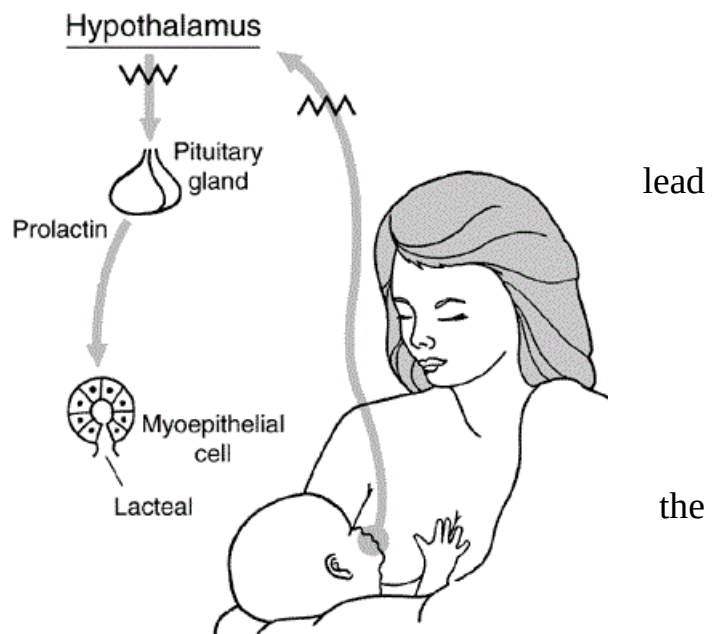
- Sucking on their hands.
- Rooting (opening their mouths wide and searching for milk).
- Fussing.



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The "let-down" or milk-ejection reflex:

- Sucking or psychologic stimuli associated with nursing (e.g., hearing the infant crying for feed) to secretion of oxytocin by the posterior pituitary.
- As a result, the myoepithelial cells surrounding the alveoli deep in the breast contract, squeezing milk into larger ducts, where it is more easily available to the sucking infant.



Establishing and maintaining the milk supply:

- The most satisfactory stimulus to the secretion of human milk is regular and complete emptying of the breasts; milk production is reduced when the secreted milk is not drained.

- Avoid fatigue, worry and unhappiness that can decrease or abolish breast secretions.

One or both breasts per feeding:

Both breasts should be used at each feeding in the early weeks then the breasts may be alternated at successive feedings, and the infant will usually be satisfied with the amount obtained from one.

Time of feeding:

- During the first month breast feeds are given on demand but not more than every 2 hours.
- Once breast-feeding is established, the infant can be fed every 3 hours for the first 3 months and later every 4 hours but there must be some degree of malleability.

Determining adequacy of milk supply:

The milk supply is sufficient if:

- The baby breast-feeds 8 to 12 times in 24 hours.
- The infant is satisfied after nursing period,
- Sleeps 2–4 hours after feed
- Gains weight adequately about 100 g every 4 days during the first 4 months).
- The baby has at least six wet diapers and two soft stools/24 hours.

COLOSTRUM

- It is the secretion of the breasts during the latter part of pregnancy and for the 2–4 days after delivery.
- It has a deep lemon-yellow colour.
- Its reaction is more alkaline than mature breast milk. Its specific gravity is 1.040–1.060 (1.030 for mature breast milk).
- The total amount of colostrum-secreted daily is 10–40 mL.
- It contains several times the protein of mature breast milk, more minerals, but less carbohydrate and fat.

- Human colostrum also contains more immunologic factors.
- It is followed after the first few days of lactation, by transitional form of milk that gradually assumes the characteristics of mature breast milk by the 3rd or 4th wk.



Contraindications of breast-feeding:

I. Maternal causes:

1. Infectious diseases such as active tuberculosis, AIDS and hepatitis B (infection may be transmitted through droplet infection-TB- or oozing serum from cracked nipple).
2. Chronic cachectic conditions such as chronic poor nutrition, nephritis, debility, cancer, congestive heart failure and uncontrolled diabetes mellitus.
3. Mental and neurologic conditions such as insanity, psychosis, substance abuse and epilepsy.

4. Breast conditions as cancer breast.
5. Pregnancy after the first trimester.
6. Temporary causes as acute maternal illness and retracted or fissured nipples breast engorgement mastitis and breast abscess.

II. Infant causes:

1. Metabolic diseases such as galactosemia, phenylketonuria.
2. Congenital malformations such as complete cleft palate to avoid aspiration.
3. Temporary causes as thrush stomatitis, cleft lip, nasal catarrh and weak suckers.

Artificial feeding

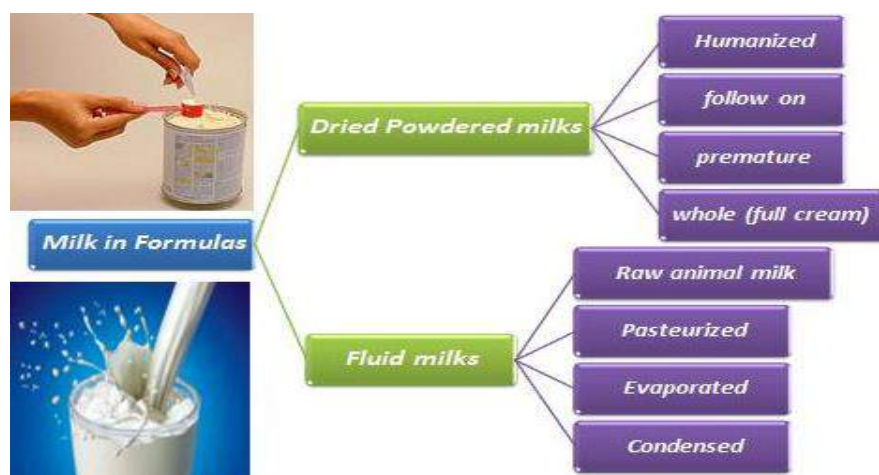


The aim of artificial feeding is to supply modified animal milk as a substitute to breast-feeding.

Indications:

1. In conditions where breast-feeding is contraindicated.
2. Death or absence of the mother.
3. Institutes.
4. Diminution of breast milk.
5. Twins.

Types of milk used for artificial feeding:



Milk used in formulas:-

I. Dried Powdered milks:

1. **Dried Humanized Milk** (contains about 1 gm proteins/dl):

- Commercially called formula 1.
- These are used from birth till the age of 6 months.
- Its composition has been made nearly identical in amount of proteins, fats and carbohydrates, as well as minerals and vitamins to human milk.
- Supplementation of such milks with extra iron, vitamin C and vitamin D has made them suitable for infant use.
- Also, recently unsaturated fatty acids, lactose and amino acid content of these milks have been made very close to human milk.
- However, infants on these humanized milks still showed fewer achievements on growth curves than breast fed infants.

2. **Dried follow-on milks** (contains about 2 gm proteins/dl):

- Commercially called formula 2.
- These are used after the age of 6 months
- Their content of protein is higher than humanized milks (2-2.5 g/dl).
- They are usually supplemented with iron to prevent iron deficiency anemia.

3. **Dried premature infant milk:**

- Used in low-birth weight infants less than 2000 g. body weight.
- They provide higher calories (80 kcal/oz.).
- They contain more sodium and minerals to suit higher urinary solute loss in these premature infants.

4. **Dried whole (full cream) milk** (contains about 3 gm. proteins/dl):

- Commercially called formula 3.
- The fat content of fluid milk is adjusted to 3-3.5%.
- Used after the first year of life.

II. Fluid milks:

1. *Raw cow milk:*

- This should not be advised for infant feeding (before one year) except after humanization.
- It forms large curds in the stomach.
- It is slowly digested.
- It is easily contaminated with pathogenic organisms.

2. *Pasteurized milk:*

- Pasteurization (heating the milk to 65 C for 20 minutes then cooling rapidly to 10 C) destroys most of pathogenic bacteria and modifies casein so that smaller, less tough curds are produced in the stomach.
- Pasteurized milk should be boiled when used for infant feeding.

3. *Evaporated milk:*

- The unopened cans may be kept for months without refrigeration.
- The casein curd produced in the stomach is softer than that of boiled whole milk.
- Homogenization of the fat also contributes to smaller curd formation.
- It is less allergenic than that of fresh milk.

4. *Condensed Milk:*

- It is sweetened with a carbohydrate content of approximately 60%.
- Although readily digestible, it has no use in infant feeding except for short periods when a high-calorie diet is desired.

5. *Goat's milk:*

- Used in many countries, including rural Egypt.
- Can be used to manage cow's milk allergies.
- Goat's milk contains less sodium, and more unsaturated fatty acids.
- Its fat is more digestible, and its curd tension is lower than that found in cow's milk.

- It is low in folic acid; so, infants fed exclusively on goat's milk are susceptible to megaloblastic anemia due to folate deficiency.
- It is susceptible to contamination by *Brucella* species.

III. Specially modified milks for disease states:

Modifications are made to suit certain diseased infants and children for example:

1. **Lactose free milk:** for cases of galactosemia and cases of lactose intolerance after gastroenteritis or malnutrition.
2. **Phenylalanine-low milk:** for cases of phenylketonuria.
3. **Low calcium milk:** for cases of hypercalcemia.
4. **Soya milks:** for cow milk protein allergy.
5. **Milk protein:** Powdered protein is used for increasing protein content of some formulas fed to premature or debilitated infants or to infants with diarrhea.
6. **Elemental formula:** It is prepared from purified chemical elements (free glucose, amino acids, and essential fatty acids). Used for children with malabsorption due to primary disease or extensive surgical resection of the small bowel. Useful in treating severely ill infants with persistent diarrhea, inflammatory bowel disease, and short bowel syndrome after extensive bowel surgery.

Technique of artificial feeding:

- As in breast-feeding, the mother and infant should be in a comfortable position, unhurried, and free from distractions.
- The infant should be hungry, fully awake, warm, and dry.
- Baby is held as though being breast-fed with head elevated slightly to prevent milk from entering the ear causing otitis media.
- The bottle should be held so that milk, not air, channels through the nipple.
- The bottle of milk is customarily warmed to body temperature (tested by dropping milk onto the wrist).

- The nipple holes should be of the size so that milk will drop slowly.
- The eructation of air swallowed during feeding is important for avoiding regurgitation and abdominal discomfort.
- A feeding may last from 5–25 min, depending on the vigor and the age of the infant.
- The excess milk left after feed should be discarded.

Caloric requirements:

- Full-term infants 100-120 kcal/kg during the first year of age
- The formula should contain about 20 kcal/oz.

Fluid Requirements

- During the first 6 months of life 150 mL/kg/24 hr and may increase during hot weather.
- Most of the fluid required is in the formula, some in juice and other foods and by water between feedings.

Number of feedings daily:

- Feedings are given every 3–5 hours during the first year of life.
- Small or weak infants may prefer feedings at 2-3 hours intervals.

Quantity of formula:

- Determined by each infant.
- A total of 150 ml/kg/day can be given during the first year of life (range 150-180 ml/kg/day).
- Rarely will an infant want to take more than 7–8 oz of milk at one feeding.
- Other caloric and nutritional needs are adequately supplemented by other foods.
- Some of the milk may be incorporated in the cereal and foods such as custard and pudding.

Preparation of formula:

- Bottles should be smooth inside, wide-mouthed with an adequate cover for the nipple.
- All utensils required should be sterilized by boiling for 5–10 min.
- The rubber nipples and caps should not be boiled more than 5 min.
- The mother's hands should be washed thoroughly.

1



It's always best to make up each feed as and when you need it. Before making up a bottle, make sure your equipment is sterilised, the work surface where you'll be preparing the bottle is clean and you've washed your hands thoroughly.

2



Boil fresh tap water in the kettle and allow it to cool to no less than 70°C (this means leaving water to cool for between 25 and 30 minutes after boiling).

3



Measure the required amount of cooled boiled water into the sterilised bottle, as shown on your infant milk powder packaging. Using the scoop provided, add the required number of scoops of powder to the bottle, levelling off each scoop with a clean, dry knife. Do not pack the powder down in the scoop.

4



Place the sterilised teat and cap on the bottle and shake well. Before offering it to your baby, cool the formula by holding the bottle under cold running water until lukewarm. Test the temperature by shaking a few drops onto the inside of your wrist.

5



When feeding your baby, hold the bottle at an angle, so the teat and bottle neck are always full of milk. This way there's less chance of your baby getting trapped wind. Throw away any milk that has not been used within one hour if the bottle has been fed from. And after two hours even if it's untouched.

Raw animal milk:

Milks	Protein (g/dL)	Carbohydrate (g/dL)	Fat (g/dL)	Minerals (g/dL)	Water	Calories (Kcal/ dL)
Human	1.5	7	4	0.2	89%	67
Cow	3.5	4.5	4	0.8	89%	67
Buffalo	3.5	4.5	7.5	0.8	83%	100

Table 2: mature human milk compared to cow's milk

Water:

The relative amount of water is about 89% and solids 11% in human and cow's milks.

Calories:

The energy value may vary slightly and is approximately 20 kcal/oz. or 67 kcal/dL in human and cow's milks.

Protein:

- Human milk contains only 1–1.5 g/dL protein (3.3 g/dL in cow's milk).
- Human milk protein consists of approximately 60% whey proteins, largely lactalbumins, and 40% casein; the cow's milk ratio is reversed to 20%: 80% with 6-fold increase in casein.
- The casein in cow's milk forms a big tough curd in the stomach while human milk forms a fine curd.
- Cow's milk proteins are frequently antigenic causing allergy, but never is human milk proteins.

Carbohydrate:

- Human milk contains about 7g/dL, and cow's milk contains about 4.5g/dL lactose.
- Lactose in breast milk helps the absorption of calcium and provides galactose for formation of galactolipids necessary for brain development.

Fat:

- The fat content of milks is about 3.5 g/dL.
- In human milk, fat content varies somewhat with maternal diet while cow's milk fat varies from 3.25 – 4 g/dL.
- The volatile fatty acids (e.g., butyric acid) constitute only about 1.3% of human milk fat but about 9% of cow's milk fat.
- These volatile fatty acids cause irritation of the gastrointestinal tract.
- Breast milk is rich in essential polyunsaturated fatty acids (e.g., linoleic acid), which facilitate brain growth.

Minerals:

- Cow's milk contains much more of all the minerals except iron and copper than human milk; total mineral content of cow's milk is about 0.8 g/dL which is 3-4 times that of human milk (only 0.2 g/dL).
- Cow's milk contains inadequate iron; breast-milk iron, although low, may be sufficient, during the first 4 –6 mo, for the infant because it is better absorbed.
- Although the need for calcium and phosphorus is great during periods of rapid growth, adequate balances are maintained on breast milk despite its low content of these minerals.

Vitamins:

- The vitamin content of human milk varies with the maternal intake.
- Cow's milk is low in vitamins C and D.

- Breast milk usually contains adequate vitamin C (if the mother eats appropriate foods) and adequate vitamin D unless she is insufficiently exposed to sunlight or is darkly pigmented.
- Cow's milk contains more vitamin K than human milk.
- Both types of milk seem to contain adequate amounts of vitamin A and the B-complex vitamins for the nutritional needs of infants in the first months of life.

Disease transmission:

- Human milk is essentially uncontaminated by pathogenic organisms and contains a lot of anti-infection agents. However, if there is mastitis with breast abscess, tuberculous breast abscess, HIV or Cytomegalovirus (CMV) infection, breast feeding should be withdrawn.
- **Hepatitis A:** Breastfeeding is safe.
- **Hepatitis B:** Breastfeeding is safe. The baby should receive a dose of hepatitis B immune globulin (HBIG) and the first of three doses of hepatitis B vaccine soon after birth.
- **Herpes simplex:** Breastfeeding is safe if there are no lesions on the breast. It's also safe to use expressed milk pumped while the lesions are present.
- **Chicken pox:** If the infection began within five days before giving birth or two days afterward direct contact with the baby is avoided; however, expressed milk can be used. After this period, breastfeeding is safe.
- Cow's milk is regularly contaminated, and milk is a good culture medium for pathogenic bacteria. Milk borne infections include streptococcal diseases; diphtheria; typhoid fever; salmonellosis; tuberculosis; and brucellosis.

Digestibility:

- The stomach empties more rapidly after human milk than after whole cow's milk. The curd of cow's milk is reduced in size by boiling.

- The curd of breast milk is fine and flocculent and readily broken down in the stomach. The fat of cow's milk is less readily digested than that of breast milk.

The main problems in animal milks include:

1. The formation of tough curd due to excessive casein.
2. The high fat content with bigger fat globules, higher content of volatile fatty acids and less essential fatty acids.
3. The high mineral content that constitutes a burden on the newborn's kidney.
4. Lower iron content

Humanization of row animal milk:

Modifications of fresh animal milk (known as humanization) helps to make it more suitable for infants and nearer to the composition of human milk.

This humanization is achieved by:

1. Dilution by mixing cow's milk and water (2:1) or buffalo milk and water (1:1).
2. Adding 5 gm of sugar to each 100 ml of the mixture.
3. Boiling for 15 minutes for modification of casein and sterilization.

Disadvantages of artificial feeding:

- Malnutrition due to errors in preparation of milk.
- Contamination with increased incidence of diarrhoea and its related mortality.
- Bacterial and viral infections are more common in artificially fed infants.
- Intolerance and allergies.
- High expenses.
- Loss of psychologic benefit of mother-infant bonding.

Advantages of artificial feeding:

One of the true advantages is the ability to produce especially modified formulas for medical conditions as phenyl ketonuria, galactosemia and lactose intolerance etc.

Feeding of toddlers and children

After the first year of life the child should receive adequate feeding which covers all requirements of macronutrients (carbohydrates, proteins and lipids) as well as micronutrients (vitamins and minerals)

Total caloric requirements can be calculated:

- 100 kcal/kg/day in the first year (1000 kcal/day at one year).
- +100 kcal more for every year from 2-10 year (2000 kcal/day at 10 years). For example, at 5 years $1000 + 5 \times 100 = 1500$ kcal/day.
- For males: + 100 kcal for every year 10 - 18 y (adult male 2800 kcal/day)
- For females: +50 kcal for every year 11- 14 years (adult female 2200 kcal/day)

Macro-nutrient distribution should be as follows:

- 50-55% from carbohydrates
- 15-20% from proteins
- 25-30% from fats

Total fluid requirements are calculated as:

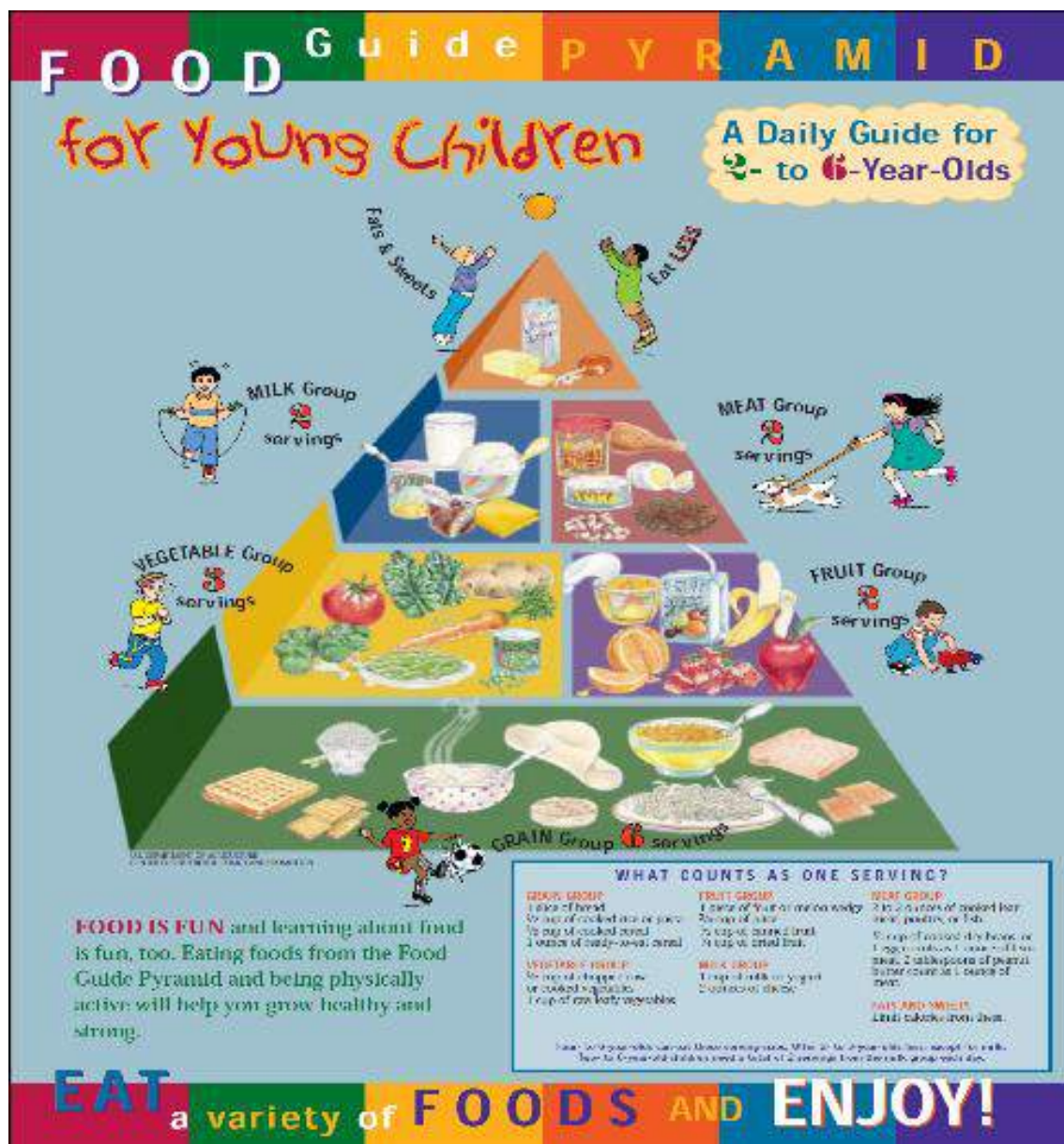
- 1 ml/kcal total energy intake unless otherwise modified. For easy planning of meals fulfilling needed composition and amounts, the food stuffs were classified into 6 groups which are:
- Grains group (containing carbohydrates).
- Fruits group (containing simple sugars),
- Vegetables group (containing minerals and fibers).
- Dairy group (milk products).
- Meats group (including legumes as beans).
- Fats group.

Foods from each group are administered in the form of a number of servings of nearly equivalent caloric value which can be selected and interchanged according to the preference of the child and family.

- A serving of grains contains 80 kcal.
- A serving of fruits contains 60 kcal.
- A serving of vegetables contains 25 kcal.
- A serving of milk products contains 80-150 kcal (according to fat content).
- A serving of meats contains 45-100 kcal (according to fat content).
- A serving of fat contains 45 kcal.

The total daily food intake can be represented graphically by the shape of a pyramid, a plate or a palm tree divided into areas showing the different food groups and the number of servings needed from each group.





WHAT COUNTS AS ONE SERVING?

GRAIN GROUP

1 slice of bread
 1/2 cup of cooked rice or pasta
 1/2 cup of cooked cereal
 1 ounce of ready-to-eat cereal

VEGETABLE GROUP

1/2 cup of chopped raw or cooked vegetables
 1 cup of raw leafy vegetables

FRUIT GROUP

1 piece of fruit or melon wedge
 3/4 cup of juice
 1/2 cup of canned fruit
 1/4 cup of dried fruit

MILK GROUP

1 cup of milk or yogurt
 2 ounces of cheese

MEAT GROUP

2 to 3 ounces of cooked lean meat, poultry, or fish.
 1/2 cup of cooked dry beans, or 1 egg counts as 1 ounce of lean meat. 2 tablespoons of peanut butter count as 1 ounce of meat.

FATS AND SWEETS

Limit calories from these.

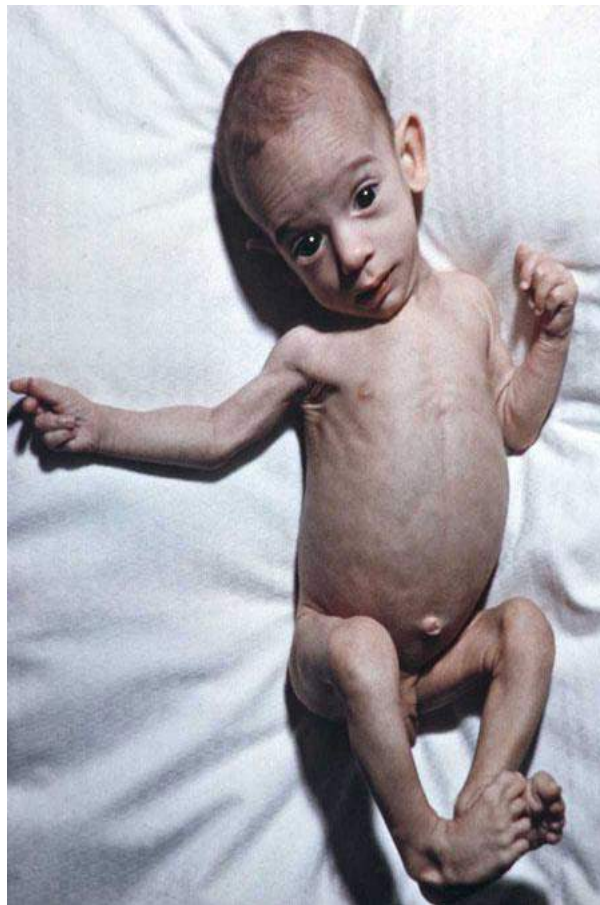
Four- to 6-year-olds can eat these serving sizes. Offer 2- to 3-year-olds less, except for milk. Two- to 6-year-old children need a total of 2 servings from the milk group each day.

Underfeeding

This means that the infant receives insufficient amount of milk. If continues untreated it leads to frank malnutrition.

Symptoms:

1. Restlessness and excessive crying
2. Lack of comfortable sleeping without an apparent cause.
3. Failure to gain weight adequately, despite complete emptying of the breast or bottle.
4. Constipation with small hard infrequent stools. However, the infant may pass frequent small loose greenish stools (starvation diarrhea).
5. Vomiting due to excessive swallowing of air from an empty breast or bottle.
6. Colic: when swallowed air reaches the intestine.



Signs:

1. There may be poor gain in weight or an actual loss.
2. The skin becomes dry and wrinkled, subcutaneous tissue disappears.
3. Signs of dehydration may be observed.
4. Deficiencies of vitamins A, B, C, and D and of iron may occur.

Diagnosis:

1. Test weighing: an average body weight gain of 100 g every 3-4 days during the first months of life is considered adequate.
2. Test feed: the infant is weighed just before and just after feed without changing the clothes, the difference shows the amount of milk taken. It is better to do the test for 3 days and take the average.

When the infant is taking adequate amount of milk without a corresponding gain of weight, investigations should be done for detection of hidden cause such as malabsorption or systemic illness.

Treatment:

1. Increasing the fluid and caloric intake by complementary or supplementary feeds.
2. Correcting deficiencies in vitamin and mineral intake.
3. Instructing the mother in the art of infant feeding.
4. Management of underlying systemic disease or psychological problem if present.

Overfeeding

This may occur in hot weather due to excessive thirst satisfied by more breast or formula feeding. Obesity is undesirable at any time in life; often the excessively fed infant becomes the obese child and adult.

Symptoms and signs:

1. Overweight.
2. Regurgitation and vomiting.
3. Distension and abdominal discomfort.
4. Diarrhoea.



Overfeeding may be quantitative or qualitative:

- Diets too high in fat delay gastric emptying, cause distention and abdominal discomfort, and may cause excessive gain in weight.
- Diets too high in carbohydrate are likely to cause undue fermentation in the intestine, resulting in distention and flatulence and cause too rapid gain in weight.
- Such diets may be deficient in essential protein, vitamins, and minerals.

Diagnosis: Test weighing and test feeds.

Treatment:

1. The intervals between feeds are increased or only one breast is given per feed.
2. The baby is given low calorie fluids between feeds or just before the feeding time.
3. Strict follow up of body weight gain and making the necessary changes in caloric value.

Weaning

- It is to accustom the infant or child to take food materials other than milk.
- Weaning should be started gradually when the milk intake becomes insufficient to meet the infant's needs.
- It is not recommended before 4-6 months so long as the general health and weight gain of the infant are satisfactory.

Sudden weaning is done in conditions such as:

1. Death of the mother.
2. Serious illness of the mother.
3. Pregnancy (after the fourth month).

The aim of weaning is to:

1. Supply sufficient nutrients in which the milk is deficient (iron, vitamins B1 and D).
2. Train the gastrointestinal tract to digest starch and more solid foods.
3. Educate the child independence by using cup or spoon.
4. Cover the extra needs of calories (an infant can't tolerate more than one liter of milk per day).

General rules of weaning:

1. It should not be started in very hot or very cold weather.
2. It should not be started during illness, early convalescence or just after vaccination.
3. Only one type of new food should be given at a time.
4. The same type of new food is given every day until the baby becomes accustomed to it.
5. No new food to be given more often than one type every 1-2 week.

6. New food should be started once a day, in a diluted small amount (e.g., 1-2 teaspoonful) then the concentration and amount can be increased gradually guided by the baby's appetite and never do enforced feeding.
7. Stop the new food if persistently disliked by the baby or if allergy or diarrhea has occurred.
8. Food is frequently pushed out by the tongue rather than back because the baby cannot yet swallow efficiently. The mother should know that this is not dislike.

Sequence of food introduction:

In addition to breast or artificial feeding the following foods can be added in sequence:

AGE	FOOD
At the end of 4th month:	• Add milk products as yogurt, soft cheese and milk pudding. • Mashed fruits and fruit juices.
Between 4-6 months:	• Add cereals, (containing iron and vit B complex) potatoes or biscuits. • Strained or puréed cooked fruits (supply minerals and some water-soluble vitamins and usually have a mildly laxative effect). • Raw ripe mashed banana is readily digested and enjoyed by most infants.
End of the 6th month:	• Add, egg yolk, hard cooked with little salt. • 4-6 months later (nearly at one year), egg white can be introduced with caution to

	minimize any possible allergic manifestations.
End of the 7th month:	• Add vegetables, freshly cooked and strained or commercially prepared (good sources of iron and other minerals and of the B-complex vitamins).
End of the 8th month:	• Add poultry or liver, well cooked and ground with other foods as rice and vegetables. • Cooked rice or macaroni • Lentil soup
From 9-12 months:	• Other foods as well-cooked meats and grilled fish • mashed beans • Increase the amount of previously introduced foods so that the infant by the end of the first year can eat the adult food.

العمر	الغذاء
نهاية الشهر الرابع	• زبادي أو جبنة بيضاء قليلة الملح أو مثلثات. • مهلبية أو أرز بالبن (بلبن الاطفال الرضع) • عصير الفواكه
الشهر الرابع – الشهر السادس	• لبن الام + ماسبق + • يمكن ادخال من وجبتين الى 3 وجبات • إدخال وجبات الحبوب الجاهزة و البسكويت و البطاطس المسلوق بيوريه. • يمكن ادخال بعض الفواكه مثل التفاح المسلوق والمهروس او الكمثري المسلوقه والمهروسه او الجوافه المهروس الموز المهروس. او عصائر الفاكهة • مراعاة ان يقدم كل صنف من هذه الاصناف علي حده والا يتم الخلط بينهم وان تكون المده بين كل صنف جديد يقدم للطفل حوالي 3 ايام مع عدم تقديم اكثر من صنفين في الاسبوع الواحد ، كذلك تقدم هذه الاصناف بطعمها الاصلي دون اضافته السكر او الملح حتي لا يعتاد الطفل علي طعم دون الاخر.
نهاية الشهر السادس	• لبن الام + ماسبق + • صفار البيض
نهاية الشهر السابع.	• لبن الام + ماسبق + • شوربة خضار مسلوقة و مهروسة جيدا
نهاية الشهر الثامن	• لبن الام + ماسبق + • أرز او المكرونة • قطعة صدر دجاج او كبدة

• شوربة عدس	
• لبن الام + ماسبق + • فول مهروس جيدا • لحم أحمر مفروم أو سمك مشوي • تقديم الوجبات في صورة ثلاث وجبات رئيسية • تتخللها الرضعات كوجبات بينية	الشهر 9- 12
• تستطيع الام ان تعطي لطفلها جميع انواع الطعام (طعام الاسرة) ويكمنه تناول الحليب دون تخفيف وكذلك البيض الكامل (بياض مع صفار)	بعد سنة

Malnutrition

Malnutrition is one of the leading causes of morbidity and mortality in childhood.

Malnutrition may be due to:

I. Improper or inadequate food intake:

- Insufficient food supply.
- Poor dietary habits.
- Emotional factors.

II. Inadequate absorption of food.

III. Increased requirements:

- Stress.
- Disease.
- Treatment with antibiotics.
- Intake of catabolic or anabolic drugs.
- Certain metabolic abnormalities.

The diagnosis of malnutrition rests on:

- An accurate dietary history.
- Deviations from average height, weight, and head circumference, for child's age.
- Past rates of growth.
- Measurements of mid-arm circumference and skin fold thickness.
- Chemical and other tests:
 1. Muscle mass is calculated as follows:
 2. Mid-arm muscle circumference = mid-arm circumference - (skin fold thickness X 3.14)
 3. Lean body mass can be estimated from 24-hr creatinine excretion.

4. Protein reserves are assessed from serum albumin and total proteins.
5. Rapid turnover proteins, such as transthyrenin, prealbumin, and transferrin for evaluation of current status and response to treatment.
6. Serum levels of essential amino acids / nonessential amino acids.

Classifications of malnutrition

I. Waterlow classification of malnutrition:

Grade	Acute Malnutrition “Wasting” % Weight-for-height	Chronic malnutrition “Stunting” % Height-for-age*
I (mild)	< 90	< 95
II (moderate)	< 80	< 90
III (severe)	< 70	< 85

- **% Weight for height:** Child’s actual weight divided by 50th percentile of weight for his / her height age, multiplied by 100.
- **% Height for age:** Child’s actual height divided by the 50th percentile of height for his / her age, multiplied by 100.

II. Wellcome classification of PEM:

Weight % of normal	Edema	
	Absent	Present
80 – 60	Under weight	Kwashiorkor (KWO)
60 or less	Marasmus	Marasmic KWO

Kwashiorkor (KWO)



- Kwashiorkor is a clinical syndrome that results from a severe deficiency of protein in addition to an inadequate caloric intake but to a lesser degree.
- The patient depends mainly on carbohydrates in his caloric intake.
- Kwashiorkor means "deposed child," that is, the child no longer suckled.
- It occurs from 6 months to 3 yr of age, usually after weaning from the breast.

Clinical Manifestations:

Early clinical manifestations are vague including lethargy, apathy, or irritability. When advanced cases, **constant signs** are found:

1. **Growth failure:** detected by suitable anthropometric measurements.
2. **Edema:** Edema usually develops early; failure to gain weight may be masked by edema. It is due to decreased plasma proteins,



salt retention (due to activation of renin-angiotensin system) and water retention (due to decreased hepatic inactivation of antidiuretic hormone).

3. **Muscle wasting with preservation of some subcutaneous fat:** The muscles are weak, thin, and atrophic, due to hypoproteinemia. There is hypotonia and delayed motor development. However, occasionally there may be a fair amount of subcutaneous fat due to excessive carbohydrate intake.
4. **Psychomotor changes:** Apathy, lethargy, indifference to surroundings and food. Miserable look and peevish cry. The infant appears silent and markedly anorexic. These changes are attributed to deficiency of amino acids and serotonin (derived from tryptophan).



5. Other signs (usual signs):

- **Dermatosis or dermatitis** is common. Erythema followed by darkening of the skin appears in irritated areas but not in those exposed to sunlight. Dyspigmentation or hypopigmentation may occur in these areas after desquamation or may be generalized. It may be due to deficiency of essential fatty acids, vit. A and amino acids as tryptophan.



- **The hair:** Hair is often sparse and thin with loss of its luster. It is easily pickable resulting in patchy baldness. In dark-haired children, dyspigmentation may result in streaks of red or gray hair color alternating with streaks of darker hair due to periodic changes of protein intake (flag sign). Hair texture becomes coarse in chronic disease. This may be due to deficiency of sulfur containing amino acids and riboflavin.



- **The liver** may enlarge early or late due to fatty infiltration. When neglected this may progress to steatohepatitis or cirrhosis
- **Renal plasma flow, glomerular filtration rate, and renal tubular function** are sometimes decreased.
- **The heart** may be small in the early stages of the disease but is usually enlarged later.
- **Anemia**, which may be microcytic, normocytic or macrocytic. It is due to multiple deficiencies of iron, proteins, folic acid, pyridoxine, and vitamin B12, zinc and copper. Chronic infections may also be responsible.

- **Secondary immunodeficiency** is one of the most serious manifestations. Relatively benign diseases of the well-nourished such as measles, can be fatal in malnourished children. Immunologic insufficiency is demonstrated by decreased concentration of immunoglobulins, low total lymphocyte counts of less than 1,500/mm³ and anergy to skin test antigens.
- **Infections and parasitic infestations** are common, as are anorexia, vomiting, and continued diarrhea.
- **Secondary vitamin and mineral deficiency** may contribute to the signs and symptoms e.g. vitamin A, D and C.

Laboratory data:

1. Decrease in the concentration of serum albumin is the most characteristic change.
2. Blood glucose values are low but glucose tolerance may be impaired.
3. Ketonuria is common in the early stage.
4. Potassium and magnesium deficiencies are frequent.
5. The serum cholesterol level is low.
6. The serum values of enzymes amylase, esterase, cholinesterase, transaminase, lipase, and alkaline phosphatase are decreased.
7. Anaemia may be normocytic, microcytic, or macrocytic.
8. Bone growth is usually delayed in severe long-standing cases.
9. Growth hormone secretion may be increased (due to stress response stimulation).

Differential Diagnosis: other causes of generalized edema, chronic infections, diseases in which there is an excessive loss of protein through urine or stools, and conditions with a metabolic inability to synthesize protein.

Bad prognostic factors: severe weight loss, presence of dehydration, markedly enlarged liver, disturbed consciousness, hypothermia, and skin hemorrhage.

Marasmus



Causes:

I. Nutritional marasmus:

- Marasmus of dietary origin may develop when the diet fed contains insufficient quantity of total calories but balanced qualitatively.
- Example is an infant exclusively breast-fed for a prolonged period with no food supplementation, or infant given highly diluted or little amount of milk formula or weaning feeds.

II. Non-Nutritional marasmus:

- Chronic infections e.g., tuberculosis.
- Metabolic disorders e.g., aminoaciduria, diabetes mellitus.
- Endocrinopathies e.g., thyrotoxicosis.
- Local diseases or malformations of the GIT.
- Malabsorption syndromes e.g., cystic fibrosis, celiac disease.
- Chronic heart diseases e.g., congestive heart failure.
- Chronic renal diseases e.g., uraemia.
- CNS disorders e.g., cerebral palsy.

Clinical Manifestations:

I. Constant signs:

- **Growth failure:** Initially, there is failure to gain weight, followed by loss of weight until emaciation results.
- **Loss of subcutaneous fat:** occurs gradually first from anterior abdominal wall, thighs, then buttocks and shoulders. Lastly, fat is lost last from the face except sucking pads of the cheeks. The infant's face may retain a relatively normal appearance for some time before becoming shrunken and triangular (senile face).
- **Muscle wasting:** Atrophy of muscles, with resultant hypotonia. The abdomen may be distended or flat, and the intestinal pattern may be readily visible.

II. Usual signs:

- **Vitamin deficiencies:** e.g. angular stomatitis, keratomalacia
- **Subnormal temperature:** with slow pulse and reduced basal metabolic rate.
- *At first, the infant may be fretful but later becomes listless, with poor appetite.*
- **GIT disturbances:** Constipation, or starvation type of diarrhea, with frequent, small stools containing mucus.

Bad prognostic factors:

1. Severe weight loss.
2. Younger age.
3. Presence of infection.
4. If the cause is not removable.

Marasmic kwashiorkor



- It is of the worst prognosis among the syndromes of PEM.
- It results from diets poor in total calories superimposed by acute deprivation or increased demands of proteins e.g. following an attack of gastroenteritis or febrile illness.
- Clinically, there are signs of marasmus in addition to generalized edema and psychomotor changes of kwashiorkor.

Complications of PEM:

1. Gastroenteritis, dehydration, and electrolyte disturbances.
2. Infections e.g., bronchopneumonia, meningitis, and septicemia.
3. Hypothermia.
4. Hypoglycemia.
5. Purpura.
6. Heart failure.
7. Renal failure.
8. Hepatic failure.
9. Sudden death.

Prevention of PEM:

- Encouragement of breast feeding.
- Adequate dietary instructions and food distribution.
- Breaking down bad dietary habits e.g., food withdrawal during diarrhoea.
- Immunization against infectious diseases.
- Early detection and treatment of PEM cases.

Treatment Of PEM:

I. Immediate management of any acute problems:

- Hospitalization for advanced cases.
- Severe or persistent diarrhoea and dehydration.
- Infection, using effective antibiotics parenterally for 5–10 days.
- Severe anaemia.
- Renal failure.
- Shock.
- Severe vitamin A deficiency.
- Hypoglycaemia,
- Hypothermia.

II. Dietetic treatment:

- A breast-fed infant should be nursed as often as he or she can tolerate.
- After dehydration is corrected, oral feeding starts with small, frequent feeds of dilute milk. Strength and volume are gradually increased, and frequency decreased over the next 5 days. By days 6–8, the child should receive 150 mL/kg/24 hr in 6 feeds.
- When high-calorie and high-protein diets are given too early and rapidly, hepatomegaly, abdominal distension, and encephalopathy may occur (Refeeding syndrome).

- Cow's milk, (or yogurt for the lactose-intolerant child), should be made with 50 g of sugar/L.
- Vegetable fat is better absorbed than cow's milk fat.
- When the condition of the child permits, semisolids and solids are gradually added guided by patient's tolerance.

III. Symptomatic treatment:

- Bacterial infections and diarrhoea must be treated properly. Treatment of parasitic infestations, if they are not severe, may be postponed until recovery is under way.
- Gentian violet 2%, antibiotic or antifungal creams for dermatosis.
- Vitamins and minerals, especially vit A, vit D, vit B complex, potassium, and magnesium. Iron and folic acid usually correct the anaemia.

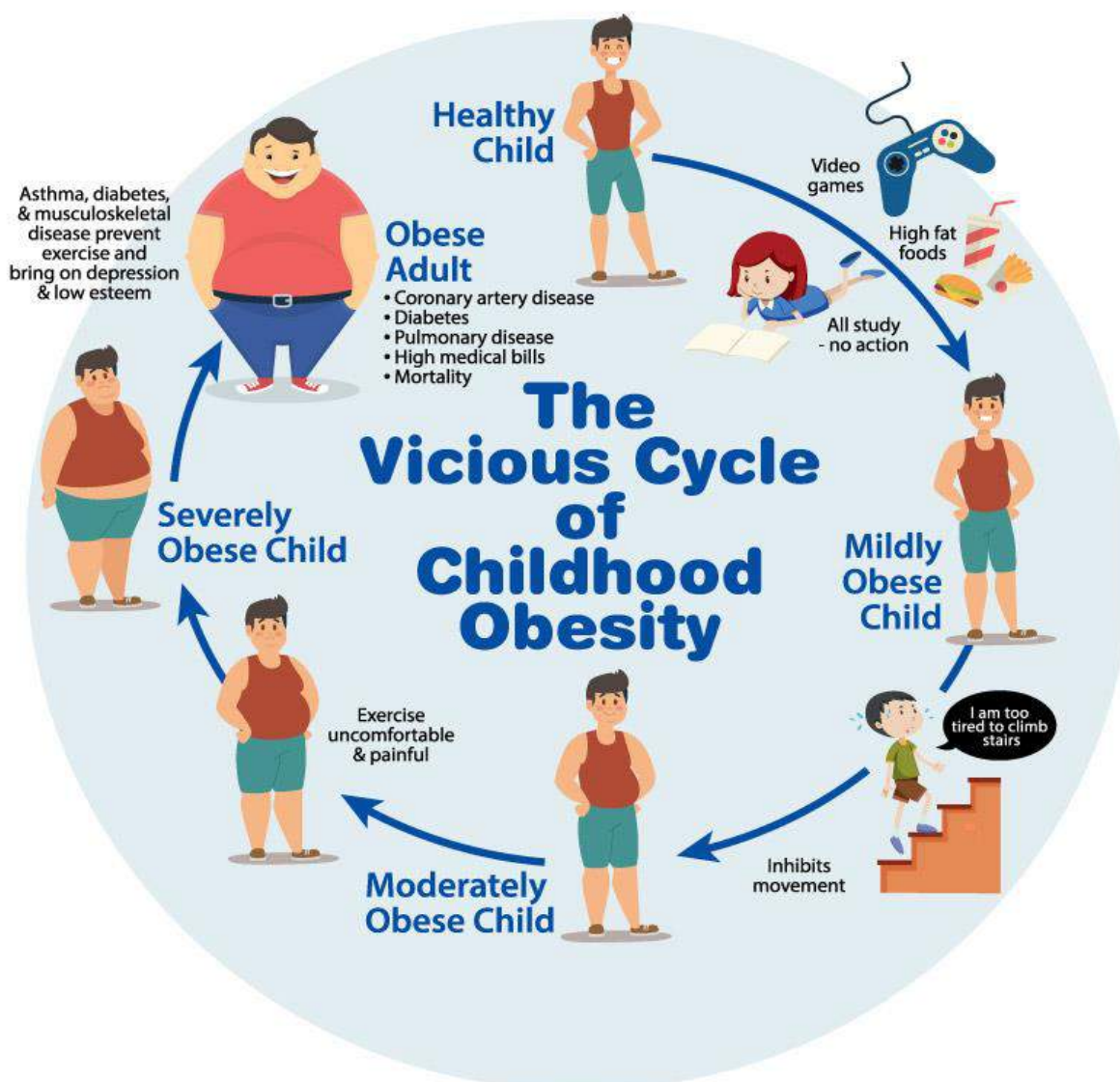
Signs of improvement:

- Sense of well-being.
- Steady improvement of appetite.
- Disappearance of oedema.
- Progressive increase in body weight.
- Healing of skin lesions and cure of infections.
- Normalization of serum proteins especially albumin.

Childhood Obesity

Obesity refers to excess body fatness. Obesity in children is defined as a Body mass index (BMI) for age at or above the 95th percentile while overweight is defined as a BMI-for age between the 85th and 95th percentiles.

$$\text{Body mass index (BMI)} = \frac{\text{Weight (kg)}}{\text{Height}^2 (\text{m}^2)}$$



Etiology of childhood obesity:

Obesity may be Exogenous or endogenous

- **Exogenous obesity:** due to life style factors as;
 1. increased intake of energy-dense foods that are high in fat and sugars
 2. Decreased physical activity and sedentary life leading to decreased energy expenditure and fat accumulation.
- **Endogenous obesity:** due to endocrinal and genetic causes which is less common than exogenous obesity;
 1. Endocrinal causes: as hypothyroidism, growth hormone deficiency and Cushing syndrome.
 2. Genetic or Syndromic causes: as Prader Willi syndrome.

Complications of childhood obesity:

1. **Metabolic complications:** insulin resistance, type 2 diabetes and hyperlipidemia
2. **Cardiovascular complications:** hypertension and premature coronary heart disease
3. **Pulmonary complications:** obstructive sleep apnea (OSA) and obesity hypoventilation syndrome.
4. Menstrual abnormalities and polycystic ovary syndrome (PCOS).
5. **Orthopedic complications:** bone deformities, fractures and chronic musculoskeletal pain.
6. **Gastrointestinal complications** include nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and cholelithiasis.
7. **CNS complications:** pseudotumour cerebri

8. **Psychosocial problem:** Low self-esteem, anxiety and depression, and social isolation are more common in overweight and obese children and adolescents who may also suffer high levels of teasing and bullying.

Investigations:

1. **Investigations for the cause of obesity:** can be done to exclude endocrinal causes of obesity as:

- Free T4, TSH
- Cortisol and ACTH

2. **Investigations for complications of obesity:**

- Oral glucose tolerance test
- Lipid profile
- Liver enzymes: ALT and AST
- Abdominal ultrasound: for exclusion of NAFLD

Treatment of childhood obesity:

The treatment of overweight and obesity in children and adolescents requires a multidisciplinary approach. The immediate goal is to bring down the rate of weight gain, followed by a period of weight maintenance and finally weight reduction to improve BMI.

1. **Dietary management:** children and their families should be advised healthy eating habits through:
- Eating breakfast daily.
 - Consuming More vegetables and fruits.
 - Decreasing consumption of sugar sweetened beverages.
 - Limiting portion sizes.
 - Promoting intake of milk and milk products.

II. Increasing physical activity: Moderate intensity regular physical activity is essential for the prevention of overweight and obesity as well as for treatment of the same. Encourage children to do at least 60 minutes of moderate or greater intensity physical activity each day. Children should reduce inactive behaviors, such as sitting and watching television, using a computer or playing video games. Advise children to do more exercise in their daily lives (for example, walking, cycling and using the stairs).

III. Weight Loss Medications: Medications may be considered in obese children with comorbidities or those with severe obesity (BMI > 99th percentile) in addition to a lifestyle modification program that includes diet, exercise and behavior modification. Orlistat is the only medication approved for treatment of childhood obesity. This drug is approved for children more than 12 years of age.

Vitamin deficiencies & excess

Vitamin (A)

Daily requirements: 1000 – 2000 U / d.

Sources:

- Retinol in animal food: liver, meat, fish, eggs, milk fat.
- Carotenes (provitamin.) in plants: carrots and dark green vegetable.

Deficiency:

- **Ocular manifestations:** night blindness, dry conjunctiva and cornea (xerosis), keratomalacia, photophobia.
- **Other manifestations:** retarded growth impaired resistance to infection.

Excess:

- **Acute:** *Pseudo tumor cerebri.*
- **Chronic:**
 - Slow growth.
 - Anorexia.
 - Enlargement of liver and spleen.
 - Increased intracranial pressure.
 - Alopecia.
 - Carotenemia.
 - Drying and cracking of skin.

Vitamin (B1)

Daily requirements: 0.5 mg / d.

Sources: Meat, fish, eggs, milk, all legumes, nuts, whole grain cereals and oil seeds.

Deficiency: Beri beri:

- Dry; polyneuritis.
- Wet; heart failure.

Vitamin (B2)

Daily requirements:

- 0.5 mg/day for infants
- 1 mg/day for children

Sources: As B₁.

Deficiency: angular stomatitis, cheilosis, glossitis, and photophobia.

Vitamin (B3) (niacin)

Daily requirements: 5 mg / d.

Sources: As B₁.

Deficiency: Diarrhea, dementia and dermatitis.

Excess: Skin flushing, itching and hepatosplenomegaly.

Folic acid

Daily requirements: 50 µg/day.

Sources: Green leafy vegetables.

Deficiency: Megaloblastic anemia.

Vitamin (B12)

Daily requirements: 0.5 µg/day.

Sources: Muscles, organ meats, fish, eggs, milk and cheese.

Deficiency: Juvenile pernicious anemia.

Biotin

Sources: Yeasts, animal products, synthesized in intestine.

Deficiency: Dermatitis and seborrhea - “inactivated by avidin in raw egg white”

Vitamin (B6)

Daily requirements: 0.6 mg / d.

Deficiency: Irritability, convulsions, hypochromic anemia, peripheral neuritis in patients receiving isoniazid and oxaluria.

Excess: Sensory neuropathy.

Vitamin (C)

Daily requirements: 30 mg / d. for infants and 50 mg / d. for children.

Sources: Citrus fruits, tomatoes, cabbage and green vegetables (cooking has destructive effect).

Deficiency: Scurvy i.e., subperiosteal hemorrhage, rosaries, bleeding gums and hemorrhage and poor wound healing.

Excess: Oxaluria.

Vitamin (D)

Daily requirements: 400 – 800 U / d. and 1500 U / d. for prematures.

Sources: Fish liver oil, vit. D fortified milk and exposure to sunlight (Ultraviolet rays).

Deficiency: Rickets.

Excess: Nausea, weight loss, polyuria, nocturia and calcification of soft tissues.

Vitamin (E)

Daily requirements: 5 mg / d.

Sources: Germ oils of seeds, green leafy vegetables, nuts and legumes.

Deficiency: Hemolysis in premature newborns.

Vitamin (K)

Daily requirements: 5 µg / d. for infants, and 15 µg / d. for children.

Sources: Green leafy vegetables and liver.

Deficiency: Hemorrhage.

Excess: synthetic analogues may produce hyperbilirubinemia in premature Infants.

Rickets

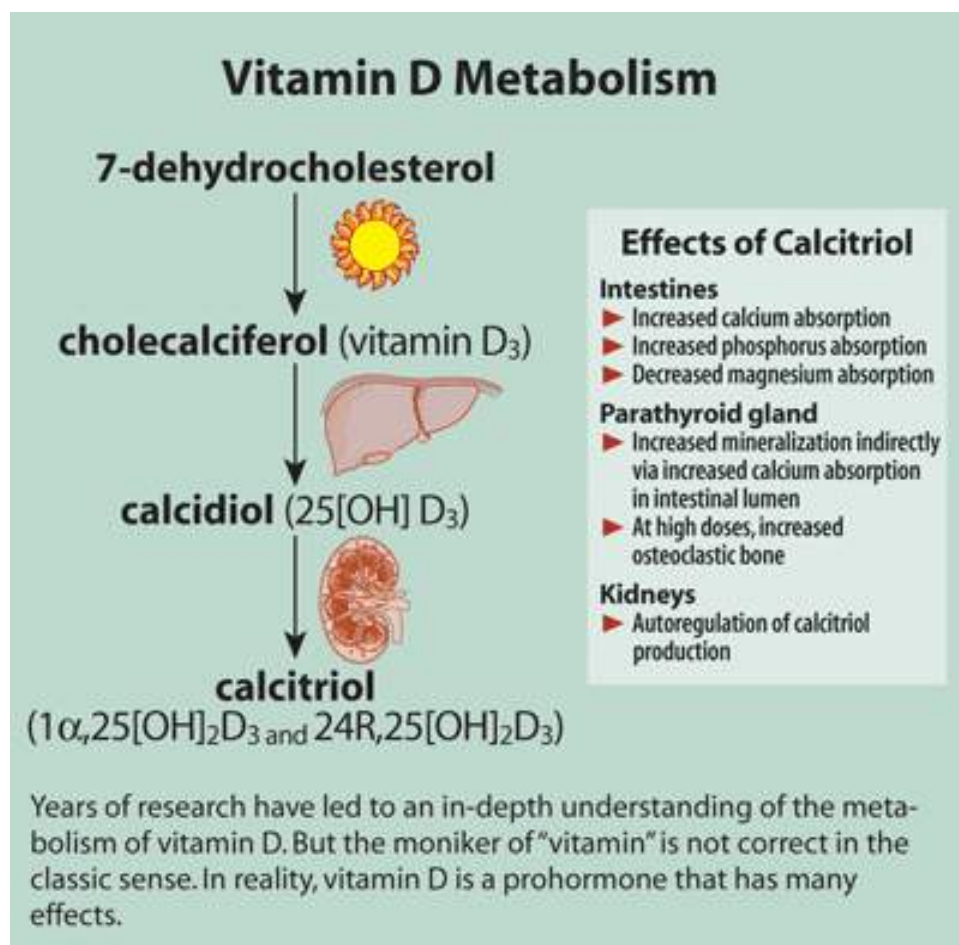
Definition:

Defective mineralization of growing bones, due to vit D deficiency or abnormal metabolism.

Vitamin D

Sources:

- Diets such as fats and oils.
- Vitamin D supplements.
- Ultraviolet sunrays effect on a precursor in the skin (7-dehydrocholesterol).



Types:

- Vitamin D₂ of plant origin.
- Vitamin D₃ of animal origin and that naturally formed in the skin.

Metabolism:

After absorption from the gut or formation in the skin, vitamin D passes through two steps of activation before it becomes ready to act:

1. **In the liver:** It is hydroxylated to 25-hydroxy Vit. D.
2. **In the kidney:** It is further hydroxylated to 1,25 dihydroxy Vit D (the active form).

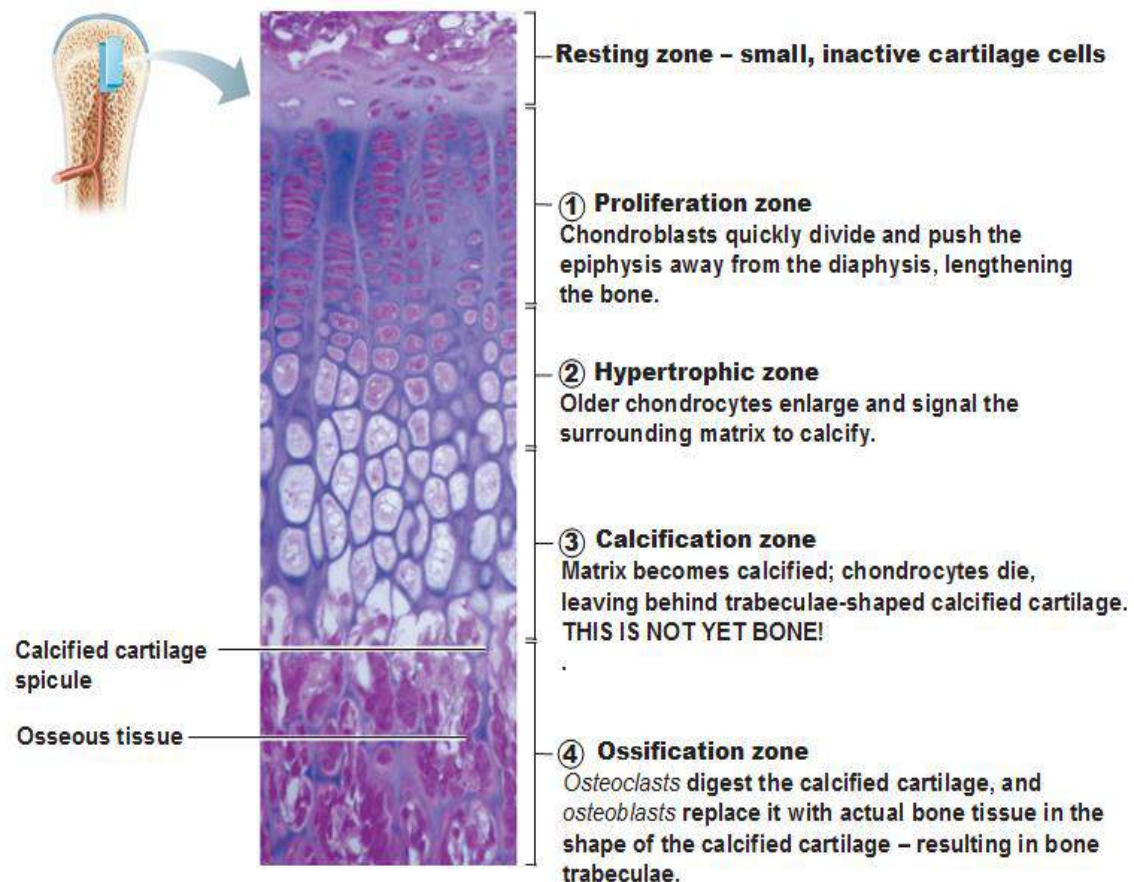
Actions:

1. **In the intestine:** *It increases absorption of Ca and P.*
2. **In the kidney:** *It increases reabsorption of Ca and P.*
3. **In bones:** *It stimulates mineralization of bones.*

Growth plate in normal bone shows:

- I. Zone of resting cartilage:** one layer of cells.
- II. Zone of proliferating cartilage:** regular columns of cells originating from resting layer.
- III. Zone of degeneration:** cells become swollen with glycogen, glycolytic enzymes and alkaline phosphatase. Calcium is deposited in the matrix. It is sharply demarcated in X ray film.
- IV. Zone of ossification:** blood vessels invade the developing bone with ossification and remodeling resulting in mature bone.

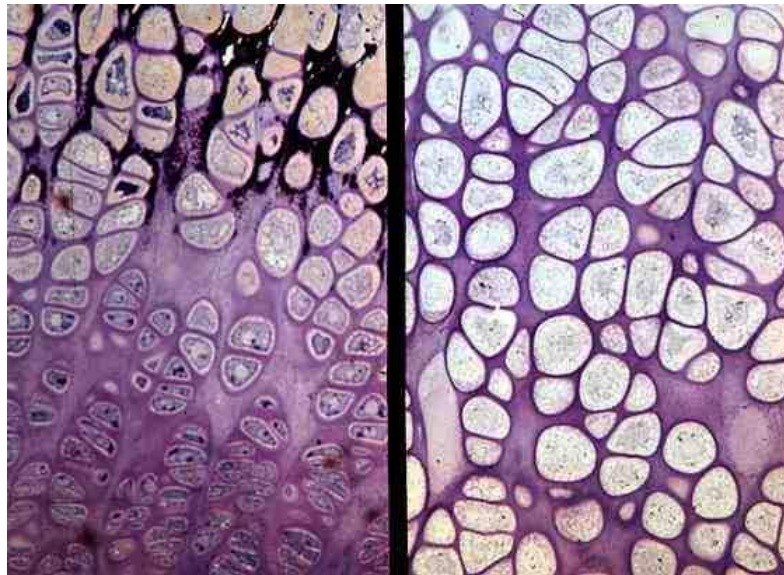
Epiphyseal Plate of Growing Long Bone



In rickets:

- I. Zone of proliferation:** increases and becomes very vascular causing enlargement of metaphyseal area and invades the adjacent zone of degeneration.
- II. Zone of degeneration:** fails to mineralize and the newly formed tissue called osteoid is excessively deposited and being soft it gives way with pressure causing bulging and deformity of metaphyseal area of long bones (this is responsible for flaring of the ends of long bones and rachitic rosary).
- III. In the shaft :** bone is resorbed and new osteoid if formed around the shaft from the periosteum.

IV. During healing of rickets: a new line of calcified bone (line of provisional calcification) appears at the end of zone of degeneration outstanding from rarefied osteoid then the area between it and the diaphysis gradually fills with normal density bone.



Non-calcified, hypertrophied growth plate in rickets (Right), compared to a normal growth plate (Left).

Radiologic Changes



Active



Healing



Healed

Active rickets:

- They occur early, are pathognomonic and diagnostic, and help in follow up. Distal ends of long bones appear flared, frayed and cupped.
- Distance between the distal end of radius and metacarpal bones appears wider than normal (by the area filled with osteoid).
- Diaphysis appears rarefied and may show double contour or deformity.

Healing rickets:

- Occurs 2-3 weeks after successful treatment. Appearance of the line of provisional calcification at the end of metaphysis, then the osteoid in between this line and diaphysis gradually ossifies.

Healed rickets:

- Bone density returns to normal with slight cupping remains as a stigma of previous rickets.

Biochemical (laboratory) manifestations:

- Serum alkaline phosphatase is elevated due to over activity of osteoblasts during the formation of excessive osteoid (normal 5-15 Bodansky units /dl).
- Serum inorganic phosphorus is decreased (normal 4.5-6.5 mg/dl).
- Serum calcium is maintained within normal values (9-11 mg/dl) due to compensatory hyperactivity of parathyroid gland.
- Vitamin D and its metabolites are decreased.

Clinical manifestations:

Vitamin D deficiency rickets most commonly occurs at the end of the first year and during the second year of life.

Early rickets:

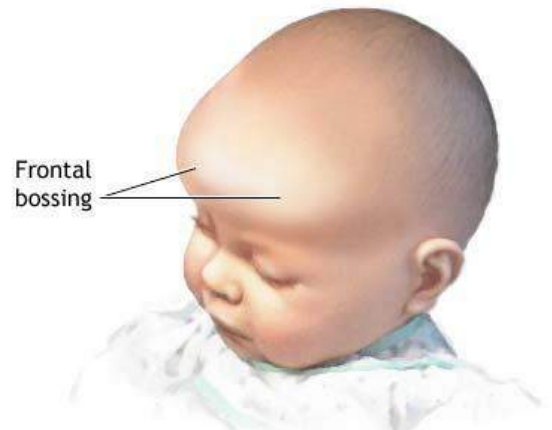
- 1. Craniotabes:** Occurs due to thinning of the inner table of occipital bone under the pressure of intracranial contents with failure of mineralization. It can be elicited by gentle pressure by both thumbs of the occipital bone, which produces a dent with crackling sensation (ping pong ball like). This can be elicited from 3 to 12 months of life.



- 2. Rosary:** Enlargement of costochondral junction of ribs giving the appearance of beads due to excessive osteoid formation.
- 3. Radiological finding of active rickets.**
- 4. Rise of serum alkaline phosphatase enzyme.**

Advanced rickets:**1. Head:**

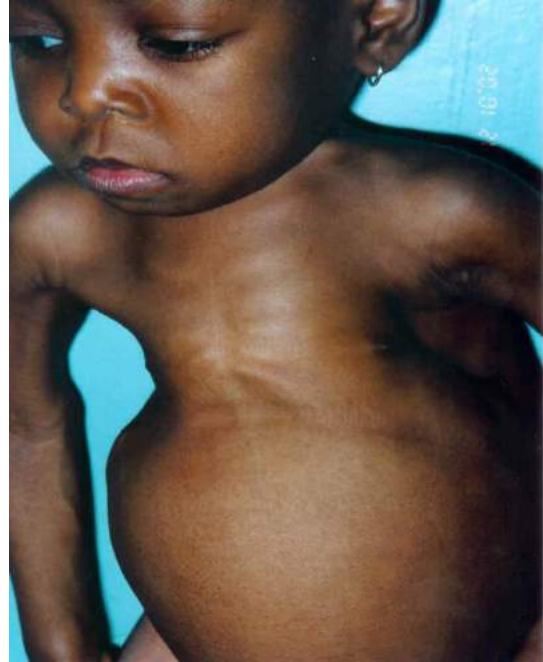
- Bossing of skull: excessive proliferation of cartilage at occipital and parietal eminences makes the skull looks like a box.
- Enlargement of head circumference.
- Delayed closure of anterior fontanel, which remains widely open.
- Delayed eruption of primary dentition with possible enamel hypoplasia.

**2. Thorax:**

- Rosary beads.
- Longitudinal sulcus: A longitudinal sulcus appears lateral to the rosaries due to compression of rib cage by atmospheric pressure at weakest point.
- Harrison's sulcus: A transverse sulcus along the lower border of the costal margin due to inward traction of the ribs at sites of diaphragmatic insertion.



- Forward protrusion of sternum and adjacent costal cartilage.
- Everted costal margin below Harrison's sulcus.
- The overall shape of the chest wall is called “pigeon chest”, which is nearly triangular in cross section.



3. Abdomen:

- Liver and spleen become palpable due to deformed chest and weak abdominal muscles. The abdomen appears protruded.

4. Pelvis:

- Pelvic inlet is narrowed by forward protrusion of sacral promontory, while pelvic outlet is narrowed by forward projection of the coccyx.
- This might be very hazardous in females during labor in the future.

5. Spinal column:

- Correctable kyphosis in the dorsal region and lordosis in the lumbar region due to muscle weakness and laxity of ligaments.

6. Extremities:

- Enlargement of metaphyseal region especially at wrists and ankles
- Marfan's sign: transverse groove above the medial and sometimes also the lateral malleolus.
- Deformities of long bones due to weight bearing.
- Greenstick fracture.
 - Rachitic dwarfism: due to spinal and lower limb deformities.
 - Weak muscles and lax ligaments causing delayed locomotor milestones.

Complications:

1. Respiratory: infections or atelectasis due to chest deformities.
2. Gastrointestinal tract: diarrhoea or constipation.
3. Bony deformities or fractures.
4. Anaemia: due to chronic infection or deficiencies.
5. Tetany: due to hypocalcaemia in late cases after exhaustion of parathyroids.

Prognosis

Usually good with improvement after exposure to sunshine in the morning or afternoon or after administration of Vitamin D. Deformities improve with normal growth but very slowly. Sometimes, severe skeletal deformities require orthopedic correction.

Prevention:

- Exposure to ultraviolet rays in sunshine or administration of Vitamin D orally.
- Daily requirements of vitamin D are 400-800 i.u /day.

- For low-birth weight infants, and patients of malnutrition or hypothyroidism during receiving their specific treatment, 1000-1500 i.u /day are needed for the accelerated rate of growth.

Treatment:

- Oral Vitamin D in a dose of 1500-5000 i.u/day for 6-8 weeks.
- Shock therapy: Vit D 600,000 i.u by I.M. injection or orally single dose.
- After 2-4 weeks, if no radiologic or laboratory evidence of complete healing occurs, the dose can be repeated.

Non-Vitamin D Deficiency Rickets

1. Vitamin D dependent type: due to defective 1-alpha-hydroxylase in the kidney or failure of end organ response to it.
2. Familial hypophosphatemic resistant rickets affects girls more, there is tubular defect in phosphate retention resulting in excessive urinary phosphate losses.
3. Tubular defects such as Fanconi syndrome with urinary loss of phosphate, glucose, amino acids and bicarbonates.
4. Chronic renal failure.
5. Acquired renal tubular damage, e.g., drugs.
6. Malabsorption syndromes: such as celiac disease, cystic fibrosis of the pancreas, cholestasis.
7. Anticonvulsant therapy causing increased metabolism of Vitamin D.

Tetany

- A state of neuromuscular excitability due to decreased ionized serum calcium. This represents about 54% of total serum calcium.
- Serum calcium may be decreased in cases of rickets after exhaustion of parathyroid glands or due to associated infection.
- Alkalosis decreases the ionized fraction of serum calcium, and tetany may occur in these situations even with normal total serum calcium.

Clinical manifestations:

- **Latent tetany:** There are no clinical manifestations except after mechanical or electric stimulation of nerves.
- **Manifest tetany:** carpopedal spasm, laryngospasm, or generalized convulsions.

Carpopedal spasm:
* flexion at the wrist
* flexion at the MCP joints
* extension of the IP joints
* adduction thumbs/fingers



22/06/2013

Hypocalcaemia

Treatment:

- I.V. administration of Calcium gluconate 5-10 ml of 10% solution, very slowly.
- After that calcium chloride or lactate orally 1 gm daily for one week.

Hypervitaminosis D

Causes:

- Excessive vitamin D intake.
- Hypersensitivity to vitamin D.

Symptoms and signs:

- The patient becomes weak, anorexic and irritable.
- Vomiting, and loses weight.
- Hypotonia, constipation.
- Polydipsia, polyuria, and dehydration.
- Pallor and macrocytic anemia.
- Hypercalcemia and hypercalciuria.
- Aortic valvular stenosis, hypertension.
- Retinopathy and clouding of the cornea and conjunctiva may occur.
- Proteinuria and manifestations of renal damage due to progressive nephrocalcinosis and nephrolithiasis.
- Metastatic calcification may occur in the heart, stomach, lungs, thyroid, and pancreas and blood vessels.
- Roentgenograms of the long bones reveal metastatic calcification of metaphyseal area and generalized osteoporosis and calcification of soft tissues around the joints.

Differential diagnosis:

1. Metastatic calcification due to chronic nephritis.
2. Hyperparathyroidism.
3. Idiopathic hypercalcemia.
4. Dystrophic calcification, which is a benign physiologic condition.

Prevention:

- Careful evaluation of vitamin D dosage.
- Warning the mother from vitamin D use without medical consultation.

Treatment:

1. Discontinuing vitamin D intake and decreasing intake of calcium.
2. Correction of dehydration and electrolyte disturbances.
3. Aluminum hydroxide gel by mouth to prevent calcium absorption.
4. Hydrocortisone.
5. Symptomatic treatment e.g. hypertension, arrhythmia.

Practice Questions

(Choose one correct answer)

- 1- What is the protein requirement of a child in gm/kg/day?
 - a) 6-8.
 - b) 4-6.
 - c) 2-3.
 - d) none of the above.
- 2- It is found in breast milk and inhibits growth of E-coli:
 - a) lactoferrin.
 - b) bifidus factor.
 - c) secretory IgA.
 - d) lysozyme.
 - a) vitamin E.
- 3- Malnutrition associated with edema and loss of appetite, commonly occurs at the time of weaning is:
 - a) metabolic syndrome.
 - b) marasmus.
 - c) Kwashiorkor.
 - d) obesity.
- 4- Which of the following is not absolute contraindication for breast feeding?
 - a) mother with hepatitis A.
 - b) mother with breast cancer.
 - c) infant with phenylketonuria.
 - d) infant with complete cleft palate.
- 5- Which of the following is an absolute contraindication of breast feeding?
 - a) smoking.
 - b) insulin therapy.
 - c) mastitis.
 - d) phenylketonuria.
- 6- . The daily caloric requirement in kcal/kg for a healthy full-term infant is approximately:
 - a) 40.
 - b) 60.
 - c) 80.
 - d) 100.



Chapter 5

Genetics and Teratology

Objectives:

1. Understand the features and types of chromosomes.
2. Classify types of genetic defects and mode of inheritance of different diseases.
3. Describe the normal human karyotype.
4. Classify types of chromosomal abnormalities according to either chromosome number or structure.
5. Illustrate different levels of genetic counseling.
6. Formulate a management plan for down syndrome
7. Compare between teratogens and mutagens and their effect on the body.

Contents:

1. Chromosome features
2. Genetic Defects and mode of inheritance
3. Chromosomal Abnormalities
4. Genetic Counseling
5. Trisomy 21 (Down syndrome)
6. Teratogenesis and Mutagenesis

HUMAN GENETICS

Human genetics deals with the variations between humans. These variations are, in part, reflections of differences that exist at the DNA level.

Chromosome features:

- (a) Chromatids. Metaphase chromosomes are divided longitudinally into two sister chromatids
- (b) Centromere. The chromatids are held together at the centromere, or primary constriction, which delineates the chromosome into a short arm (p) and a long arm (q).
- (c) Centromere position. Chromosomes are divided into three groups based on centromere location.
 - 1) Metacentric chromosomes: (such as chromosome 1), have a central centromere.
 - 2) Submetacentric chromosomes: (such as chromosome 6), have a centromere that is displaced from the center.
 - 3) Acrocentric chromosomes: (such as chromosome 13), have a centromere near one end.

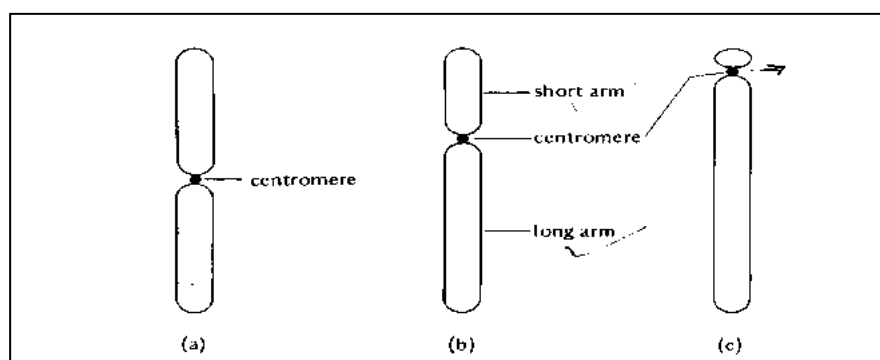
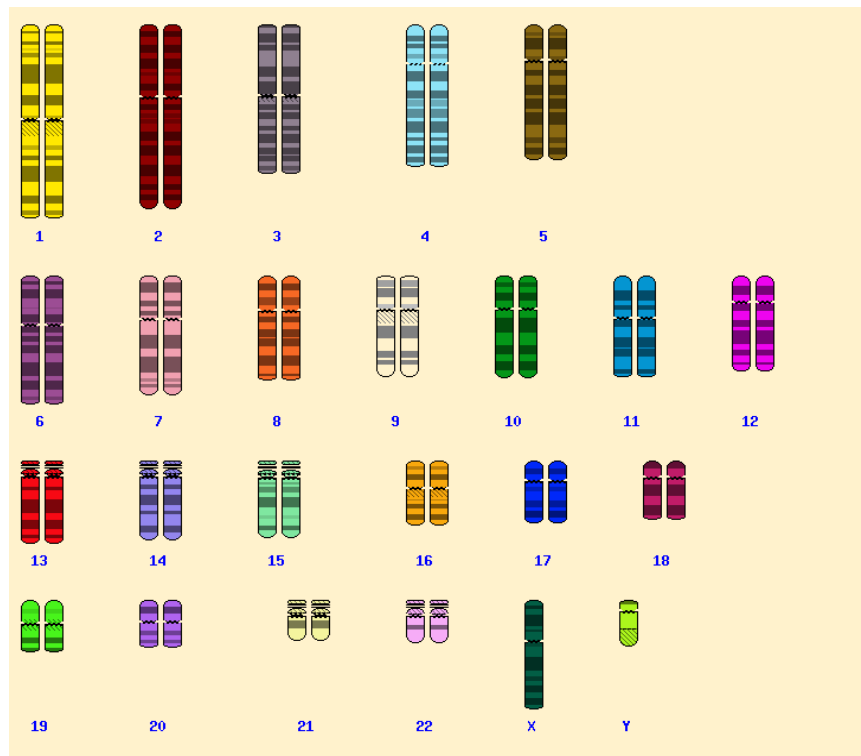


Figure 1: Types of chromosomes according to the position of centromere.



(a) Metacentric (b) Submetacentric (c) Acrocentric

Figure 2: Normal human karyotype

The normal human karyotype;(fig.2)

It consists of 23 pairs of chromosomes: 22 homologous pairs of autosomes and one pair of sex chromosomes.

The autosomes, by convention, are divided into seven groups:

A (chromosomes I to 3),

B (chromosomes 4 and 5),

C (chromosomes 6 to 12),

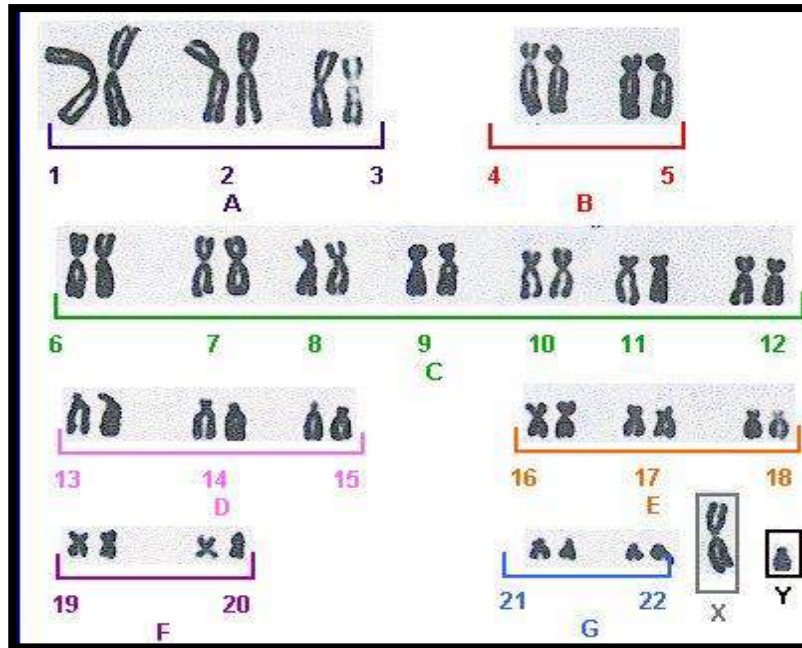
D (chromosomes 13 to 15),

E (chromosomes 16 to 18),

F (chromosomes 19 and 20),

G (chromosomes 21 and 22).

The sex chromosomes are **XX** or **XY**.



Diagnostic cytogenetic analysis can be performed with metaphase or prometaphase chromosomes obtained from rapidly dividing cells in tissue culture, or, in some cases, directly from tissues with high mitotic activity.

Genetic Defects and Mode of Inheritance

- The genetic diseases may range from loss or gain of entire chromosomes or large chromosome segments (Chromosomal abnormalities) to just change of a single base pair within a gene (single gene mutations).
- A third type of genetic diseases is a process in which a disorder results of interaction between one or more abnormal genes and environmental factors (**Multifactorial inheritance**).

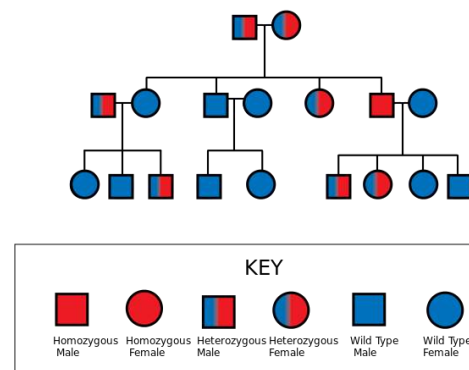
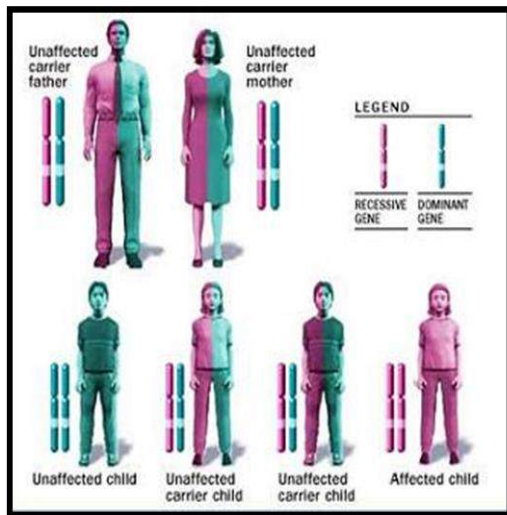
I - Single Mutant Gene:

- Each single mutant gene will exhibit one of 4 patterns of Mendelian inheritance:

Autosomal recessive	X - linked recessive
Autosomal dominant	X - linked dominant
- Disease is said to be autosomal or X-linked depending on whether the mutant gene is located on an autosome or X chromosome.

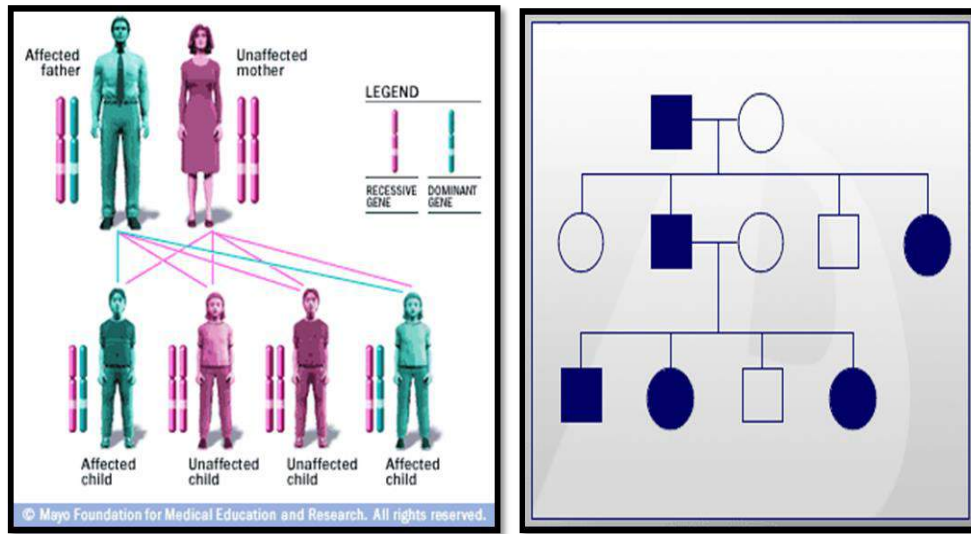
- Also, it is classified as recessive when the one mutant gene cannot express the disease, while dominant when only one mutant gene is sufficient to express the disease.

1 - Autosomal recessive inheritance:



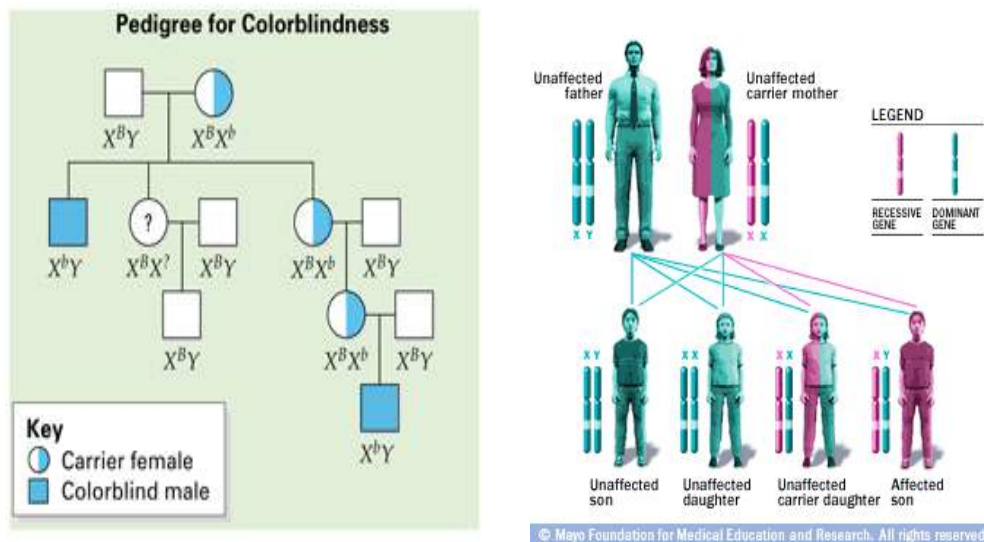
- It has the following characteristics:
 - **The parents:** Phenotype: usually normal.
 - **Genotype:** It is always heterozygous for this abnormal gene i.e., carrier for the disease. They usually related to each other (high incidence of consanguinity).
 - **The risk of occurrence and recurrence:** The child of 2 heterozygous parents has a 25% chance of being homozygous. Males and females are affected with equal frequency.
 - **The pedigree:** It usually "horizontal" i.e. affected individual are in the same generations.
 - **The most common diseases:** Thalassemia, sickle cell disease, and glycogen storage disease.

2 - Autosomal Dominant Inheritance:



- It has the following characteristics:
 - **The parents:** One only (paternal or maternal) has a one dominant mutant gene i.e. genotype abnormal and also phenotype express the disease. The other is normal as regard to genotype and phenotype. There is no relation between consanguinity and this disease.
 - **The risk of occurrence and recurrence:** The child of one affected parent has a 50% chance of being affected.
 - **Males and females** are affected with equal frequency.
 - **The pedigree:** It tends to be "vertical" i.e. there are affected individuals in several generations.
 - **The most common diseases** are: Hereditary spherocytosis, Huntington chorea, and achondroplasia.

3 – Sex- linked recessive inheritance



- It has the following characteristics:
 - **The parents:** The mother is genotypic carrier and phenotypic normal. The father is genotypic and phenotypic normal. There is no relation between consanguinity and this disease.
 - **The risk of occurrence and recurrence:** Fifty % of a carrier mother's sons will be diseased and 50% of a carrier mother's daughters will be carriers.
 - **The pedigree:** It tends to be "oblique" i.e. the affected individuals usually are carrier mother's brothers and carrier mother's sons.
 - **The most common diseases** are: Glucose - 6 - phosphate dehydrogenase deficiency, hemophilia A and B, and Duchenne muscular dystrophy.

4 - Sex - Linked Dominant Inheritance:

- It is a rare pattern of inheritance.
- The example of this mode is vitamin D-resistant rickets.

II - Multifactorial Inheritance:

- The points that characterize this pattern are:
- There is a similar rate of recurrence (2-10%) among all 1st degree relatives.
The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection.
- The likelihood that both identical twins will be affected is less than 100%.
- The risk of recurrence is increased when multiple family members are affected.
- The risk of recurrence may be greater when the disorder is more severe.
- The most common diseases are: allergic diseases, pyloric stenosis, and developmental dislocation of the hips.

Chromosomal Abnormalities:

These disorders are an important cause of mental retardation and congenital anomalies. They include abnormalities of either chromosome number or structure.

1 - Abnormalities of chromosome number

Human cell, in which number of chromosomes is 23, is called haploid cell. When the number of chromosomes is multiple of haploid (i.e. 46), the cell is called euploid.

Cell deviation from these is called aneuploid i.e. it has either extra chromosome (trisomies i.e., 47 chromosomes) or loss of chromosome (monosomies i.e., 45 chromosomes).

The most common example of abnormalities of chromosomal number is:

- Trisomy 21, Down syndrome (47 +21)
- Monosomy, Turner syndrome (45, X.)

2 - Abnormalities of chromosome structure

When a piece of a chromosome is missing, this is called "deletion", while "translocation" means transfer of chromosomal material from one chromosome to another.

The most common example of chromosomal structure abnormalities is:

- Translocation, Down syndrome {46+ t (14q –21q)}.
- Deletion, Cri du chat {46, (5p-)}.

Genetic Counseling

- **Genetic counseling (G.C.)** is defined as " an educational process that seeks to assist affected and/or at risk individuals to understand the nature of a genetic disorder, its transmission and the options available to them in management and family planning.
- **G. C** is an important form of preventive medicine. It is expensive but it is an effective way of diminishing society burden of chronic disease, which is far more expensive.

I - Premarital G.C.

1 - General advice

The chance of both parents carrying the same rare recessive gene is greater if they are related. The likelihood of the patient's disease being recessively inherited is thus increased in the presence of consanguinity.

2 - Specific advice:

Premarital screening carrier cases of some common recessive disorder e.g. thalassemia, is an important task. A premarital advice for those carriers may lead to prevention of such incurable diseases.

II - Preconception G.C.

1 - General advice:

The increasing risk of trisomy with increasing parental age must be put in mind.

2 - Specific advice:

Parents with previous baby with definite genetic disorder must be informed about the nature of this disease, the risk of recurrence and the available options, e.g. family planning if already have children (in the case of autosomal recessive disorder).

III – Post conception G.C.**1 - General advice:**

Avoidance of any teratogens e.g., radiation, drugs and infections during pregnancy.

2 - Special advice:

Pregnancy at risk of genetic disorder gets benefit of prenatal diagnosis. This may include ultrasound, amniocentesis and chorionic villus sampling and fetal blood sampling.

After a definite diagnosis of a genetic disorder, some disease may get benefit from intrauterine treatment e.g. hydrocephalus.

On the other hand genetic indication for interrupting pregnancy is still controversial (for religious causes) e.g. trisomy.

IV - Neonatal Screening**1 - General advice**

Universal neonatal screening is helpful for detection of common genetic disorder in which early detection is mandatory e.g. hypothyroidism.

2 - Specific advice

The high-risk newborn infant for specific genetic disease must be screened early for this disease, e.g. developmental dislocation of the hip.

Prenatal Diagnosis

Definition

1. Prenatal diagnosis is the process that aims at reaching a diagnosis regarding the presence or absence as well as the nature of a possible genetic or dysmorphic disorder present in a fetus.
2. Prenatal diagnosis allows the detection of birth defects and genetic disorders before delivery giving the parents the option of pregnancy termination or additional time for emotional adjustment.

Indications

1. **Prenatal diagnosis is indicated in cases with increased risk of birth defect or genetic disease such as:**
 1. Women >35 years (risk of Down syndrome)
 2. Elevated maternal serum alpha fetoprotein (risk of open defect, e.g. neural tube defects)
 3. Low maternal serum alpha fetoprotein (risk of Down syndrome)
 4. Prior history of autosomal trisomy (risk of trisomy)
 5. Parents with balanced chromosomal translocation (risk of unbalanced karyotype). Balanced translocation means translocation of a part of a chromosome to another chromosome within the same cell so that the genetic material of the whole cell is not changed.
 6. Family history of genetic disorder or carrier parent (risk of specific disorder in family)
 7. Family history of isolated structural defect (risk of same structural defect).

Techniques used in prenatal diagnosis

- 1-Maternal serum alpha fetoprotein (AFP)
- 2-Fetal ultrasound

3-Amniocentesis

4-Chorionic villus sampling (CVS)

5-Percutaneous umbilical blood sampling (PUBS)

6-Fetoscopy

Trisomy 21 (Down syndrome)

Down syndrome (DS) has a consistent and specific phenotype (mental retardation and mongoloid facies) and constant genotype (presence of three copies of chromosome 21).

Incidence:

Down syndrome occurs in approximately 1 in 600 births but the chance of occurrence varies with the mother's age.

The sex ratio at birth is 1.24 males to 1.0 female.

Genotypes of Down syndrome:

1 - Meiotic non-disjunction Trisomy 21:

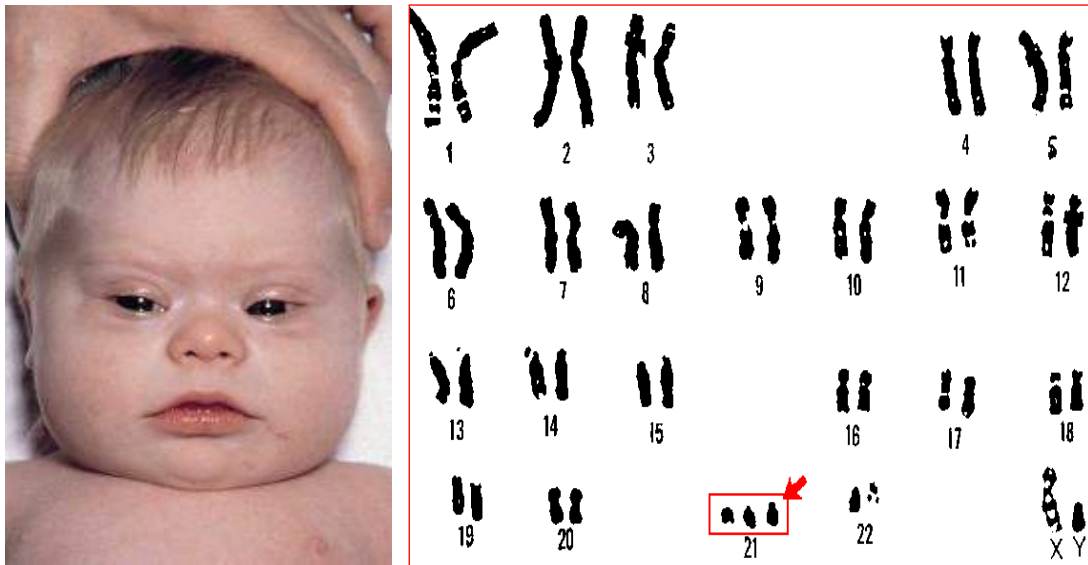
- All the cells show an additional No. 21 chromosome, i.e. 47, XX, +21. This type is resulting from meiotic non-disjunction.
- Approximately 95% of all Down syndrome are of this type.
- About 70% of trisomy 21 is born to mothers over 30 years.
- However, both parents are usually normal as regards to phenotypes as well as genotypes.

2 - Translocation Trisomy 21:

- All cells show normal number of chromosomes (46), however an extra-chromosome 21 is attached to another one (13,14, 15 or 21) i.e. 46, XX, +t (14q 21q).
- Approximately 4% of Down syndrome is of this type.
- The 2 underlying mechanisms of translocation are:
 - a) Sporadic type:** half of translocated Down syndrome arise de novo in the affected individual. Both parents are usually normal.
 - b) Inherited type:** another half inherited the disease from a translocation carrier parents i.e. 46, XX, t (14q 21q).

3 - Mosaicism:

- The incidence of this is about 1% of Down syndrome. They have various proportions of trisomy 21 (47, XX, + 21) and normal cells (46, XX) resulting from mitotic non-disjunction. This group may be of normal intelligence, depending on the number of trisomic cells present.
- The parents are usually normal, however, parental mosaicism had been discovered in some cases.



Clinical Manifestations:

1 - Early presentations:

- There is an increased frequency of prematurity, and birth weight is usually somewhat decreased.
- Prolonged physiological jaundice may be present.

2 - General manifestations:

- **The head:** It tends to be brachycephalic (occipital flattening). Head circumference is likewise smaller than average. The fontanelles may be late in closing. The hair is often fine and soft and may be sparse. The face is usually rounded with a flat profile.

- **The eyes:** They have many characteristic signs. The palpebral fissures slant upward and outward, and epicanthic folds are often present. The epicanthic folds and flat nasal bridge may give the appearance of hypertelorism, but interorbital distance is usually not increased. Small white spots, referred to as Brushfield spots, may be visible on the iris.
- **Ears:** They tend to be small and ear canals may be atretic.
- **Mouth cavity:** High arched palate may be present. In older children the tongue is often protuberant due to narrow oral cavity. Eruption of the teeth is frequently delayed and the positioning irregular. The neck short, and the nuchal skin excessive.
- **Hands** are short, and there is often a single transverse palmar crease (simian crease) and incurved fifth finger (clinodactyly). A single fifth finger crease is common. There is often a wide gap between the first and second fingers and toes. The dermal ridge patterns provide valuable diagnostic evidence.

3 - CNS manifestations:

- During the first years of life profound hypotonia and laxity of joints are often evident but lessen, as the child grows older.
- The most significant feature of Down syndrome is varying degrees of mental retardation. The milestones including speech, locomotion and social behavior are all delayed. The intelligent quotient (I.Q.) ranges from 20 to 75 with a mean of 50.

Complications of Down syndrome:

1. **Congenital heart diseases (CHD):** At least 40% have CHD, of which the most characteristic are endocardial cushion defects, followed by ventricular or atrial septal defects.

2. **Gastrointestinal malformation:** These include duodenal stenosis or atresia, esophageal atresia, anal atresia, and megacolon.
3. **Intercurrent infection:** Frequent respiratory, eyes and skin infections. Serous otitis media may end by hearing loss. Down syndrome has a decreased immune defense mechanism.
4. **Oncology:** There is a 10 to 30 fold increased risk of acute lymphoblastic leukemia compared with the general population.
5. **Sexual development:** Males may be infertile owing to interstitial fibrosis of the testes and hypoplasia of semeniferous tubules.
6. **Neurological complications:** In about 10 - 15% of Down syndrome has unstable atlanto-axial joint with subsequent dislocation and neurological complications.
7. **Congenital hypothyroidism** may coexist and requires thyroid replacement.
8. **Ophthalmic complications:** refractive errors and keratoconus.

Investigations:

1 - Cytogenetic studies:

- Although the clinical picture of DS is often straight forward, cytogenetic analysis should always be obtained.
- This test provides confirmation of the diagnosis as well as determine the genotypes of DS for accurate genetic counseling.
- Chromosomal study can be obtained from any dividing nucleated cell. Because blood is easy to obtain, cytogenetic studies are usually done on lymphocytes. If there is a suspicion of mosaicism, fibroblast cytogenetic studies must be considered.
- Karyotyping must be done for diseased infant and for parents.

2 - Laboratory findings:

- Polycythemia in the first days of life has been noted, as well as transient congenital leukemoid reaction that resolves by age 5 months.
- Complete blood pictures and bone marrow examinations are mandatory when leukemia is suspected.

3 - Imaging studies:

- Pelvis X-ray may reveal flattening of the inner edges of the ileum and widening of the iliac wings.
- The second phalanx of the little finger is often small or absent.
- Screening lateral cervical radiograph has been recommended at about age 6 years to diagnose unstable atlanto-axial joint.
- Echo-Doppler evaluation is mandatory for all cases even if there are no clinical cardiac abnormalities

Genetic counseling:

i – Preconception:

Advise the mother not to be pregnant in advanced ages to prevent the occurrence of DS and other genetic disorders.

ii - Prenatal:

Pregnant women with the risk of having DS (old age, translocated carrier) may get benefit from prenatal diagnosis. This procedure can be achieved by:

- a. Screening tests:** decreased maternal serum alpha - fetoprotein and unconjugated estriol while increased human chorionic gonadotropin.
- b. Confirmation test:** amniocentesis or chorionic - villus sampling for chromosomal analysis.
- c.** After definite prenatal diagnosis medical abortion may be indicated in some countries.

iii - Postnatal:

Family with DS must be aware of the nature of the disease and recurrence risk (RR), which depends upon cytogenetic analysis of infant and parents.

Recurrence risk

Recurrence risk of Down syndrome due to various cytogenetic patterns:

<u>Infant</u>	<u>Parents</u>	<u>Recurrence risk</u>
Trisomy 21:	Normal Mosaic (M or F)	1-2% Depends upon degree of mosaicism
Translocation:		
14/21	Normal	Slightly increased
14/21	Carrier (mother)	10- 15%
14/21	Carrier (father)	3-5 %
21/21	Carrier (M or F)	100%
Mosaic:	Normal Mosaic (M or F)	Slightly increased Depends upon degree of mosaicism

Teratogenesis and Mutagenesis

- **Both teratogens and mutagens** can cause alterations in the structure and functioning of the body, but the mechanisms differ.
- **Teratogens** cause damage by altering embryonic or fetal development directly. **Mutagens** cause changes within the genetic material that may lead to inherited disease if the germ cells are affected or to cancer if somatic cells are involved.

TERATOGENESIS

- A teratogen is an agent that can produce a permanent alteration of structure or function in an organism after exposure during embryonic or fetal life.
- Teratogens include environmental factors, medications, drugs of abuse, and occupational chemicals.

Clinical teratology is concerned with the following:

1. The relationship between the anomalies in a child and teratogenic exposure.
2. The risk of anomalies for a child of a woman who has been exposed to a teratogen.
3. The risks to a pregnant woman of treatment or exposure to a given agent.

Principles of clinical teratology:

Teratogens act at vulnerable periods of embryogenesis and fetal development.

- a. In general**, the embryo is most sensitive to damage between 2 and 10 weeks after conception (4 to 12 weeks after the beginning of the last menstrual period). During this time, most structures and organs are differentiating and forming. Each structure has its own period of greatest sensitivity within this time.
- b. The first 2 weeks after conception** is generally considered to be a period that is resistant to the induction of malformations by teratogens. At this point, the embryo consists of few cells, and damage is usually either repaired completely or results in death of the embryo.
- c. By 10 weeks after conception**, most structures in the embryo have been formed, so malformations are unlikely to be produced by subsequent exposures.

Teratogenic factors are thought to be responsible for about **10%** of all congenital anomalies.

These factors fall into several groups:

1) Maternal metabolic imbalance: as children of women with insulin-dependent diabetes mellitus have a risk of congenital anomalies that is two to three times greater than that of the general population.

2) Infectious agents can involve the embryo or fetus transplacentally.

For example:

- ✓ Congenital toxoplasmosis (may be asymptomatic or present with a variety of abnormalities. Severely affected infants may exhibit chorioretinitis, hydrocephaly or microcephaly, intracranial calcification, and mental retardation.
- ✓ Rubella (German measles) embryopathy produces fetal growth retardation, hepatosplenomegaly, purpura, jaundice, microcephaly, cataracts, deafness, congenital heart disease, and mental retardation.
- ✓ Congenital cytomegalovirus (CMV) infection may produce fetal growth retardation, hepatosplenomegaly, hemolytic anemia, purpura, jaundice, intracranial calcification, and microcephaly.

3) Ionizing radiation causes DNA damage and can injure the developing embryo.

4) Environmental agents and occupational chemicals:

1. Hyperthermia, regardless of cause, that produces sustained elevation of maternal body temperature to levels substantially above normal (e.g., 40 °C)
2. Lead

5) Drugs of abuse

(1) **Alcohol:** Classic fetal alcohol syndrome occurs among the children of women with chronic, severe alcoholism during pregnancy.

(2) **Cocaine:** Maternal use of cocaine during pregnancy has been associated with placental abruption and the occurrence of vascular disruptions such as encephaloclastic lesions in the fetus.

(3) **Medications:**

1. **Thalidomide** exposure in the first trimester of gestation may produce limb reduction defects, facial malformations, and other congenital anomalies.
2. **Aminopterin** and other **cytotoxic drugs** kill rapidly growing cells in the fetus and cause growth deficiency and a variety of other anomalies.
3. An increased rate of congenital anomalies is observed among the children of epileptic women treated with **anticonvulsant medications** during pregnancy.

MUTAGENESIS

A **mutagen** is an agent that can alter the DNA or chromosomes.

1. While teratogens act only during embryonic or fetal development, mutagens may act at any time of life. Thus, mutations may occur in the gamete, zygote, embryo, fetus, child, or adult.
2. Teratogens affect the development of a tissue, organ, or structure. In contrast, a mutation always affects a single cell.
 - a) If this single cell is a germ cell, the mutation may be transmitted to subsequent generations.
 - b) If a single cell in a very early embryo sustains a mutation, many tissues of the embryo (including the germ cells) may be affected as embryogenesis progresses.
 - c) If a single cell in an embryo, fetus, child, or adult sustains a mutation; only cells derived from the mutated cell will carry the mutation. Most cells in the individual will not contain the mutation.

Practice Questions**(Choose one correct answer)**

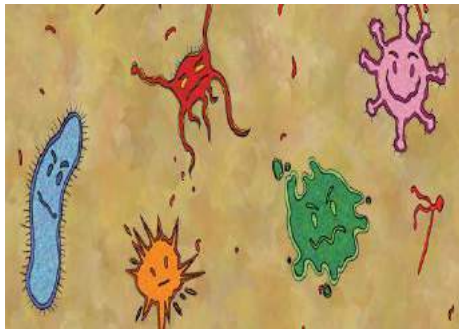
- 1- **Mutagen:**
 - a) acts in the first 2 weeks after conception.
 - b) acts between 2-10 weeks after conception.
 - c) acts between 10-12 weeks after conception.
 - d) acts at any time of life.

- 2- **Chorionic villus sampling enables prenatal diagnosis at gestational age of:**
 - a) two weeks.
 - b) four weeks.
 - c) eight weeks.
 - d) twelve weeks.

- 3- **In sex linked recessive diseases; the pedigree is:**
 - a) horizontal.
 - b) vertical.
 - c) oblique.
 - d) sporadic.

- 4- **Autosomes are arranged into:**
 - a) four groups.
 - b) five groups.
 - c) six groups.
 - d) seven groups.

- 5- **Recurrence risk of Down syndrome is 100% if:**
 - a) mother is non-disjunction.
 - b) mother is mosaicism.
 - c) mother is translocation carrier 14 to 21.
 - d) mother is translocation carrier 21 to 21.



Chapter 6

Infection

Objectives:

1. Discuss definition, types and etiology of fever.
2. Understand management of fever of unknown origin.
3. Enumerate causes of fever with rash.
4. Understand causes, pathophysiology, clinical picture and management of common infectious diseases in pediatrics.

Contents:

1. Fever or Pyrexia.
2. Fever of unknown origin.
3. Fever and rash.
4. Viral infections:
 - Measles
 - German measles
 - Chickenpox
 - Mumps
 - Poliomyelitis
 - Encephalitis
5. Bacterial Infections:
 - Scarlet fever
 - Pertussis
 - Diphtheria
 - Typhoid fever
 - Meningitis
6. Parasitic infestations:
 - Amebiasis
 - Giardiasis
 - Ascariasis
 - Oxuriasis
 - Schistosomiasis

Fever or Pyrexia

Fever is defined as an elevation of body temperature above the normal daily variation (a rectal temperature $>38^{\circ}\text{C}$ or oral temperature $>37.5^{\circ}\text{C}$).

Most fevers are self-limiting, relatively harmless and important immunological defense mechanism.

Pathophysiology:

- The normal body temperature is regulated by the hypothalamus which acts like a thermostat.
- Infections release substances known as pyrogens reaching the hypothalamus and releasing arachidonic acid which is converted into prostaglandin that resets the set-point of this thermostat to a higher point resulting in the development of fever.
- Most antipyretics work by decreasing the production of prostaglandin.

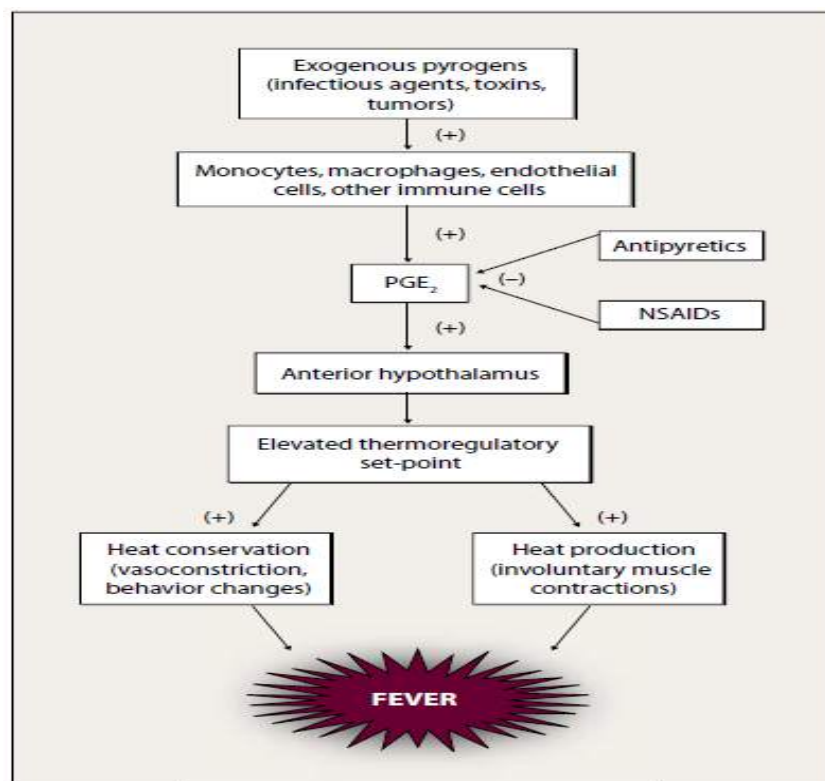


Figure 1 Pathophysiologic Mechanism of Fever
Abbreviations: NSAIDs = nonsteroidal anti-inflammatory drugs; PGE₂ = prostaglandin E₂

How should temperature be measured?

- Rectal temperature is the 'gold standard' for measuring central body temperature.
- Axillary temperature (about 0.5°C lower than the rectal temperature)
- Tympanic membrane temperature (miss fever in 30–40% of children) is less accurate and less reliable.

Types of Fever:

I. Continuous Fever:

The temperature doesn't reach base line at any time in the 24 hours, the variation between upper and lower limit doesn't exceed 1 °C.

II. Remittent Fever:

The temperature doesn't reach base line at any time in the 24 hours, the variation between upper and lower limit exceeds 1° C (Figure 2).

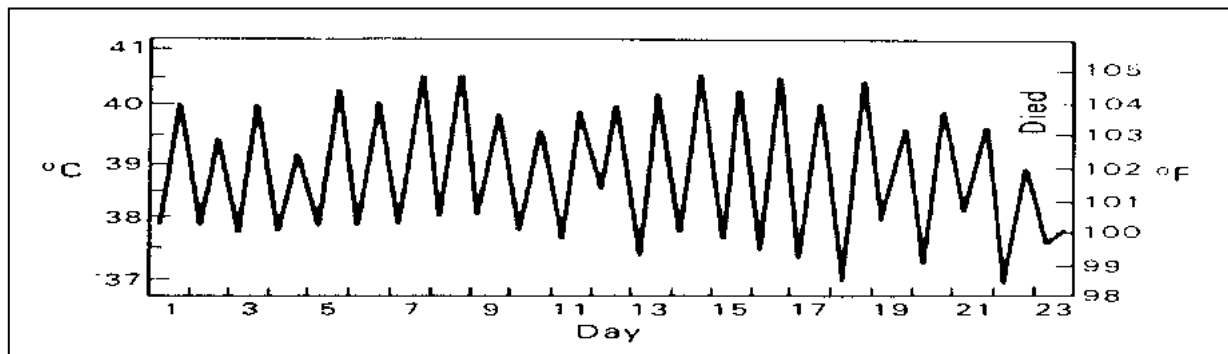


Figure 2: Remittent Fever

III. Intermittent Fever:

At any time in the 24 hours, the temperature reaches base line, (occurs in urinary tract infection, cholangitis and pus under tension) (Figure 3).

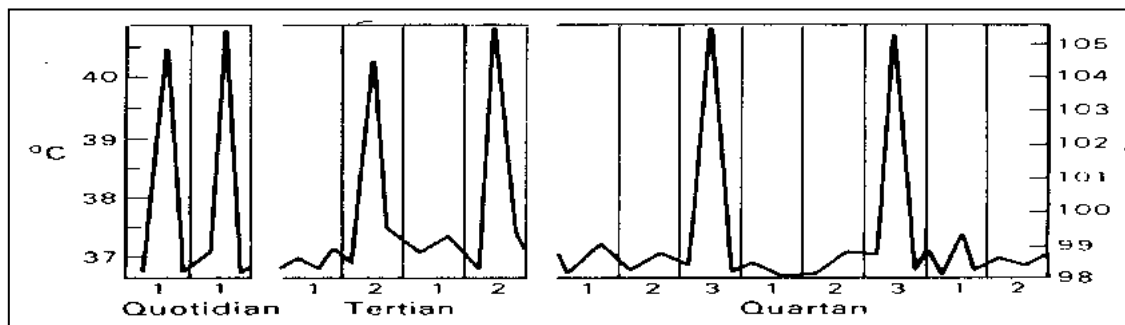


Figure 3: Intermittent Fever.

IV. Undulant Fever:

There are several days of continuous or remittent fever followed by several days of normal temperature which occurs successively. This occurs in: brucellosis, relapsing fever and Hodgkin's disease.

V. Recurrent Fever:

Episodes of fever of more than six month's duration.

Etiological classification of fever

I. Infections

- **Systemic infection**: bacteremia, TB, Brucellosis, toxoplasmosis & infectious mononucleosis
- **CNS infection**: encephalitis, meningitis, brain abscess.
- **Respiratory infection**: common cold, pharyngitis, otitis media, pneumonia.
- **Heart infections**: myocarditis and infective endocarditis
- Enteric infection
- Infection of the liver and biliary tract
- Urinary tract infection
- **Exanthems** e.g., Measles, Rubella, Varicella etc.
- **Abscess** (localized infection)

2. **Collagen vascular or connective tissue diseases:** e.g. Rheumatic fever, Juvenile Rheumatoid Arthritis
3. **Neoplastic Diseases** e.g. leukemia
4. **Dehydration**
5. **Drugs and immunization:** *Drug fever, atropine poisoning, immunization reaction and Salicylate intoxication*
6. **Blood diseases:** e.g. transfusion reactions, leukemia, sickle cell anemia
7. **High environmental temperature.**

Treatment:

I. Treatment of the cause.

II. Symptomatic treatment:

1. Antipyretics

- Provide symptomatic relief, but not change the course of infectious diseases.
- The recommended dose of paracetamol is 10-15 mg/kg/dose (max 600 mg), orally, no more than every 4 h, liver toxicity rarely occurs with paracetamol.
- The recommended dose of ibuprofen is 5–10 mg/kg/dose (max 400 mg), orally, given 6–8-hourly. Ibuprofen is not recommended for babies < 6 months old. Ibuprofen can be associated with gastrointestinal bleeding.

2. Environment

- Tepid sponge bathing. (Not alcohol, not ice water)
- A room temperature can be reduced by opening a window or using a fan (directing the fan away from the child as the cold air can induce shivering and a resultant rise in temperature).

- Clothing should not be underdressed or overwrapped. Infants lose excess heat from their heads, and it is important to keep their heads uncovered when they have a fever.
- Hydration: encourage the child to drink cool drinks. Breast feeding should continue.

Fever of Unknown Origin (FUO)

Definition:

Children with fever of 38 °C or greater (documented by a health care provider) for which the cause couldn't be identified (after 3 weeks of evaluation as an outpatient, after routine investigations, or after **one** week of evaluation in a hospital).

Causes:

Most common causes are infections, connective tissue diseases and neoplasms (in order of frequency).

I. infections:

1. Systemic bacterial infections:

- T.B, Salmonellosis, septicemia, brucellosis, and meningococcemia.

2. Localized bacterial infections:

- Abscesses (abdominal, brain, dental, hepatic, pelvic, rectal, subphrenic, peritonsillar)
- Otitis media, Sinusitis, Mastoiditis, pharyngitis, tonsillitis.
- Endocarditis, Pneumonia, Osteomyelitis, Pyelonephritis.

3. Spirochetes:

- Relapsing fever, leptospirosis, Lyme disease & syphilis

4. Viruses:

- Hepatitis, cytomegalovirus, infectious mononucleosis and HIV

5. Fungal: e.g. histoplasmosis

6. Parasitic:

- Amebiasis, giardiasis, malaria, toxoplasmosis and visceral larva migrans.

II. Rheumatologic Diseases:

Juvenile Rheumatoid Arthritis, Systemic lupus erythematosus (SLE), Rheumatic Fever, Dermatomyositis, and Kawasaki disease.

III. Neoplasms:

Leukemias, Lymphomas, Neuroblastoma, and Wilm's tumor.

IV. Miscellaneous:

1. Drug fever.
2. Serum Sickness.
3. Familial Mediterranean fever.
4. Sickle cell crisis.
5. Diabetes Insipidus.
6. Inflammatory Bowel disease.
7. Thyrotoxicosis.
8. CNS dysfunction (Severe brain damage and Epilepsy can cause fevers).
9. Immunodeficiency.

V. Undiagnosed Fever

Diagnosis:

I. Careful history.

II. Through physical examination.

III. Investigations:

1. Initial Tests:

- ***CBC with a differential cell count:***

- Patients with polymorphonuclear leukocytosis greater than 10,000/uL have a severe bacterial infection

- Absolute neutrophilia less than 5.000/uL is an evidence against bacterial infection other than typhoid fever.
- *Blood film may reveal malaria.*
- *Blood Culture*
- *E.S.R:*
 - Exceeding 30mm/hr indicates inflammation.
 - Exceeding 100mm/hr suggests T.B., malignancy or rheumatologic diseases.
- *C-reactive protein:*
 - (>6 mg/dL). It can help to identify children at risk of occult serious bacterial infection.
- *Liver functions.*
- *Renal functions.*
- *Urine Analysis:* UTI is a common source of FUO.
- *Stool analysis.*
- *Tuberculin Skin Testing.*
- *Common serological tests:* typhoid (Widal), brucella, infectious mononucleosis (monospot).
- *Radiographic Examination* of the chest, sinuses, mastoiditis or G.I. tract may be indicated by specific history and physical findings
- *HIV serology:* significant variability in manifestations of primary HIV infection.
- *Additional Tests:* based on the results of history, physical exam and results of initial testing.
 - Bone marrow examination may reveal leukemic infiltration, metastatic neoplasm, fungal or parasitic diseases and histoplasmosis.
 - Specific serological tests: toxoplasmosis, tularemia.
 - Serum anti-nuclear antibody: in children over age 5 with family history of rheumatologic disease
 - Immunoglobulins: serum IgG, IgA and IgM in children with evidence of

recurrent or persistent infections and in those with persistent fever and a negative initial evaluation

- Imaging and other evaluations:
 - CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, and intra-abdominal and intrathoracic lymph nodes
 - Abdominal ultrasound.
 - Radioactive scan may be helpful in detecting osteomyelitis and abdominal abscesses.

Fever and Rash

- Fever accompanied by rash is a common finding in pediatric patients.
- The rash may be:
 - **Macula:** A color change of the skin
 - **Papules:** A raised lesion less than 1 cm in diameter
 - **Maculopapular:** A combination of macules and papules e.g. scarlet fever, measles, German measles, roseola infantum, sweat rash, drug rash.
 - **Purpura:** Cutaneous lesions caused by leakage of red blood cells, may be/not be palpable with a diameter more than 5 mm and
 - **Petechia:** is a similar lesion to purpura but smaller than 5 mm diameter
 - **Vesicle:** is a blister like lesions less than 1 cm diameter containing fluid and the larger lesion is called Bullae e.g. chickenpox, herpes simplex, herpes zoster and popular urticaria.
 - **Pustule:** a pus-containing vesicles, that may leave scar after healing,
 - **Enanthem:** A mucosal rash on the mucous membranes (e.g. Koplik spots in measles, petechial lesion on soft palate in rubella).

Viral Infectious Diseases

Measles (Rubeola)

Etiology:

Measles virus (RNA virus).

Mode of infection:

- Droplet infection.
- Contaminated articles by secretions of infected child.

Incubation period: 1 to 2 weeks

Infectivity period:

From 4 days prior to 4 days after onset of rash.

Age incidence:

The target age groups are 9 to 23 months. However, many cases have been reported in infants less than 9 months of age. In immunized persons, measles occurs most often among 9 to 19 years old. Compared with the pre vaccine era, incidence rates have decreased in all age groups.

Clinical manifestation:

1. Typical illness

1. Prodromal (catarrhal) stage:

- Severe; It lasts for about 3 ± 1 day.
- It is characterized by:
 - Fever: it is an early sign. The temperature increases gradually to a value of 39.5 ± 1.0 over a four-day period, with abrupt rise as the rash appears. When the rash appears on the feet, the temperature drops abruptly.
 - Malaise: There is a general malaise starting with appearance of fever and patient usually appears ill until 1 day after the temperature drops.

- Coryza: Sneezing, rhinitis, and nasal congestion are common.
- Conjunctivitis: Conjunctival injection, lacrimation, and photophobia are usually present.
- Cough: increases in severity throughout the prodromal period and has a brassy quality.
- Koplik's spots: pathognomonic enanthem, characterized by small bluish-white spots on a red background may be seen on the buccal mucosa from 2 days before to 2 days after onset of rash.

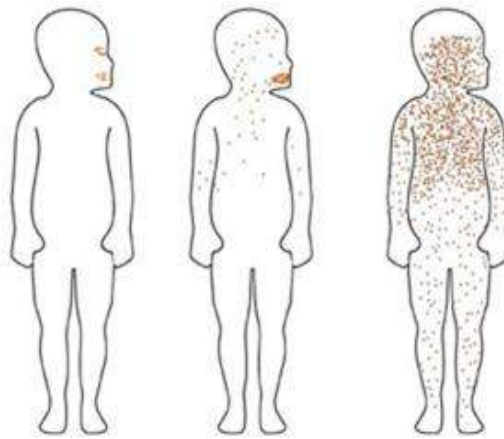


Figure 4: Progression of measles infection



Figure 5: Koplik's spots on the buccal mucosa of a child with measles

2. *Eruptive (exanthema) period:*

- Usually appears 2 to 4 days after onset of fever.
- The rash is initially maculopapular, but becomes confluent, particularly on the face.
- The rash classically starts behind the ears and on the forehead and then spreads to the trunk and extremities by the third day.
- The rash lasts 5 to 7 days and fades in order of appearance.

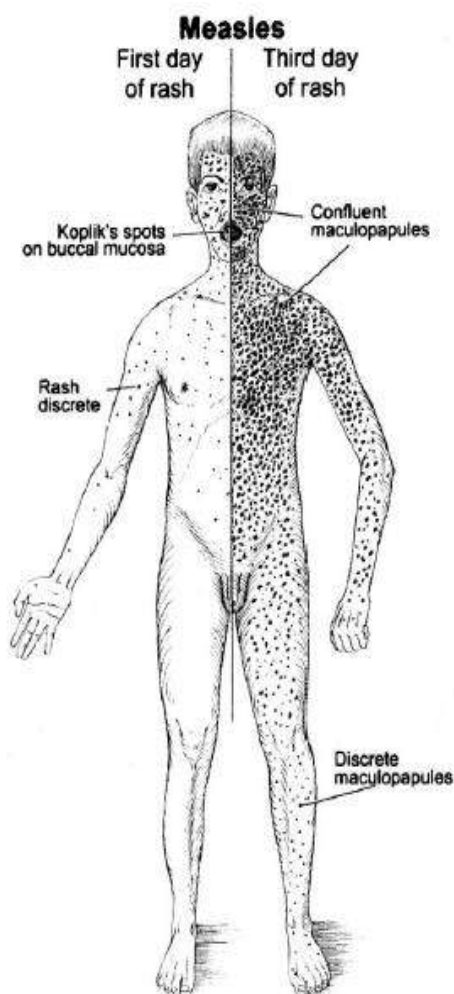


Figure 6: Development and distribution of measles rash

II. Modified measles:

Modified measles is an infection, which occurs, in the partially immune individual. It is characterized by a generally mild illness, which usually follows the regular sequence of events in measles.

III. Atypical measles:

It is a rare manifestation of measles infection that occurs in some persons who received killed measles vaccine in the past. It is characterized by fever, pneumonia, edema, and hepatic insult.

IV. Measles in the immunocompromised host:

Measles infection in patients with immune deficiency is usually severe, protracted, and frequently fatal.

Complications:

I. Respiratory complications:

1. **Otitis media:** it is the most common complication of measles.
2. **Pneumonia:** it is the most common cause of death in measles. It may be caused by:
 - Measles virus itself (Hecht's pneumonia).
 - Secondary bacterial infection, particularly the pneumococcus, streptococcus, staphylococcus, and H. influenza.
 - Exacerbation of an existing tuberculous process.
3. **Other respiratory complications:** may include sinusitis, laryngitis, bronchitis, and bronchiolitis.

II. Neurologic complications:

1. **Encephalitis:** Pathogenesis of encephalitis is:
 - *Direct invasion of virus to brain tissue:* which occurs early even during prodromes.
 - *Immunologic mechanism:* which occurs 4 to 7 days after onset of rash.
 - *Slow, viral infection (subacute sclerosing panencephalitis):* which begins

insidiously an average of 7 years following initial infection and characterized by progressive personality changes, myoclonic seizures, motor impairment, coma and death

- *Other rare manifestations:* as Guillain-Barre syndrome, and cerebral thrombophlebitis.

III. Hematological complications:

1. Black (hemorrhagic) measles
2. Thrombocytopenic purpura.
3. DIC
4. Purpura fulminants and gangrene of legs.

IV. Cardiac complications:

Transient carditis or pericarditis may occur rarely.

V. Measles in pregnancy:

It may result in fetal mortality and morbidity.

Investigations

- antibody rising titer is usually a practical method for diagnosis.

Differential Diagnosis

- Measles must be differentiated from rubella, roseola, enterovirus, scarlet fever, and drug eruption.

Treatment

I. General lines: Isolation, bed rest and adequate fluid intake.

II. Symptomatic & supportive lines:

1. Antipyretic.

2. Sedative
3. Antitussive.
4. Oral vitamin A (400,000 IU).

III. Specific treatment: No specific treatment

IV. Treatment of complications: Broad spectrum antibiotics should be used when secondary bacterial infection is present.

Prevention: Immunization.

German measles (Rubella) (Three-day measles)

Etiology:

Rubella virus (RNA virus).

Mode of infection:

- Droplet infection.
- Transplacental.

Incubation period: 2 to 3 weeks

Infectivity period: Seven days before rash to 5 days after; up to 10-12 months for congenital.

Clinical manifestations:

I. Prodromal(catarrhal) phase: (mild and short;1-2 days)

- Fever is mild ($< 38.3^{\circ}\text{C}$) or absent.
- Mild catarrhal symptoms are usually present.
- The most characteristic sign is cervical lymphadenopathy.

II. The exanthem:

- On the first day maculopapular rash begins on the face and spreads quickly.
- During the second day the rash may assume a pinpoint appearance.

- The eruption usually clears by the third day.

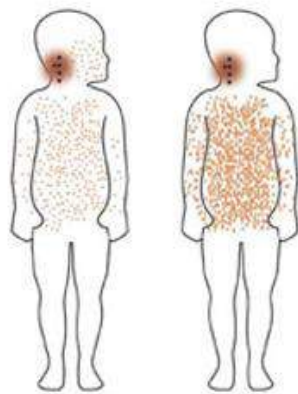


Figure 7: Progression of rubella infection



Figure 8: Rubella rash on back of child



Figure 9: Rubella rash on chest and arms.

III. Congenital rubella syndrome

- Low birth weight.
- Ophthalmic (micophthalmia, blindness, cataract)
- Auditory (deafness)
- Congenital heart diseases (PDA most common).
- Cerebral (microcephaly, hydrocephalus, mental retardation).
- Hepatitis.
- The skin manifestations are called "blueberry muffin lesions".



Figure 10: Infant with "Blueberry Muffin" skin lesions of congenital Rubella

Complications:

1. Encephalitis.
2. Thrombocytopenic purpura.
3. Arthritis of small joints.
4. Congenital rubella syndrome: If the mother is infected within the first 20 weeks of pregnancy.
5. Others: carditis, and pericarditis are rare complications of rubella.

Investigations:

I. Direct viral isolation from nasal or throat specimens.

II. Indirect demonstration of antibodies:

1. Hemagglutinin - inhibition (HI) antibody test.
2. Rubella - specific IgM antibody test.

Differential Diagnosis:

Rubella must be differentiated from drug eruption, measles, infectious mononucleosis, and enteroviral exanthems.

Treatment: No specific therapy.

Prevention: See immunization and isolation measures.

(Chickenpox) Varicella

Etiology: Varicella-Zoster virus (DNA, herpes virus).

Mode of infection:

- Droplet infection.
- Contact with skin lesions.

Incubation period: 2:3 weeks

Infectivity period: 1 day before the appearance of the rash until all lesions are crusted (about 7-8 days).

Clinical manifestations:

I. In normal children:

- ***Prodromal stage:*** usually short (about 24 hours), with mild symptoms (mild fever, anorexia).
- ***The exanthem:***
 - It usually starts on the trunk then involve face, little involvement of the limbs(centripetal)
 - Started as red papule then vesicles then crustations.
 - Pleomorphic (all stages can be seen at the same time).
 - Itchy.
 - Mucous membranes can be affected.

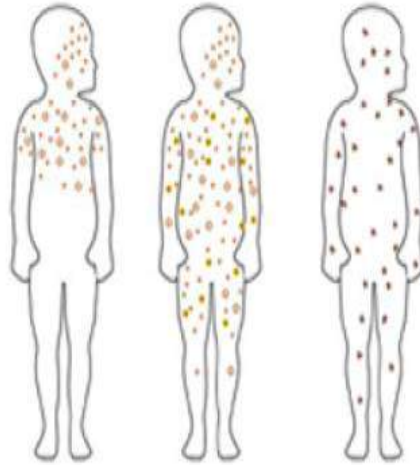


Figure 11: Progression of chickenpox infection

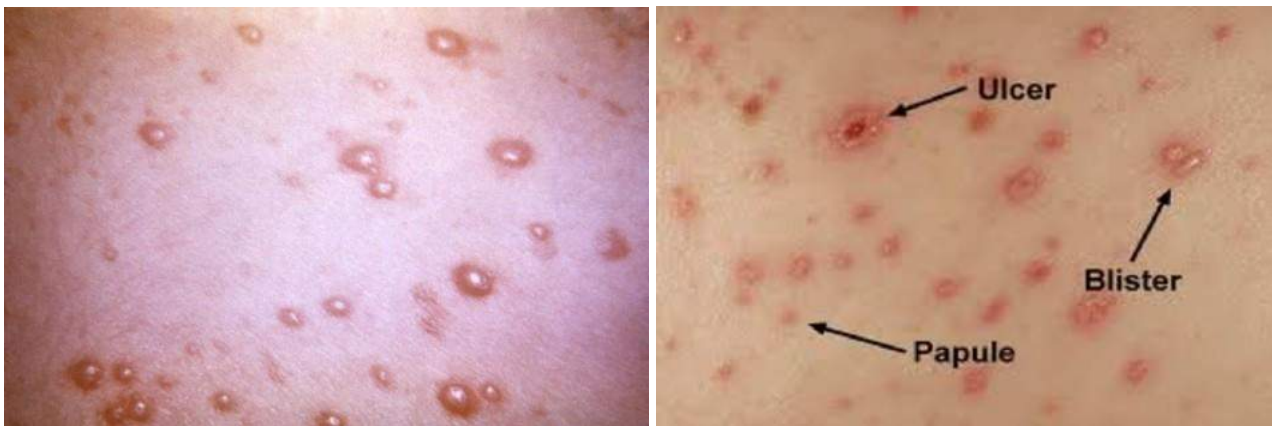


Figure 12: Characteristic skin rash in chickenpox infection

II. In immunocompromised children:

- A severe, disseminated, and fulminant course.

Complications:

“Complications in normal children are uncommon”

- **Secondary bacterial infections of the vesicles:** with staphylococci or streptococci are the most frequent complications.
- **CNS complications:** The most common form is encephalitis, which usually has a good prognosis, Guillian-Barre Syndrome.

- **Other complications:** Reye syndrome, purpura, and pneumonia are rare complications.
- **Complications in immunocompromised Children** are usually common and may be fatal.

Investigations:

- *Rarely required.*
- However, isolation of virus from scraping of the lesion may be useful.

Treatment

I. General lines: The fingernails should be trimmed. Daily bathing is advised.

II. Symptomatic treatment:

- Local and systemic antipruritic agents may be required.
- Antipyretic other than aspirin may be indicated.

III. Specific therapy:

Acyclovir (500 mg/m²/dose given over 2 hr every 8 hr) is indicated in immunocompromised children.

IV. Treatment of complications

Systemic antibiotic therapy is indicated only if secondary bacterial infection occurs.

Prevention: See immunization and isolation measures.

Prognosis:MKM

- Varicella in children is a relatively self-limited disease, which offers lifelong immunity.
- In immunodeficiency state, disease may be life -threatening.

Mumps

Etiology: Mumps virus (RNA).

Mode of infection: Droplet infection.

Incubation period: 2 to 3 weeks

Infectivity period: from 7 days before to 9 days after the onset of parotitis.

Epidemiology:

- Age: Mumps is most common in children under 15 yr.
- Season: It is most common in spring and winter.

Clinical Manifestations:

I. **Prodromal stage:** mild fever malaise, headache may precede the swelling.

II. **Parotid swelling:**

- It is often the first sign of illness.
- The swelling may be unilateral or bilateral.
- The swelling usually peaks in 1-3 days and slowly subsides within 3-7 days.
- The entire parotid gland is swollen.
- It fills the space between mastoid and posterior border of the mandible and extends under and back of the ear lobe pushing ear lobe forwards and upwards.
- Submandibular gland swelling may occur.



Figure 11: Parotid swelling caused by mumps

III. Systemic manifestations: Swelling is usually accompanied by moderate fever, less frequently headache, abdominal pain, or skin rashes.

Complications:

I. CNS complications:

- Meningoencephalitis: Virus may directly affect neurons or indirectly through immunologic mechanism.
- Aseptic meningitis.
- CNS involvement is usually has a good prognosis, however, aqueductal stenosis may occur.

II. Orchitis:

- It is the most feared of complication.
- Proceeded by fever toward the end of the first week of illness.
- There is severe pain, swelling, and tenderness.
- Impairment of fertility may occur.

III. Oophoritis: fever and abdominal pain

IV. Pancreatitis: A mild involvement of pancreas may occur producing fever, vomiting, epigastric pain and tenderness.

V. **Deafness:** Mumps is a leading cause of unilateral sensorineural deafness, which may be transient or permanent.

VI. **Ocular:** These include dacryoadenitis, papillitis, or uveo-keratitis.

VII. **Other complications:** Nephritis, thyroiditis, myocarditis, purpura are rare complications of mumps.

Differential Diagnosis:

I. **Other parotid swellings:** Other viral infections, suppurative parotitis, recurrent parotitis, and tumors of parotid.

II. **Other neck swelling:** Cervical lymph nodes enlargement, and osteomyelitis of ramus of mandible.

Investigations:

I. Direct isolation of virus from saliva, urine, nasopharyngeal swab or spinal fluid.

II. Indirect estimation of circulating antibodies.

Treatment: Only symptomatic treatment is indicated.

Prevention: See immunization and isolation measures.

Poliomyelitis (Infantile Paralysis)



Etiology: Polioviruses are enterovirus (RNA with serotypes 1,2,3).

Mode of infection:

- Feco-oral infection.
- Droplet infection.

Incubation period: 1 to 2 weeks.

Infectivity period:

- Most infectious from 7 to 10 days before and after the onset of symptoms, but poliovirus may be present in the stool from 3 to 6 weeks.
- The Global Polio Eradication Program has dramatically reduced poliovirus transmission throughout the world. As of 2013, polio remains endemic in only three countries: Nigeria, Pakistan, and Afghanistan.

Pathogenesis:

- The virus enters through the mouth, and primary multiplication of the virus occurs

in the pharynx and gastrointestinal tract. The virus is usually present in the throat and in the stool before the onset of illness.

- The virus invades local lymphoid tissue, enters the bloodstream, and then may infect cells of the central nervous system.
- Replication in motor neurons of the anterior horn and brain stem results in cell destruction and causes the typical manifestations of poliomyelitis.

Pathology:

Neuronal lesions occur in:

- I. Spinal cord (anterior horn cells)
- II. Brain stem (motor cranial nerve nuclei and vital centers in medulla).
- III. Brain (motor cerebral cortex)

Clinical Presentations:

The response to poliovirus infection is highly variable and has been categorized based on the severity of clinical presentation.

I. Asymptomatic:

- Approximately 90-95% of those infected has asymptomatic infection.
- Acquire solid immunity.
- Infected persons shed virus in the stool and are able to transmit the virus to others.

II. Minor illness (Abortive):

- Approximately 5% (4%-8%) of polio infections consist of a nonspecific illness without clinical or laboratory evidence of central nervous system invasion
- Three syndromes observed with this form of poliovirus infection are:
 - Upper respiratory tract infection (sore throat and fever)
 - Gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation)

or, rarely, diarrhea)

- Influenza-like illness.
- Characterized by complete recovery in less than a week.

III. Non – paralytic:

- The presentations are those of abortive type followed by clinical picture of aseptic meningitis.
- This lasts from 2 to 10 days followed by complete recovery.

IV. Paralytic:

- Less than 1% may present major disease with involvement of CNS.
- Paralytic poliomyelitis may follow the above-mentioned types or the paralysis may be the first presentation.
- Paralytic polio is classified into three types, depending on the level of involvement:

1. Spinal poliomyelitis:

The muscular paralysis is characterized by:

- *Asymmetrical* (one limb is affected more than the other).
- *Patchy* (affecting some groups sparing others in the same limb)
- *Pure motor*, sensations are intact.
- *Flaccid paralysis* (lower motor neuron lesion) with loss of deep reflexes of affected muscles.
- *The weakness* may affect the following groups:
 - a. Muscles of the neck leading to loss of head support.
 - b. Muscles of the trunk leading to inability to sit alone.
 - c. Muscles of abdomen leading to bulging of affect J part during inspiration

and expiration.

- d. Respiratory muscles lead to respiratory insufficiency.
- e. Muscles of upper limb: the deltoid is usually affected.
- f. Lower limbs: the most common sites to be affected, especially quadriceps femoris, hamstrings, tibials anterior, and peroneals.
- g. Bladder is rarely affected; only transient retention may occur for few days with severe affection of both legs.

2. *Bulbar poliomyelitis:*

It is a rare and dangerous form of polio. It is characterized by:

a. *Affection of cranial nerves:*

- i. Involvement of 9th & 10th cranial nerves leading to hoarseness of the voice, nasal regurge, stridor, difficulty in swallowing, and pooling of secretions in the throat,
- ii. Rarely, involvement of 8th or 3rd cranial nerves.

b. *Affection of vital centres:*

- i. Respiratory center leading to irregular respiration, which may lead to respiratory failure.
- ii. Cardiac center leading to fluctuation of blood pressure and arrhythmia.

3. *C - Encephalitic poliomyelitis:*

Irritability, disturbed conscious level seizures, and coarse tremors are noted.

Complications:

I. Spinal:

- Respiratory infection and/or failure.
- Acute gastric dilatation or melena.

- Urine retention and calculi.

II. **Bulbar:** hypertension, arrhythmias and respiratory failure.

III. **Encephalitic:** Permanent cerebral damage.

Investigations:

1. Direct isolation of virus from throat and stool.
2. Demonstration of a rise in neutralizing antibody titer when 2 samples are collected at 2-4 weeks apart.
3. CSF usually contains an increased number of white blood cells (10–200 cells/mm³, primarily lymphocytes) and a mildly elevated protein (40–50 mg/100 mL).

Clinical course:

I. **Incubation period:**

1 to 2 weeks with a maximum range of 3 to 35 days.

II. **Acute poliomyelitis:**

1- ***Preparalytic stage:*** (2-6 days)

- a. General phase: about 1-2 days.
- b. Meningeal phase: about 1-4 days.

2 - ***Paralytic stage:*** (2-4 weeks)

(It is present as long the affected muscles are painful and tender)

III. **Subacute poliomyelitis:** (6-12 months)

- 1- Regressive course: the common course in which recovery of slightly affected muscles occurs.
- 2- Progressive course: a rare type in which progressive damage of muscles previously spared occur "late post poliomyelitis muscular atrophy ".

IV. **Old poliomyelitis:** Stationary course with permanent muscular disability.

Differential diagnosis:

- I. **General phase:** Clinically it is impossible to differentiate this presentation from common cold.
- II. **Meningeal phase:** to be differentiated from other causes of aseptic meningitis.
- III. **Acute stage:** the disease may simulate other causes, which lead to sudden onset of inability to move a limb e.g.:
 1. Pseudoparalytic: arthritis, osteomyelitis, and fractures.
 2. Paralytic: Guillain - Barre Syndrome (symmetrical & ascending paralysis without sensory level. In CSF, there are few cells with high protein content). Peripheral neuritis (foot and wrist drop with glove and stock hypoesthesia), Transverse myelitis (radicular pain followed by acute paraplegia with sensory level) .
- IV. **Subacute & old poliomyelitis:** The residual paralysis & wasting may simulate other causes of floppy infant e.g. atonic C.P., other motor neuron disease, and myopathies.

Treatment:**I. Acute stage:**

- Non - paralytic: Avoidance of exertion for 2 weeks.
- Paralytic:
 1. **Spinal:**
 - Analgesics.
 - Hot packs: 15-30 min every 2-4 hr.
 - A neutral position, with the feet at a right angle, knees slightly flexed, and hips and spine straight.
 - Passive movement should start almost immediately and certainly within the first week
 2. **Bulbar:**
 - Maintenance of patent airway by gravity drainage or aspirator.
 - Maintenance of fluid and electrolytes by IVF and/ or gavage feeding

- Mechanical respirator in cases of respiratory paralysis.

II. Subacute stage: Active and passive motions are indicated as soon as the pain has disappeared. Once fever has finally settled intensive physiotherapy can be introduced.

III. Old stage: Operative correction of residual disability.

Prevention: Salk & Sabin vaccines (see vaccinations).

Prognosis:

- Acute stage: Mortality is usually due to respiratory paralysis. The death rate for paralytic polio is generally 2%–5% among children and increases to 25%–75% with bulbar involvement.
- Regressive stage: Residual disability is usual.

Encephalitis

Inflammation of the brain, most commonly due to viral infection.

Etiology:

I. Infectious: (direct CNS damage)

1. *Viral*:

- *Paramyxovirus group*: measles - mumps.
- *Enterovirus group*: polioviruses.
- *Herpes virus group*: herpes simplex - VZ virus - CM virus - EB virus.
- *Rubella*.
- *Others*: rabies - arbovirus - adenovirus.

2. *Non-viral*:

- *Bacterial*: bacterial meningitis
- *Rickettsial*: typhus encephalitis
- *Fungal*: histoplasmosis
- *Protozoal*: toxoplasmosis, schistosomiasis.

II. Parainfectious (allergic reaction):

1. *After specific disease*:

- *Measles*
- *Mumps*
- *Rubella*

3. *After vaccination*:

- *Measles vaccine*
- *Pertussis vaccine*
- *Rabies vaccine*

III. Others:

1. **Subacute sclerosing panencephalitis, SSPE** (a late complication of measles).
2. **Rye syndrome** (a combination of acute encephalopathy with fatty degeneration of the liver).

Clinical presentations:

- **Onset and course:**

The onset is usually acute with variable course, regressive, progressive or fluctuating.

- **There are three groups of manifestations:**

- **General manifestations:**

- The initial manifestations are usually those of any systemic illness; fever, vomiting, headache, and irritability.

- **Encephalitic manifestations:**

- **Mental state:** drowsiness and in severe cases coma.
- **Cranial nerves:** cranial nerves may be involved.
- **Motor system:** convulsions, bizarre movements, with or without paralysis of one or more limbs are usually present.
- **Reflexes:** loss of bladder and bowel control may occur.

- **Meningeal manifestation:** Mild signs of meningeal irritation may be present.

Investigations:**I. CSF:** In viral encephalitis CSF usually shows:

- **Aspect:** clear.
- **Pressure:** normal or moderately increased.
- **Protein:** normal or slightly elevated.
- **Glucose:** usually normal.

- *Cells:* leukocyte count may range from none to several thousands, all are lymphocytes.

II. Serological tests: Direct or indirect methods for identification of causative agent are mandatory.

III. Imaging methods: Cranial sonar and / or CT brain may be indicated especially for exclusion of brain abscess.

Differential Diagnosis:

I. Bacterial meningitis: *Sings of meningeal irritation are more evident, with characteristic CSF changes.*

II. Brain abscess: *signs of single focal brain lesion with characteristic imaging finding.*

Prevention:

The proper vaccination schedules with good hygienic measurements are the main preventive methods.

Treatment:

I. General lines: Hospitalization & isolation are mandatory. Severe cases should be monitored in an intensive care unit.

II. Symptomatic:

- Antipyretic and anticonvulsive drugs are usually indicated.
- Treatment of cerebral edema may include intravenous furosemide (1.0 mg/kg), mannitol (0.5 -1.5 g/kg), and Dexamethazone (0. 1-0.2 mg/ kg).

III. Specific:

- Acyclovir is specific antiviral agent for herpes simplex encephalitis.
- Corticosteroids have a special benefit in allergic encephalitis.

Complication: Residual disability usually needs physiotherapy.

Prognosis:

1. Mild cases may improve completely.
2. Death may occur during acute stage in severe fulminant cases.
3. Recovery with sequelae is common. Sequelae may be MR, CP, epilepsy, visual, auditory, and/ or permanent paralysis.

Bacterial Infectious Diseases

Scarlet Fever

Etiology: Group A β -hemolytic streptococci that elaborates [erythrogenic] toxins.

Mode of infection: Droplet infection.

Incubation period: 1-7 days with an average of 3 days.

Clinical manifestations:

- **Prodromal symptoms and signs:** The onset is acute and is characterized by fever, vomiting, headache, toxicity and sore throat.

➤ **Fever:**

Abrupt rise of temperature and may peak at 39.6-40°C on the second day and gradually returns to normal within 5-7 days in untreated patients.

➤ **Sore Throat:**

- *The tonsils* are hyperemic and edematous and may be covered with a gray-white membrane.
- *The pharynx* is inflamed and covered by a membrane in severe cases.
- *The tongue* may be edematous and reddened. During the early days of illness, the dorsum of tongue has a white coat through which the edematous papillae appear [**white strawberry tongue**]. After several days, the coat desquamates; the red and edematous papillae persist [**red strawberry tongue**].



Figure 12: White and red strawberry tongue

- *The palate and uvula* may be edematous, reddened, and covered with petechiae.

➤ **Exanthem (rash):**

- Within 12-24 hrs. of onset of disease, the typical rash appears.
- The exanthem is red, punctate or finely papular, and blanches on pressure.
- The rash appears initially in the axillae, groin, and neck but within 24hr becomes generalized, but most intense in these three sites, in addition to pressure sites.

**Figure 13: Characteristic skin rash in scarlet fever**

- The forehead and cheeks appear flushed, and the area around the mouth is pale



Red cheeks and pale area around the mouth in
scarlet fever

[circumoral pallor].

- Petechiae may occur owing to capillary fragility.
- Areas of hyper pigmentation that do not blanch with pressure may appear in the deep creases, particularly in the antecubital fossae [pastia lines].
- Desquamation begins on the face in fine flakes toward the end of the first week and proceeds over the trunk and finally to the hands and feet. The duration and the extent of desquamation vary with the intensity of the rash; It may continue for as long as 6 weeks.



Figure 14: Desquamation in hand of patient with scarlet fever

Diagnosis:

I. **Clinical diagnosis:** as mentioned before.

II. **Laboratory diagnosis:**

1. **Throat culture:** to detect the causative organism (group A β -hemolytic streptococci).
2. **Increased Anti - Streptolysin O [ASO] titer:** Normal value: 170-330 Todd units in school aged children, rises within 2 weeks after acute infection.
3. **Leukocytosis** may or may not be detected.
4. **Elevations in ESR and C-reactive protein** are non-specific.

Differential Diagnosis:

Scarlet fever must be differentiated from other exanthem diseases including:

1. **Measles:** excluded by its prodrome of conjunctivitis, photophobia, dry cough, and Koplik's spots.
2. **Rubella:** disease is mild post auricular lymphadenopathy usually is present, and throat culture is negative.
3. **Infectious mononucleosis:** characterized by pharyngitis, rash, lymphadenopathy, splenomegaly, and atypical lymphocytes.
4. **Enteroviruses infections:** The exanthems produced by several enteroviruses can be confused with scarlet fever, but differentiation can be established by the course of the disease, associated symptoms, and the results of cultures.
5. **Roseola:** characterized by cessation of fever with the onset of rash and the transient nature of the exanthem.
6. **Drug eruption.**
7. **Severe sunburn** can also be confused with scarlet fever.

Complications:

I. Immediate Complications:

- Caused by extension of streptococcal infections from the nasopharynx: sinusitis, otitis media, mastoiditis, cervical retropharyngeal or parapharyngeal abscess or bronchopneumonia.
- Complications caused by hematogenous dissemination of streptococci: Meningitis, osteomyelitis or septic arthritis.

II. Late complication: rheumatic fever and acute glomerulonephritis.

Treatment:

1. **Penicillin** is the drug of choice for the treatment of scarlet fever. Intramuscular procaine penicillin 50.000 U/Kg/24 for 10 days. A single intramuscular injection

of a long acting benzathine penicillin G (600,000 U for children <25 Kg and 1.200.000 U for children > 25 Kg).

2. Erythromycin (40mg/kg/day) can be used in patients allergic to penicillin.

Pertussis (Whooping Cough)

Etiology: *Bordetella pertussis*. A similar illness has been associated with infection by *B. para-pertussis*.

Mode of infection: Droplet infection.

Incubation period: 1 to 2 weeks

Clinical manifestations:

➤ **Catarrhal stage: 1-2 weeks:**

Rhinorrhea, conjunctival injection, lacrimation, mild cough and low-grade fever, a diagnosis of pertussis usually is not considered during this stage.

➤ **Paroxysmal stage (2-4 weeks or longer):**

Episodes of cough:

- Repetitive series of 5-10 coughs in a single expiration are followed by forceful inspiration against narrow glottis(whoop).
- Facial redness, bulging eyes, protrusion of tongue, lacrimation, salivation and distension of neck veins are prominent during the attack.
- Post-tussive emesis is characteristic of whooping cough Attacks.
- Triggered by yawning sneezing, eating, drinking and physical exertion.
- Between attacks, the patient may appear comfortable some patients, especially young infants, have no whoop.

➤ **Convalescent Stage (1-2 weeks):**

Gradually decrease in frequency and severity of paroxysms but cough may persist for several months.

Diagnosis:

I. Clinical diagnosis: as mentioned before.

II. Laboratory diagnosis:

- Leukocytosis (20,000-50,000 cells/mm³ of blood) with absolute lymphocytosis is characteristic at the end of the catarrhal during the paroxysmal stages of the disease.
- Detection of the organism by nasopharyngeal swabs that are cultured on Bordet- Gengou media.
- Detection of antibodies against pertussis toxin.

III. Chest x ray: may show perihilar infiltrates, atelectasis or emphysema.

Differential Diagnosis:

- Other causes of paroxysmal cough: including foreign body, bronchial asthma, mediastinal syndrome, and cystic fibrosis
- Other causes of upper respiratory tract infections: tonsillo-pharyngitis, laryngitis and sinusitis.
- Other causes of lower respiratory tract infections: bronchopneumonia and interstitial pneumonia.

Complications:

I. Pulmonary:

- Pneumonia: The most frequent complication.
- Activation of latent pulmonary TB.
- Atelectasis: may develop secondary to viscid mucus plugs.
- Bronchiectasis.
- pneumothorax due to rupture of the alveoli during coughing.
- Otitis media.

II. Other complications:

- Convulsions: secondary to hypoxia, hyponatremia or high fever.
- Epistaxis, melena, subconjunctival hemorrhage, spinal epidural hematoma, intracranial hemorrhage.
- Ulcer of the frenulum of the tongue, rupture of the diaphragm, umbilical, inguinal hernia, rectal prolapse.
- Dehydration and malnutrition.

Prevention:

I. Active immunization: DTaP vaccine.

II. For contacts:

- Erythromycin is effective in preventing pertussis in newborn infants of mothers with pertussis.
- Close contacts of less than 7 years:
 - Booster dose of DPT.
 - Erythromycin, 50 mg/kg 24hr for 14 days.
- Close contacts of more than 7 years of age
 - Erythromycin, 50 mg/kg 24hr for 14 days.

Treatment:**I. Supportive care:**

- Isolation.
- Bed rest.
- Symptomatic treatment: maintenance of the hydration and nutrition, oxygen if there is distress, gentle suction for viscid secretions

II. Antibiotics:

- Erythromycin, 50 mg/kg 24 hrs. for 14 days.
- May abort the disease if given within 14 days.
- Eliminate organisms from the nasopharynx within 3-4 days, thereby reducing infectivity period.

Diphtheria

Etiology: *Corynebacterium diphtheria* (gram+ve bacilli producing powerful exotoxin).

Mode of infection: Droplet infection.

Incubation period: 1 to 6 days.

Clinical manifestations:

I. Nasal Diphtheria:

- Serosanguinous, followed by mucopurulent discharge that excoriates the nares and upper lips with foul odor.
- Mild systemic manifestations.

II. Pharyngeal diphtheria: (most common site)

- Onset is insidious with mild sore throat, Low-grade fever.
- Within 1-2 days, a membrane appears, initially thin and gray resembling a spider web that gradually extends from the tonsil to the soft or hard palate. The adherent membrane may spread to cover the tonsils and pharyngeal wall, or it may progress into the larynx and trachea. Attempts to remove it are followed by bleeding.



Figure 15: Pseudomembrane of diphtheria

- Cervical lymphadenopathy when associated with edema of the soft tissue of the neck leading to the appearance of a "bull neck"



Figure 16: Bull neck of diphtheria

III. Laryngeal Diphtheria:

- Either primary or secondary to pharyngeal diphtheria.
- Progressive stridor, and hoarseness of voice, may lead to severe laryngeal obstruction that may be fatal.

IV. Other types of diphtheria:

- Cutaneous.
- vulvo-vaginal.
- Conjunctival.

Diagnosis:**I. Clinical Diagnosis:****II. Laboratory Diagnosis:**

- Swab from the membrane and Isolation of *C. diphtheria*, on Loeffler culture media.

Differential diagnosis:**I. Nasal diphtheria:**

- Foreign body nose.
- Sinusitis.
- Adenoiditis.
- Snuffles of congenital syphilis.

II. Tonsillar or pharyngeal diphtheria:

- Streptococcal pharyngitis.
- Infectious mononucleosis.
- Primary herpetic tonsillitis.
- Non-bacterial membranous tonsillitis.
- Blood dyscrasias, such as agranulocytosis and leukemia.
- Post- tonsillectomy faucial membrane.
- Pharyngeal involvement in toxoplasmosis, cytomegalovirus and salmonellosis.

III. Laryngeal diphtheria:

- Foreign body larynx.
- Epiglottitis.
- Peripharyngeal or retropharyngeal abscesses.
- Laryngeal papillomas, hemangiomas or lymphangiomas.

Complications:***I. Respiratory:***

- Respiratory obstruction and death.
- Bronchopneumonia.
- Atelectasis.

II. Cardiovascular:

- Toxic myocarditis.
- Heart block
- Congestive heart failure.

III. Neurologic:

- Palate and pharyngeal muscles paralysis 1st wk→nasal tone, food regurge.
- Ocular muscle during the 5th wk→ptosis and squint.
- Phrenic nerve paralysis between 5th and 7th wk→ respiratory failure.
- Paralysis of limbs.

IV. Other complications:

- Vasomotor instability with hypotension, 2-3 weeks after onset.
- Gastritis, hepatitis, and nephritis.

Prevention:***I. Immunization:*** DTaP vaccine.***II. Contacts:***

- Isolation of the patient.
- Cultures from close contacts.
- If negative, give the vaccine.
- If positive, give the antitoxin, isolate, and give antibiotics.

Treatment:**I. General:**

- Isolation for 2 weeks.
- Bed rest and good diet.

II. Specific treatment:**1. Antitoxin:** to neutralize the toxin

- As early as possible.
- Do skin sensitivity test first.
- 10.000:100.000 IU IM or IV single dose.

2. Antibiotics: (to kill the organism)

- Procaine penicillin 300,000 (for patients < 10 kg) - 600,000 (for patients > 10 Kg) units IM once daily for 14 days.
- If patients sensitive to penicillin, should be given erythromycin 40 mg/kg/24 hr in four divided doses for 14 days.
- The end - point of therapy is three consecutive negative cultures.

III. Treatment of complications:

- Myocarditis: oxygen, diuretics, digitalis.
- Circulatory failure: plasma or blood transfusion.
- Neuritis: physiotherapy.

Typhoid Fever (Enteric Fever)

Etiology:

- I. *Salmonella typhi*: Causing typhoid fever
- II. *Salmonella paratyphi A, B, C*: Causing Paratyphoid fever (milder than typhoid fever) *Salmonella* organisms are gram – negative bacilli.

Mode of infection:

Feco-oral route from carriers or cases by contaminating water and food.

Incubation period: 2 weeks.

Pathogenesis:

- The organisms enter the body through the mouth.
- Proliferate in Payer's patches in small intestine.
- Penetrate the GIT mucosa to reach the blood stream.
- Distributed to the RES organs (liver, spleen, and other organs) and multiply.
- After multiplication, the organism re-enter blood stream reaches any organ
- Large numbers of salmonellae are then discharged into the intestine.

Clinical Manifestations:

I. *In infants*: Varies from mild gastroenteritis to severe septicemia.

II. *In older children*:

1. *First week*:

- Gradual onset of headache, fever, anorexia, malaise, lethargy, myalgia.
- Abdominal pain and tenderness.
- Diarrhea, rarely constipation.
- Cough is common.

2. Second week:

- Fever rises and becomes continuous.
- Fatigue anorexia, weight loss.
- Abdominal pain and diarrhea increase in severity.
- Mental depression, delirium and stupor may occur
- Hepatomegaly
- Macular rose spots are observed in 40-80% of patients in lower chest and abdomen.

3. Third week:

- If no complications occur, symptoms and physical findings resolve.

Complications:

1. **GIT:** Intestinal perforation, severe hemorrhage, acute cholecystitis.
2. **Renal:** Pyelonephritis, cystitis.
3. **Cardiac:** Toxic myocarditis, endocarditis and heart failure.
4. **Pulmonary:** Pneumonia
5. **CNS:** Toxic encephalopathy, cerebral thrombosis, cerebellar ataxia, aphasia, perceptive deafness and transverse myelitis, meningitis.
6. **Others:** Septic arthritis, osteomyelitis.

Diagnosis:

I. Clinical Diagnosis: As mentioned before.

II. Laboratory Diagnosis:

1. Complete blood picture:

- Normochromic, normocytic anemia Leukopenia and thrombocytopenia due to bone marrow toxic suppression.

2. Bacteriological cultures (for detection of the organisms are diagnostic):

- Blood cultures are usually positive in the first week.

- Urine and stool cultures are usually positive in the 2nd and 3rd week.

3. *An increase in O agglutinins* (Widal test):

- with a titers of $> 1 : 160$ are suggestive evidences of infection after the 1st week of infection.

4. *An Enzyme - linked immunosorbent assay (ELISA):*

- procedure has also developed to detect *S. typhi* VI antigen in urine with high sensitivity and specificity.

Differential Diagnosis: -

I. *During the initial stage of typhoid fever.*

1. Bronchitis.
2. Bronchopneumonia.
3. Gastroenteritis.
4. Influenza.

II. *During the secondary septicemia stage:*

1. T.B.
2. Systemic fungal infections.
3. Brucellosis.
4. Tularemia.
5. Rickettsial diseases.
6. Shigellosis.
7. Malaria
8. Septicemia.
9. Leukemia, lymphoma.
10. Surgical abdomen.

Prevention:

- For children living in endemic area, the vaccine may provide some protection against water - borne disease. Two doses of 0.5 ml S.C. 3 week apart are given.

- An oral vaccine "attenuated living" has been tested in Egypt with 95% protective effect.
- Attention to personal hygiene, hand washing and sanitary practice is essential for persons involved in the preparation of food.
- Isolation of patients till urine, stool cultures are negative in 3 consecutive cultures.

Treatment:

I. General:

- Bed rest and good diet.
- Antipyretics.
- Good disposal of excreta.

II. Specific treatment:

1. Antibiotic therapy:

a. *Chloramphenicol* (antibiotic of choice):

- Dose 50 -100 mg / kg / 24 hr divided into 4 doses. This should be continued for at least 14 days.

b. *Ampicillin* (slower clinical response and more treatment failure):

- Dose 100 - 200 mg / kg / 24 hr. divided at 6 - hour intervals.

c. *Amoxicillin* (better results than Ampicillin):

- Dose 100 mg/kg/day.

d. *Ceftriaxone and cefoperazone* (effective in resistant cases).

2. Treatment of Complications:

- a. Platelet transfusion for thrombocytopenia - induced hemorrhage.
- b. Cholecystectomy for chronic gall bladder infection.

Prognosis:

- Depends upon:
 1. Age.
 2. Presence of malnutrition or underlying chronic or debilitating disease.
 3. Presence or absence of complications.
- Relapse occurs in 4 - 8% of cases not treated with antibiotics. Chronic carriers: its incidence is low in children.

Meningitis

Inflammation of pia and arachnoid membranes of the brain and spinal cord.

Etiology:

I. Bacterial Meningitis (septic):

1. ***During the first 2 months:*** Group B streptococci, E. coli, L. monocytogenes.
2. ***Children from 2 mo-12 yrs.:*** N. meningitides, S. pneumonia, H. influenza b.
3. ***Children with altered immune mechanism:*** S. aureus, P. aeruginosa.

II. Viral, fungal meningitis (aseptic meningitis).

III. T.B. meningitis

Pathogenesis:

Bacterial meningitis originates in one of three ways:

- I. **Hematogenous spread:** The causative organisms are inhabitants of the nasopharynx. Bacterial colonization usually precedes the bacteremia. Through the choroid plexus, bacteria gain entry to CSF and subarachnoid space.
- II. **Extension from cranial sutures:** (ear, paranasal sinuses, and orbit): Infected thrombi spread along diploic veins into the dural sinuses and from there along meningeal veins into the brain.
- III. **Iatrogenic:** Introduced during lumbar puncture procedure.

Pathology:

I. Meningeal reactions:

- Exudate may be distributed around the brain and spinal cord, may be pus.
- Vascular arteritis and thrombosis of vessels.

II. Brain substances:

- Damage of cerebral cortex due to thrombosis, hypoxia, bacterial invasion or toxic encephalopathy

III. Spinal and cranial nerves:

- Inflammation of spinal nerves and roots produces meningeal signs.
- Inflammation of cranial nerves produces cranial neuropathies.

IV. Increased intracranial pressure:

- It is due to cell death (cytotoxic cerebral edema), and increased capillary vascular permeability (vasogenic cerebral edema).

Clinical Manifestations:***I. Onset and course:***

- Meningococcal meningitis: Sudden onset with rapidly progressive course is the presentation of
- H. influenza and pneumococcal meningitis: sub-acute onset with relatively slow progressive course.

II. General manifestations (nonspecific):

- Due to bacteremia and include fever, anorexia, poor feeding, tachycardia, and hypotension. Meningococcal meningitis is usually associated with characteristic purpuric spots.

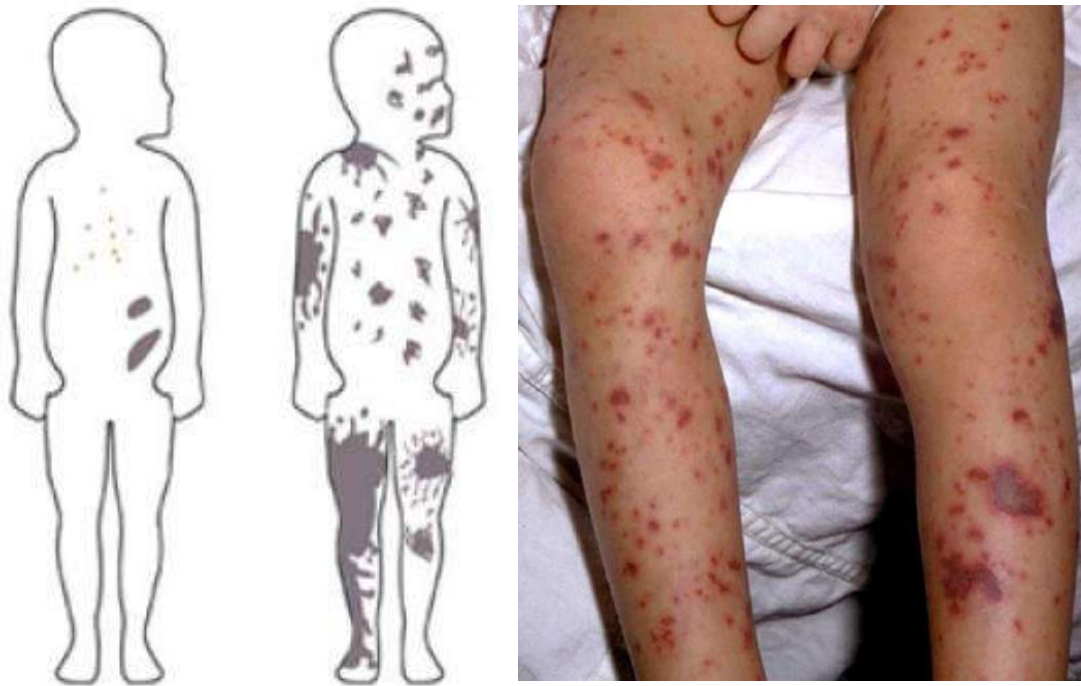
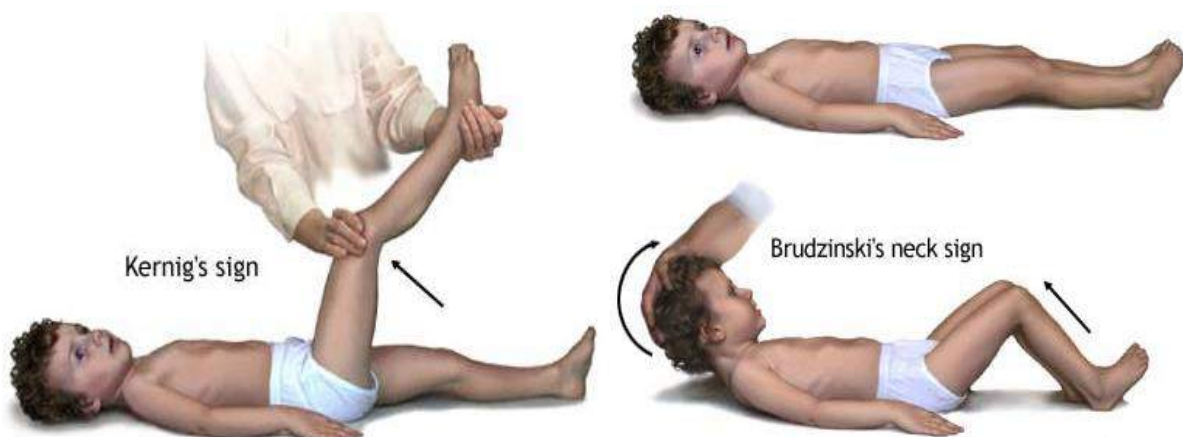


Figure 17: Development and distribution of skin rash in meningococcal infection

III. Meningeal manifestations:

1. **Passive tests:** Neck rigidity, Kernig's sign, and Brudzinski sign.
2. **Active tests:** Kiss - the - knee test, and Tripod sign.



IV. Signs of cortical dysfunction:

1. **Mental state:** irritability, lethargy, stupor or coma.
2. **Cranial nerves:** cranial neuropathies of II, III, VI, and VII may occur.
3. **Motor system:** seizures (focal or generalized), focal paralysis of one or more limbs.

V. Signs of increased intracranial pressure:

1. **Before closure of fontanel:** tense, bulging anterior fontanel.
2. **After closure of fontanel:**
 - Severe headache and irritability.
 - Blurring of vision.
 - Projectile vomiting.
 - Cushing response: hypertension with bradycardia.
 - Later on, oculomotor or abducent nerve paralysis.
 - Very late signs: include decerebrate or decorticate posturing, stupor, coma or signs of herniation.

Complications:**I. Neurologic complications:**

1. Subdural effusion and subdural empyema.
2. Hydrocephalus communicating or non-communicating.
3. Brain abscess.
4. Recurrent seizures.
5. Mental retardation.
6. Motor defects.
7. Cranial nerve palsies.

II. Systemic complications:

1. Adrenal hemorrhage.
2. Arthritis

3. Pericarditis

Differential Diagnosis:

1. **Meningism:** non-infectious meningeal irritation e.g. upper lobe pneumonia.
2. **Aseptic meningitis:** meningitis with no microorganism detected in CSF, mostly viral.
3. **Encephalitis**
4. **T.B. meningitis**

Investigations:***I. CSF analysis:***

	Normal	Bacterial meningitis	Viral meningitis	T.B meningitis
Color	Clear	Turbid	Clear	Turbid
Pressure	Normal	High	Normal or slightly high	High
Protein	20:40 mg/dl	High	Normal or slightly high	High
Glucose	40:80 mg/dl	Low	Normal or slightly low	Low
Cells	0:5 lymphocytes	High Mainly polymorphs	High Mainly lymphocytes	High Mainly lymphocytes

- The gram stain is usually positive.
- Culture to detect pathogenic organisms.

II. Blood culture:

- Should be performed especially when there is a contraindication for LP.

III. CBC: shows polymorph leukocytosis.

IV. Imaging study: (Cranial sonar or CT brain).

- To detect complications.

Treatment:**I. General treatment:**

1. Hospitalization and isolation.
2. Repeated medical & neurologic assessment.
3. Intravenous administration of medications.

II. Symptomatic treatment:

1. **Seizures:** see (Convulsion).
2. **Increased ICP:** see (encephalitis).
3. **Anti-inflammatory agents:** Dexamethasone
 - 0.15 mg / kg / every 6 hr IV for 2:4 days
 - Reduce the inflammatory response and decrease the neurological complications auditory complications.

III. Specific treatment:**1. Empiric antibiotic therapy:**

- Ampicillin (300 mg / kg / 24 hrs. every 6 hrs.) + Cefotaxime: 200 mg / kg / 24 hours., every 6 hrs. OR for Ceftriaxone: 100 mg / kg / 24 hrs., for 14 days

2. Specific antibiotic therapy:

- *Meningococcal meningitis:* Intravenous penicillin-G 300,000 U/kg/24hr for 7 days.
- *H. Influenza meningitis:* Intravenous ampicillin for 10 day is the drug of choice when organism is sensitive to ampicillin and does not produce a B-lactamase.
- *Pneumococcal meningitis:* IV penicillin is the drug of choice for penicillin sensitive organism. Chloramphenicol is the treatment of choice for resistant strains.

Prevention:

I. Chemoprophylaxis: Rifampin (20 mg/kg/dose every day for 4 days) should be used for:

1. Patients with H.influenzae meningitis prior to discharge from hospital.
2. All house hold contacts of patients with H.influenzae or meningococcal meningitis.

II. Immunization: See (vaccinations).

Prognosis:

- Prognosis is usually good with early detection and prompt antibiotic therapy.
- However bad prognosis either mortality or morbidity will occur among untreated cases, late recognition, infant less than 6 months, seizures occurring more than 4 days into therapy, or occurrence of coma.

Parasitic Infectious Diseases

Amebiasis

Amebiasis is a disease caused by the parasite *Entamoeba histolytica*.

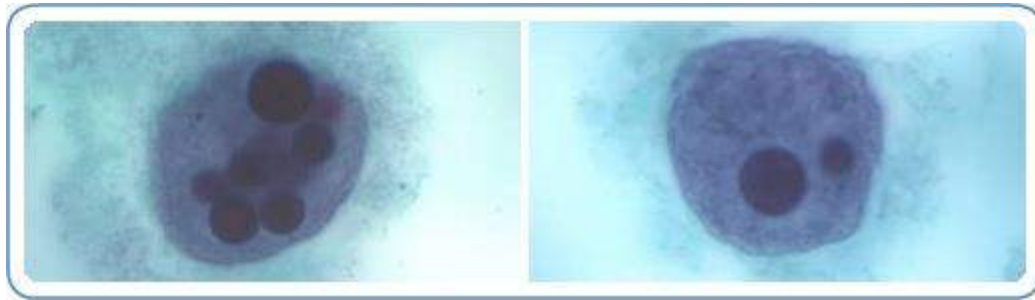


Figure 18: Trophozoites of *E. histolytica* with ingested erythrocytes.

- Human infection with *Entamoeba histolytica* is prevalent worldwide.
- *E. histolytica* parasitizes the lumen of the gastrointestinal tract and causes few or no disease sequelae in most infected subjects.
- In a small proportion of individuals, the organisms invade the intestinal mucosa or may disseminate to other organs, especially the liver.

Epidemiology:

- Endemic foci are particularly common in the tropics and particularly in areas with low socioeconomic and sanitary standards.
- Humans are the major reservoir.
- Amebiasis is the third leading parasitic cause of death on a global scale.
- Food or drink contaminated with *E. histolytica* cysts and direct fecal-oral contacts are the most common means of infection.
- Untreated water and human feces used as fertilizer are important sources of infection. Food handlers carrying amebic cysts may, therefore, play a role in spreading the infection.

Clinical Manifestations:

Most infected individuals are asymptomatic, and cysts are found in their feces.

I. Intestinal amebiasis:

- It may occur within 2 wk of infection or be delayed for months.
- Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients.
- The onset is usually gradual with colicky abdominal pains and frequent bowel movements (6-8 movements/24 hrs.).
- Diarrhea is frequently associated with tenesmus.
- Stools are blood-stained and contain a fair amount of mucus with few leukocytes.
- Acute amebic dysentery occurs in attacks lasting a few days to several weeks; recurrence is very common in untreated individuals.
- Amebic colitis affects all age groups, but its incidence is strikingly high in children between the ages of 1 and 5 yrs.

II. Hepatic amebiasis:

- It is a very serious manifestation.
- In children fever is the hallmark of amebic liver abscess.
- Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscess occurs in less than 1% of infected individuals.
- Changes at the base of the right lung, such as elevation of the diaphragm and parenchymal compression, may also occur.
- Laboratory examination shows a slight leukocytosis, moderate anemia, and nonspecific elevations of liver enzymes.
- Stool examination for amebae is negative in more than 50% of patients with documented amebic liver abscess.

- In most cases, computed tomography (CT) imaging, or isotope scans can localize and delineate the size of the abscess cavity.
- Amebic liver abscess may be associated with rupture into the peritoneum or thorax, or through the skin when diagnosis and therapy are delayed.

Diagnosis:

- Patients with invasive amebic colitis test positive for occult blood.
- Detecting the organisms in:
 - I. Stool:** sigmoidoscopically obtained smears, tissue biopsy samples, or, rarely, in aspirates of a liver abscess.
 - Fresh stool samples should be examined within 30 min of passage.
 - At least three stool samples should be examined by an experienced person.

II. Endoscopy and biopsies:

- Performed when stool samples are negative and the index of suspicion for amebic colitis remains high.

III. Aspirates of a liver abscess:

- The indirect hemagglutination test:
 - Diagnostic titers of at least 1:128.
 - May be initially negative in patients presenting with very acute disease.

Treatment:

- The luminal amebicides, such as iodoquinol and diloxanide furoate, are primarily effective in the gut lumen,
- Metronidazole, chloroquine, and dehydroemetine are effective in the treatment of invasive amebiasis.
- All individuals with *E. histolytica* trophozoites or cysts in their stools, whether symptomatic or not, should be treated.

1. **Diloxanide furoate** is the drug of choice for asymptomatic cyst passers. The

recommended dose is 10 mg/kg/24 hr orally for 10 days. Toxicity is rare, but the drug should not be used in children under 2 yrs. of age.

2. Invasive amebiasis of the intestine, liver, or other organs requires the use of **Metronidazole**, a tissue amebicidal drug; it is administered orally in a daily dose of 50 mg/kg for 10 days. Metronidazole is also a luminal amebicide but less effective than diloxanide furoate for this purpose.
3. If the case is severe or if metronidazole cannot be used, **Dehydroemetine** is the recommended alternative therapeutic agent. It is administered by the SC or IM route (never IV) in a dose of 1 mg/kg/24 hrs. for 10 days. Patients should be hospitalized when this drug is given because cardiac or renal complications may occur
 - A course of diloxanide furoate is recommended following completion of Metronidazole or dehydroemetine therapy.
4. **Chloroquine** is also useful in the treatment of amebic hepatic abscess because it is concentrated in the liver. Amebic liver abscesses are treated with specific therapy as outlined earlier; however, Aspiration of large lesions or left lobe abscesses may be necessary:
 - If rupture is imminent or
 - If the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs.
 - Stool examination should be repeated 2 weeks following completion of antiamebic therapy as a test of cure.

Control of Amebiasis:

- Exercising proper sanitary measures
- Avoiding fecal-oral contact
- Regular examination of food handlers

- Thorough investigation of diarrhea episodes may identify the source of infection in some communities.
- There is no prophylactic drug for amebiasis.

Giardia Lamblia Infection (Giardiasis)

- *Giardia lamblia* is a microscopic parasite that causes the diarrheal illness known as giardiasis. The clinical picture ranges from asymptomatic colonization to acute or chronic diarrheal illness.
- *Giardia lamblia* is found on surfaces or in soil, food, or water that has been contaminated with feces from infected humans or animals.

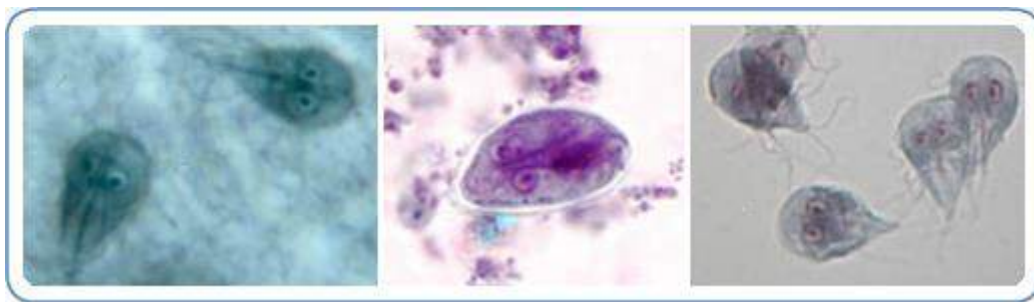


Figure 19: Giardia intestinalis trophozoites and cyst.

- Giardia is protected by an outer shell that allows it to survive outside the body for long periods of time and makes it tolerant to chlorine disinfection. While the parasite can be spread in different ways, water (drinking water) is the most common method of transmission.
- The infection is more prevalent in children than in adults.
- *G. lamblia* infects humans through ingestion of cysts in contaminated water, food, or by the fecal-oral route (hands or fomites).

Epidemiology and Risk factors:

- Giardiasis is a global disease. It is endemic in areas of the world with poor levels of sanitation and is also an important cause of morbidity in the developing world.
- Giardia infection rates go up in late summer.
- Giardia is a particularly significant pathogen in people with malnutrition, immunodeficiencies, or cystic fibrosis.

- Giardiasis is an important cause of chronic diarrhea in children with immunodeficiency, suggesting the importance of immunity in controlling giardiasis.

Clinical Manifestations:

- The majority of individuals are probably asymptomatic.
- Symptoms develop 1-3 weeks after exposure to the parasite.
- The most common presentation is diarrhea, weight loss, crampy abdominal pain, and failure to thrive or a sprue-like illness.
- The disease may be self-limited or produce severe protracted diarrhea and malabsorption.
- Lactose intolerance is common after infection with Giardia and may mimic relapse or reinfection.

Diagnosis:

I. Stool analysis: *G. lamblia* trophozoites or cysts may be found.

II. Duodenal aspirate or biopsy

III. The Entero test is a simple method for detecting *G. lamblia* in duodenal fluid of children that avoids the cost and anesthetic risk of upper intestinal endoscopy.

IV. Antigen detection tests: highly sensitive and specific.

Treatment:

When Giardia causes symptoms in children or adults, it should be treated because of the potential for chronic or intermittent symptoms.

I. Treatment of choice:

1. ***Tinidazole:*** single oral dose of 50 mg/kg
2. ***Nitazoxanide:***
 - 1-3 years: 100 mg (5 mL) bid for 3 days.
 - 4-11 years: 200 mg (10 mL) bid for 3 days.

Alternative:

3. **Metronidazole** (15 mg/kg/day three times a day for 7 days).

II. Second line:

Furazolidone (2 mg/kg four times a day for 10 days).

Ascariasis

- It is caused by the largest roundworm *Ascaris Lumbricoides*.
- *Ascaris* infection is one of the most common intestinal worm infections.
- *Ascaris* infection occurs worldwide in areas with warm, moist climates, especially in tropical and subtropical areas where sanitation and hygiene are poor.



Figure 20: Adult female *A. lumbricoides* and fertilized eggs

Clinical Findings:

- It may be asymptomatic.
- Presenting by abdominal pain, weight loss, anorexia or hyperphagia, diarrhoea or vomiting.
- Heavy infections can cause intestinal blockage.
- Cough due to migration of the worms through the body.

Laboratory Findings:

- **Stool analysis:** eggs or worms may be seen.

Treatment

- **Mebendazole or Flubendazole** (100 mg twice daily for 3 days)
- *Effective sewage disposal systems.*

Enterobiasis (Oxyuriasis)

Caused by pinworms (small, thin, white roundworm) **Vermicularis**.



Figure 21: Adult male of *E. vermicularis* and eggs of human *E. vermicularis*

Epidemiology and risk factors:

- Pinworm infection is treatable, but reinfection, which occurs easily, should be prevented. A person can also re-infect themselves or be re-infected by eggs from another person.
- Humans are the only species that can transfer this parasite. Household pets like dogs and cats cannot become infected with human pinworms.
- Pinworm eggs can survive in the indoor environment for 2 to 3 weeks.

Biology:

- A person is infected with pinworms by ingesting pinworm eggs either directly or indirectly.
- These eggs are deposited around the anus by the worm and can be carried to common surfaces such as hands, toys, bedding, clothing, and toilet seats.
- By putting anyone's contaminated hands (including one's own) around the mouth area or putting one's mouth on common contaminated surfaces, a person can ingest pinworm eggs.

Clinical Findings

- It may be asymptomatic.
- However, the most common symptom is perianal itching predominantly at night; this is caused by an inflammatory reaction to the presence of adult worms and eggs on the perianal skin.
- With heavy infection, secondary bacterial infection can occur due to the irritation and scratching of the anal area.
- Other complaints include insomnia due to disturbed sleep, or even abdominal pain.

Laboratory Findings

I. Scotch tape test:

- Swabbing of skin around the anus in the morning before bathing or defecation and examining it usually eggs or even adult worms are seen, the tape method should be conducted on 3 consecutive mornings.

II. Direct visualization:

- of the worms in the perianal region 2 to 3 hours after the infected person is asleep.

III. Analyzing samples from under fingernails: under a microscope.

IV. Stool examination: is not necessary since worms and eggs are not passed in stool.

Treatment

- Treat all house-hold members at the same time to prevent re-infections.
- ***Flubendazole:***
 - 100 mg single dose; repeated after 2 weeks.
 - The second dose is to prevent re-infection by adult worms that hatch from any eggs not killed by the first treatment.

Schistosomiasis

Etiology:

➤ Five species:

- *Schistosoma hematobium*.
- *Schistosoma mansoni*.
- *Schistosoma japonicum*.
- *Schistosoma mekongi*
- *Schistosoma intercalatum*.

Epidemiology:

➤ Geographic distribution:

- *S. mansoni*: tropical Africa, South America
- *S. hematobium*: northern Africa
- *S. japonicum and S. mekongi*: East and South Asia
- *S. intercalatum*: West and Central Africa.

Clinical Manifestations: (3clinical patterns)

I. Schistosome dermatitis (swimmer's itch):

- Due to cercarial penetration of the skin, presented by pruritis, and papular rash.

II. Acute schistosomiasis:

- Serum sickness-like illness occurs with the onset of oviposition.
- Symptoms include fever, chills, arthralgia, myalgia, abdominal pain and diarrhea.
- Signs include rash, tender Hepatomegaly, splenomegaly, and lymphadenopathy.
- Blood eosinophilia is present.
- Symptoms resolve spontaneously after several weeks in most patients.

III. Chronic schistosomiasis:

- **Sites:** intestine, liver, and urinary tract.
- Fibrosis of the liver (*S. mansoni* or *S. japonicum*) or ureters and bladder (*S. hematobium*) and its sequelae.

1. Intestinal schistosomiasis:

- In the large intestinal wall due to eggs of *S. mansoni*.

➤ Clinical features:

- May be asymptomatic.
- Other complains of abdominal pain, anorexia, vomiting, diarrhea and tenesmus.
- *Examination:* mild diffuse abdominal tenderness and distention.

➤ Complications:

- Iron deficiency anemia
- Colonic polyposis: bloody diarrhea, pericolic mass.
- Protein losing enteropathy and growth failure.
- Partial or complete bowel obstruction.
- Rectal prolapse.

➤ Diagnosis:

- **Detection of eggs:** in stool or rectal tissue biopsy
- **Procto-sigmoidoscopy:** inflammation, ulcer, bleeding
- **Barium enema:** polyps.

2. Hepatosplenic schistosomiasis:

- Due to schistosome eggs embolize the liver.
- Granuloma formation in the portal tract with fibrous tissue deposition.

- Periportal fibrosis leads, in more severe cases, to portal hypertension with the eventual development of porto-systemic collateral blood flow.

➤ **Clinical features:**

- Hepatomegaly.
- Splenomegaly.
- Portal hypertension and porto-systemic collaterals:
 - Esophago-gastric varices, abdominal wall veins, hemorrhoids.
 - Bleeding from esophageal varices leads to hematemesis and melena.
- The late stage of the disease is characterized by a shrunken liver, marked splenomegaly, esophageal varices, ascites and edema.
- Manifestations of hepatocellular failure:
 - Jaundice, encephalopathy, impaired prothrombin synthesis and raised transaminases usually are absent unless co-infection with another hepatotropic virus exists.

➤ **Complications:**

- Malnutrition and growth failure.
- Hypersplenism.
- Hepatotropic viral co-infection: HBV and HCV.
- Nephropathy: due to deposition of circulating immune complexes.
- Recurrent bacteremia.
- Development of portal hypertension and porto-systemic collaterals.
- Eggs may be carried to other organs, in the lungs can cause pulmonary hypertension and cor pulmonale and in the spinal cord and brain that may cause transverse myelitis and seizures.

➤ **Laboratory findings:**

- **Anemia:** iron deficiency anemia.
- Eosinophilia

- Normal serum transaminases
- Leukopenia and thrombocytopenia

➤ **Diagnosis:**

- Detection of eggs: stool analysis or rectal tissue biopsy
- Testing for HBV and HCV serologic markers.
- Ultrasonography: assessment of the severity of the disease and to exclude cirrhosis or other liver disease.
- Endoscopy and barium swallow for esophageal varices.
- Hemodynamic studies and splenoportography are needed in preoperative evaluation.
- Liver biopsy to exclude coexisting liver disease.

3. Urinary schistosomiasis:

- Due to deposition of *S. hematobium* eggs in the bladder and ureters produces granulomatous reaction and scarring.

➤ **Clinical features:**

- **Early:** Asymptomatic or urinary frequency, dysuria, terminal hematuria and suprapubic pain may be present.
- **In advanced stages:**
 - Obstructive uropathy: hydroureter, hydronephrosis.
 - Secondary bacterial infection: chronic pyelonephritis.
 - Chronic renal failure.
 - Carcinoma of the bladder.

➤ **Diagnosis:**

- Urine examination: eggs, RBC, or leukocytes
- Ultrasonography
- Intravenous pyelography
- Cystoscopy

Diagnosis of Schistosomiasis:

- Definitive diagnosis is based on finding viable eggs in stool, urine or biopsy specimens.
- Serological test: detection of circulating schistosomal antigens in the sera and urine by ELISA.

Treatment:***I. Chemotherapy:***

- Three effective drugs are used: praziquantel, oxamniquine, and metrifonate.

1. *Praziquantel:* (treatment of choice)

- For all species of schistosomes.
- Dose: 60 mg/kg orally in 3 divided doses in one day.
- Side effects are mild and include abdominal pain, nausea, dizziness, headache fever, and diarrhea.

2. *Oxamniquine:*

- Acts only against *S. mansoni*.
- Dose: 20 mg/kg for three days.
- Side effects: dizziness, headache, vomiting, diarrhea and less commonly convulsions

3. *Metrifonate:*

- Acts only against *S. hematobium*.
- Dose: 10 mg/kg given on 3 doses at 2-week intervals.
- Side effects: nausea, vomiting and bronchospasm.

II. Other treatments:

- Portal hypertension management: medical; endoscopic sclerotherapy for esophageal varices, and decompressive surgery.

Prevention:

- Avoiding infection.
- Provision of clean water and improving sanitation.
- Health education.

Control:

- Mass or targeted population chemotherapy with praziquantel.
- Snail eradication by molluscides and improving irrigation systems.

Practice Questions

(Choose one correct answer)

- 1- Incubation period for mumps is:
 - a) 1 – 7 days.
 - b) 7 – 14 days.
 - c) 14 -24 days.
 - d) 21 – 28 days.
- 2- If pneumonia complicated measles infection, which of the following could be the cause of pneumonia:
 - a) the virus itself.
 - b) secondary bacterial infection.
 - c) exacerbation of an existing tuberculous process.
- 3- Remittent fever is characterized by:
 - a) the temperature doesn't reach base line at any time in the 24 hours, the variation between upper and lower limit exceeds 1 °C.
 - b) the temperature reaches base line at any time in the 24 hours, the variation between upper and lower limit exceeds 1 °C.
 - c) the temperature doesn't reach base line at any time in the 24 hours, the variation between upper and lower limit doesn't exceed 1 °C.
 - d) the temperature reaches base line at any time in the 24 hours, the variation between upper and lower limit doesn't exceed 1 °C.
- 4- The most common CNS complication of varicella is:
 - a) cerebellitis.
 - b) encephalitis.
 - c) meningitis.
 - d) transverse myelitis.
- 5- CNS involvement in paralytic poliomyelitis is characterized by:
 - a) it affects small muscles than large muscles.
 - b) it affects brain more commonly than the spinal cord.
 - c) sensory cranial nerves are more severely involved.
 - d) motor cranial nuclei are affected in bulbar poliomyelitis.



Chapter 7

Pediatric Emergencies

Objectives:

1. Discuss stages of cardiopulmonary resuscitation.
2. Identify poisoning and steps of management.
3. Define types of respiratory failure.
4. Enumerate steps of management of respiratory failure.
5. Understand different types and causes of shock.
6. Understand the difference between altered consciousness and coma.

Contents:

1. Paediatrics resuscitation.
2. Acute poisoning.
3. Respiratory failure.
4. Shock.
5. Altered states of consciousness and coma.

Cardiopulmonary Resuscitation (CPR)

The diagnosis of cardiopulmonary arrest (CPR) must be made rapidly (absent pulse and respiration). Prompt and orderly resuscitative efforts are essential, and assignment of responsibilities is mandatory.

The team of resuscitation includes:

- The leader (the most experienced person), makes all therapeutic decisions, assigns others their roles, and continually reassesses the quality of the resuscitation.
- Vascular access should be accomplished by the next available person.
- Appropriate doses of medications and times of giving them are recorded.
- Historian, one person must obtain a history from the parents or caretakers.

Stages of CPR:

CPR consists of 3 successive stages: basic life support (BLS), advanced life support (ALS), and prolonged life support (PLS).

I. Basic life support (BLS): aims to provide emergency oxygen delivery to vital organs especially the brain and the heart. It includes the ABCs of resuscitation:

1. Airway control:

- Immobilize the cervical spine if spinal cord injury is a possibility.

Clear the oropharynx with a suction catheter. Avoid blind finger sweeps.

- The head tilt –chin lift maneuver removes obstruction caused by the tongue.
- The head must be in the midline, in the “sniffing” position by placing a folded towel under the occiput.
- Oral airway placement may improve airway status.

2. Breathing support:

Begin mouth-to-mouth or bag-to-mouth ventilation with 100% oxygen. Assess the adequacy of ventilation by observing chest expansion. If chest wall expansion is insufficient, endotracheal tube (ETT) placement is indicated.

3. Circulation support:

- The patient is placed on a hard, solid surface, and external cardiac compressions are started immediately.
- Ventilation/compression ratio is 2:30 with the rate of compression is 100 per minute for infants and children.
- For infants, the two-finger technique is used where two fingers of one hand is used. The hand-encircling technique is preferred, where the infant is grasped with the fingers supporting the back and the thumbs over the middle third of the sternum. For toddlers, the heel of one hand is used and in the older child, two hands interlaced are used; in both cases, compressions are done two fingerbreadths above the xiphoid.

II. Advanced life support (ALS): aims to restore spontaneous circulation by supporting circulation and treatment of the life-threatening arrhythmias.

1. Vascular access and fluid administration:

Peripheral venous access should be attempted. Proceed quickly to intraosseous needle placement at the proximal tibia if peripheral access fails. Central access (femoral) is best achieved using the catheter-over-a guide wire technique. Start infusion with volume expanders as Ringer's lactate or normal saline in an amount of 20 ml/kg over 10 minutes.

2. ECG monitoring and treatment of life-threatening arrhythmias:

- Bradycardia is treated with atropine.
- Asystole is treated with epinephrine and atropine,

- Ventricular fibrillation or pulseless ventricular tachycardia is treated by:
 - Electrical defibrillation at a dose of 2 Joules/kg, repeated up to 3 times if needed.
 - Epinephrine to change fine fibrillations into coarse ones.
 - lidocaine
- Bicarbonate is used in prolonged arrest and for documented acidemia.

Drugs used in resuscitation:

Drug	Dose	Route	Indications
Atropine	0.02 mg/kg	IV,-ETT	Bradycardia
Bicarbonate	1-2 mEq/kg	IV	Metabolic acidosis
Dextrose	0.5 gm/kg	IV	Hypoglycemia
Epinephrine	0.1 ml/kg (of 1:10.000)	IV, ETT	Asystole, bradycardia, hypotension
Lidocaine	1-2 mg/kg	IV, ETT	Ventricular ectopy
Naloxone (Narcan)	0.01 mg/kg	IV	Opiate intoxication

III. Prolonged life support (PLS): aims to identify and treat the cause of arrest and to promote recovery of the brain, heart and other vital organs.

1. **Recognition and treatment of the cause:** such as hypothermia, tension pneumothorax, cardiac tamponade, hypovolemia, metabolic imbalance, toxin ingestion or closed head injury.

2. **Monitoring:**

- Cardiovascular system: (by ECG, blood pressure, and central venous pressure).
- Pulmonary system: (by arterial blood gases and chest x-ray).
- CNS: (observe for seizures and signs of increased intracranial pressure).
- Renal system :(for renal function).

- Hematological system: (for DIC).

3. **Multiple system support:**

- Cardiovascular support: (volume expanders, inotropes).
- Respiratory support: (oxygen therapy, mechanical ventilation).
- Neurologic support : (control of convulsions, reduction of increased intracranial pressure).
- Metabolic support: (correction of temperature abnormalities, water imbalance, acid-base and electrolyte disturbances, blood sugar abnormalities).
- Hematologic support: (correction of anemia and DIC).

Poisoning

Ingestion of toxic products by children is a common occurrence. Children under 5 years of age account for 80% of recorded cases of poison ingestion.

Poison identification:

- The initial history should include the identification of the product ingested (containers or bottles should be brought).
- Physical examination will often reveal supporting evidence for a particular ingestion.
- When the nature of the substance ingested is unknown, the list of common symptoms or signs is presented in the following table.
- The specific substance causing a poisoning should be confirmed by qualitative analysis performed on blood or urine. Gastric fluid analysis will be of value if done within 2-3 hours of ingestion.

Supportive therapy:

- I. Cardiopulmonary support:** The ABCs items of cardiopulmonary resuscitation are applied for poisoned child.
- II. Fluid support:** Replace the previous and ongoing fluid losses while correcting electrolyte disturbances.
- III. Hematologic support:** Correction of hemolytic anemia with packed RBCs or exchange transfusion.
- IV. CNS support:** For control of seizures and prolonged care of comatosed child.
- V. Renal support:** Renal function is monitored and hemodialysis is instituted as needed.

Gastrointestinal decontamination:

- I. Gastric evacuation:** it is the cornerstone of intervention after a toxic ingestion. Its efficacy falls when it is instituted more than one hour after ingestion. Ipecac syrup is the method of choice for gastric emptying, where it induces emesis within 15 minutes of intake. Orogastric lavage is as effective as ipecac and offers the advantage of speed and the prompt administration of adsorbent and cathartic.
- II. Adsorbents:** activated charcoal forms a stable complex with the toxin, thus preventing its absorption. It is not given before ipecac and is not effective against metals, alcohols, hydrocarbons, or caustics. It is given in a dose of 1gm/kg in water orally.
- III. Cathartics:** as magnesium citrate and sorbitol. They hasten transit of gastrointestinal contents, thus decreasing systemic absorption of the toxin.

Elimination enhancement: methods of enhancing excretion of poisons include

- I. Fluid and osmotic diuresis:** by intake of hypertonic fluid.
- II. Diuretics:** such as furosemide (2 mg/kg/dose) are used to increase urine output.
- III. Ionized diuresis:** excretion of acidic compounds, such as salicylates and barbiturates, is enhanced by alkalinization of urine which is accomplished by IV sodium bicarbonate.
- IV. Extracorporeal poison removal:** such as by hemodialysis, peritoneal dialysis and exchange transfusion.

Common symptoms and signs of toxic exposures (Toxidromes)	
System involved	Substance involved
<u>Central nervous system:</u> • Depression and coma • Convulsions • Hallucinations • Hyperpyrexia	• Sedatives, narcotics, tranquilizers, tricyclic antidepressants, anticonvulsants, alcohol, hypoglycemic agents, aromatic hydrocarbons, lead, mercury, lithium and CO. • Amphetamines, xanthines, sympathomimetics, psychotropics, cocaine, ergot, strychnine, lead, organophosphates, • Amphetamines, psychotropics, alcohol withdrawal, antihistamines, cocaine, tricyclic antidepressants. • Atropine, salicylates.
<u>Cardiovascular system:</u> • Arrhythmias • Tachycardia • Bradycardia • Hypotension	• Digitalis, quinidine, tricyclic antidepressants, cocaine • Amphetamines, xanthines, sympathomimetics, cocaine, tricyclic antidepressants

	• Beta blockers, cardioglycosides, quinidine, calcium-channel blockers. • Antihypertensive agents, tricyclic antidepressants, narcotics
<u>Gastrointestinal system:</u> • Nausea, vomiting, and diarrhoea • Increased salivation • Decreased salivation	• Almost any toxic substance can produce these symptoms and signs. • Insecticides • Antihistaminic, antimuscarinic agents
<u>Respiratory system:</u> • Hypoventilation • Hyperventilation	• CNS-depressant agents • Salicylates, cocaine, nicotine, CO₂
<u>Ocular system:</u> • Mydriasis • Miosis	• Atropine, sympathomimetics, psychotropics, cocaine • Narcotics, organophosphate insecticides, parasympathomimetics
<u>Cutaneous system:</u> • Cyanosis • Jaundice	• Nitrites, aniline dyes • Carbon tetrachloride, benzene, phenothiazines

Antidotes: the number of ingestions for which there is a specific antidote is small.

The following table shows antidotal therapy of some specific poisoning:

Poison	Antidote	dose
• Carbon monoxide	Oxygen	100% or hyperbaric O ₂
• Chlorpromazine	Diphenhydramine	0.5 -1 mg/kg, IV or IM.
• Cyanide	Na nitrite, Na thiosulphate	depends on hemoglobin level.
• Organic phosphorous	Atropine	0.1 mg/kg, IV every 10-30 min until papillary dilatation.
• Opiates, narcotics	Naloxone (Narcan)	0.1mg/kg, IV, may be repeated twice
• Iron	Deferoxamine	10–15 mg/kg/hr, (IV infusion)
• Isoniazide	Pyridoxine (B ₆)	5 gm, IV
• Methemoglobinemia	Methyline blue	1-2 mg/kg, IV over 10 min
• Lead	EDTA	250 mg/M ² /dose, IM, every 4 hrs.

Respiratory failure

Definition:

Respiratory failure is defined as significant alterations in the arterial PO₂ and PCO₂ due to alterations in the respiratory functions.

Pathophysiology:

Gas exchange alterations in respiratory failure results from abnormalities in:

- The mechanical properties of the lungs and chest wall,
- The function of the respiratory muscles or their innervation, or
- The respiratory control.

Types of respiratory failure:

- I. Peripheral (type I = lung) failure:** due to poor arterial oxygenation, develops due to causes of respiratory distress, and present clinically with respiratory distress, with blood gases showing arterial hypoxemia + hypoventilation and acute metabolic acidosis.
- II. Central (type II= respiratory pump) failure:** due to alveolar hypoventilation, develops due to causes of respiratory pump failure and present clinically with shallow breathing, cyanosis, coma or paralysis. with blood gases showing hypoventilation + arterial hypoxemia and acute respiratory acidosis.

Etiology:

I. Lung diseases:

- 1. Airway obstruction:** (central or peripheral) : Tracheomalacia, subglottic stenosis, epiglottitis, croup, vocal cord paralysis , FB aspiration, Bronchiolitis, and bronchial asthma .

2. **pulmonary diseases:** Aspirations, pneumonia, ARDS, pulmonary edema, pulmonary hemorrhage or embolism, and massive lung collapse.

II. neuromuscular diseases: Guillain-Barre syndrome, botulism, birth trauma, wernig Hoffman disease, poliomyelitis, and brainstem disorders.

Clinical manifestations:

- Respiratory failure should be anticipated rather than recognized, so that alteration in gas exchange can be prevented.
- Assessment should include respiratory rate, signs of respiratory distress, cyanosis, consciousness, and signs of respiratory obstruction.
- Symptoms and signs of the underlying disease.
- Symptoms of acute hypoxemia and hypercapnia include headache, lower back ache, restlessness, dizziness and impaired consciousness.
- Multisystem complications of acute respiratory failure include GIT hemorrhage, cardiac arrhythmia, renal failure and malnutrition.

Diagnosis:

- Underlying disease.
- Clinical manifestations of the patient.
- Radiological assessment of the cause of respiratory failure.
- Pulse oximetry and capnography
- PaCO₂ over 50 mmHg → imminent respiratory failure.
- PaCO₂ over 60 mmHg → respiratory failure.
- PaO₂ below 55 mmHg in room air.
- Metabolic and or respiratory acidosis.

Treatment:

- I. Oxygen therapy.
- II. Ventilatory support; The objective of mechanical ventilation is to provide adequate gas exchange.
- III. Treatment of the underlying disease.
- IV. Extracorporeal membrane oxygenation (ECMO)
- V. Inhaled nitric oxide.

Shock

Definition:

A clinical state in which there is inadequate tissue perfusion to meet metabolic demands.

Types and causes of shock:

Hypovolemic	Distributive	Cardiogenic	Obstructive	Septic
• Dehydration • Hemorrhage • Burns	• Anaphylaxis • Neurogenic • Drug toxicity • Early septic shock	• Acute heart failure • Ischaemic heart disease • Traumatic • Toxic in late septic shock	• <u>Venous:</u> - Pneumothorax - Pulmonary embolus: clot, fat or air - Cardiac tamponade. • <u>Arterial:</u> - Critical aortic stenosis. - Critical aortic coarctation - Critical pulmonary stenosis.	• Fulminant sepsis without localization • Secondary to focal infection

Pathophysiology:

I. Early compensated shock:

- During this initial stage, the body compensatory mechanisms develop to maintain perfusion to vital tissues.
- This occurs through stimulation of the baroreceptors, chemoreceptors, ending in excessive release of endogenous catecholamines.

- These in turn augment the mean arterial blood pressure through increasing heart rate and contractility and peripheral vasoconstriction.
- This results in selective redistribution of blood to vital (brain, heart, lungs, kidneys) at the expense of non-vital organs (skin and extremities).

Thus, during this stage, clinical manifestations of shock include:

1. The clinical manifestations of the cause of shock (e.g, dehydration).
2. Tachycardia.
3. Normal blood pressure.
4. Signs of poor peripheral perfusion that include:
 - Cold extremities, and increased core/skin temperature difference ($> 2^{\circ}\text{C}$).
 - Slow capillary refill time over fingernails (> 5 seconds).
 - Skin mottling and peripheral cyanosis.

II. Established shock: With continued hypoperfusion, failure of compensatory mechanisms occurs with subsequent hypotension.

The **clinical triad** of tachycardia, hypotension and poor peripheral perfusion becomes evident. **In addition**, manifestations of **hypoperfusion of vital organs** start to appear:

1. Metabolic acidosis (deep & rapid respiration),
2. Renal hypoperfusion (oliguria or urine flow less than 1ml/kg/hour)
3. Brain hypoperfusion (irritability followed by drowsiness and confusion).

III. Advanced decompensated shock: Manifestations of acute **failure** of different systems occur with a variable severity and different combinations.

Manifestations of multiple organs system failure:

- **Kidneys:** Acute renal failure (Oliguria, metabolic acidosis).
- **Lungs:** Adult respiratory distress syndrome (ARDS).
- **GIT:** Ischemia, stress ulcers, hemorrhage, ileus.
- **Liver:** Acute hepatic failure.
- **Blood:** DIC, thrombocytopenia.
- **Metabolic:** Metabolic acidosis
- **Brain:** Hypoxic ischemic encephalopathy with coma.
- **Heart:** Myocardial ischemia, serious arrhythmias.

IV. Irreversible (refractory) shock:

- **Clinically:** myocardial ischemia (serious arrhythmias) and brain ischemia (deep coma) are well evident.
- **Metabolic acidosis** is severe or profound and is refractory to therapy.

Treatment:

- I. ABC's,**
- II. Cardiovascular system support,**
- III. Other systems support,**
- IV. Specific treatment,**
- V. Monitoring .**

I. Always Start With The ABC'S:

1. **Airway:** keep airway open as explained in resuscitation.
2. **Breathing:** oxygenation through different routes as mentioned in resuscitation.
3. **Circulation:** establish an IV line or other access for volume resuscitation.

II. Cardiovascular system support:

1. **Oxygen therapy:** 100% oxygen is given by a facemask and the concentration can be gradually decreased over the next few hours. Endotracheal intubation and mechanical ventilation should be considered in case of marked distress.
2. **Preload augmentation:** Expansion of intravascular volume with volume expanders (crystalloids and colloids) is initially indicated in all types of shock to improve tissue perfusion:
 - **A crystalloid (Ringer lactate or saline):** It is initially given I.V. in an amount of 20 ml/kg over 10 - 15 minutes. The dose can be repeated once or even twice in case of poor response (persistent poor peripheral perfusion and/or hypotension).
 - **A colloid (albumin or plasma):** It may be also given in an amount of 10 ml/kg, IV over a period of 15 minutes. It has the advantages of maintaining oncotic pressure and less tendency to leak into the interstitial spaces.
 - **Whole blood transfusion:** 10 - 20 ml/kg can be also given in hemorrhagic shock or when hemoglobin level is very low.

Failure of response to 50 - 70 ml/kg of volume expanders over the first 1 - 2 hours should suggest cardiogenic shock or obstructive shock.

3. Contractility augmentation:

Drugs	Dose ($\mu\text{g/kg/min}$)	Effects
Dopamine	Low (0.5 – 4)	Renal vasodilator
	Medium (5-10)	Inotropic
	High (11 – 20)	Peripheral vasoconstrictor
Dobutamine	2 – 20	Inotropic
		Peripheral vasodilator
		Pulmonary vasodilator

4. **Afterload reduction:** The use of afterload reducing agents (e.g. nitroprusside or nitroglycerine) should be considered to improve myocardial performance in patients with severe cardiogenic shock not adequately responding to inotropic drug support.

Drugs	Dose ($\mu\text{g/kg/min}$)	Effects
Nitroprusside	0.5 – 10	Arterial dilatation (+++)
		Venous dilatation (+)
Nitroglycerin	1 – 20	Venous dilatation (+++)
		Arterial dilatation (+)
Amrinone	1 – 20	Vasodilator
		Inotropic

5. **Treatment of arrhythmias:** Initial treatment of any acute arrhythmias should include correction of hypoxia, acidosis and electrolyte disturbance (hypocalcemia, hypomagnesemia, hypokalemia or hyperkalemia). Antiarrhythmic drugs for bradyarrhythmias include atropine and

isoproterenol. Supraventricular tachyarrhythmias is treated with adenosine, verapamil or propranolol. Lidocaine is the main drug for ventricular tachyarrhythmias

III. Multisystem Support:

1. Respiratory support:

- Early oxygen therapy in all cases to prevent or delay respiratory fatigue.
- Endotracheal intubation and CPAP for pulmonary edema.
- Endotracheal intubation and CPAP or mechanical ventilation for ARDS.
- Hyper oxygenation and hyperventilation for acute pulmonary hypertension.

2. Renal Support:

- Keep urine output above 1 ml / kg /hour.
- Give volume expanders, diuretics and low dose dopamine in oliguria.
- Consider peritoneal dialysis in severe cases.

3. Metabolic support:

- Correct hypothermia and hyperthermia (both increase metabolic demands).
- Correct metabolic acidosis with sodium bicarbonate.
- Correct electrolyte disturbances (hypocalcemia, hypomagnesemia or hyperkalemia).
- Correct hypoglycemia or hyperglycemia.

4. Gastrointestinal support:

- Antacids. cimetidine and cold saline wash for gastric stress ulcers.
- Intestinal decontamination may be considered to prevent gut translocation of bacteria. Rest of GIT in ileus (give maintenance IV. fluids, parenteral nutrition)

5. Hematological support:

- Correct coagulopathies with vitamin K, fresh frozen plasma and platelets.
- Consider heparinization if peripheral gangrene occurs.

IV. Specific Treatment:

- **In sepsis or septic shock:** Early combined parenteral antibiotic therapy is essential.
- **In hypovolemic shock:** Specific replacement of the lost fluid (water, plasma, blood) is essential.
- **In obstructive shock:** management depends on the cause of obstruction.
- **In cardiogenic shock:** specific treatment of the underlying cause, if available, should be instituted. For instance, arrhythmias should be promptly corrected and rheumatic carditis should receive anti-inflammatory therapy including corticosteroids.
- **In anaphylactic shock:** Early drug therapy with adrenaline, hydrocortisone and antihistamines is important.

V. Monitoring:

- **Key items to monitor:** Electrolytes, glucose, blood gases (pH and oxygenation), central, venous pressure, hemodynamic, coagulation status, urine output, and neurologic status.

Altered consciousness and coma

Definition of Consciousness:

A conscious individual is:

- I. Aware of himself and environment.
- II. Capable of responding correctly to verbal and mechanical stimuli.
- III. Able to recall past events.

Physiology of Consciousness:

Normal consciousness requires perfect functions of:

1. **The reticular activating system (RAS):** which is a collection of nuclei in the reticular formation of the brain stem.
2. **Both cerebral hemispheres:**
 - Normally, increased activity of the RAS, produces the alert conscious state whereas, decreased activity of the RAS reduces the activity of the cerebral cortex and produces sleep.
 - Altered states of consciousness:
 - Interruption of the state of consciousness may occur at one or both these levels:
 - RAS: a small lesion is sufficient to produce coma.
3. **Cerebral cortex:** an extensive lesion is necessary to produce coma.

Assessment of the state of consciousness:

The state of consciousness can be assessed by Glasgow coma scale.

The **Glasgow coma scale** is a useful tool for the grading of the degree of altered consciousness and the severity of CNS insult. Glasgow coma scale is used for adults

and older children and its modification is used in infants and young children. The scale is simple, easy, can be applied at bed side and does not need any investigations

Glasgow Coma Scale (GCS)

ACTIVITY	BEST RESPONSE		
	Adults/Older Children	Infants (modified GCS)	Score
Eye Opening	▪ Spontaneous	▪ Spontaneous	4
	▪ To speech	▪ To speech	3
	▪ To pain	▪ To pain	2
	▪ None	▪ None	1
Verbal	▪ Appropriate speech	▪ Coos, babbles	5
	▪ Confused speech	▪ Irritable, cries	4
	▪ Inappropriate words	▪ Cries to pain	3
	▪ Incomprehensible or none specific sounds	▪ Moans to pain	2
	▪ None	▪ None	1
Motor	▪ Obeys commands	▪ Normal spontaneous movement	6
	▪ Localizes pain		5
	▪ Withdraws to touch	▪ Withdraws to touch	4
	▪ Decorticate to pain	▪ Withdraws to pain	3
	▪ Decerebrate to pain	▪ Decorticate to pain	2
	▪ None	▪ Decerebrate to pain	1
		▪ None	

Significance of Glasgow coma scores:

I. Diagnosis of different grades of altered consciousness:

- Fully conscious child or infant is given GCS of 15.

- Mild to moderate grades of altered consciousness are given GCS from 14 – 11 as with lethargy, confusion and delirium.
- Severe grades as with stupor are given GCS from 9 – 10.
- As coma is defined as no eye opening (score 1), not obeying commands (score 5), and no recognizable words uttered (score 2), so the sum of G.C.S. = 8. So, patients whose score = 8 or less are in coma. The lower the score the deeper is the coma.

II. Follow – up of comatose children: Glasgow coma scores helps in follow-up of patients and in assessment of response to therapy.

III. Prediction of prognosis of comatose child: Glasgow coma scores on admission can be used to predict mortality e.g. score ≤ 5 or less on admission, the probability of death is 90%, and the probability of death is decreasing to 1% with a score of ≥ 10 .

Etiologic Classification of Coma:

I. Local CNS causes:

1. **Head trauma** may produce:

- Cerebral concussion.
- Cerebral contusion.
- Cerebral laceration.
- Brain edema.
- Extra and subdural hematoma.

2. **Vascular:** Hemorrhage, thrombosis, and embolism.

3. **Epilepsy** (Post-convulsion coma).

4. **Central nervous system infections:**

- Meningitis.
- Encephalitis.
- Brain abscess.

- Cerebral malaria.

5. Brain tumors.

II. Systemic causes:

1. Metabolic disorders:

- Metabolic acidosis: Diabetic ketoacidosis and acidosis complicating diarrheal diseases.
- Hypoglycemia: Infants of diabetic mothers and insulin over dosage in diabetic patients.
- Hypoxemia: Congestive heart failure, blue spells in infants with congenital cyanotic heart disease, acute respiratory failure and carbon monoxide poisoning.
- Hyponatremia and hypernatremia.

2. Renal failure.

3. Hepatic failure.

4. Severe systemic sepsis .

5. Heat stroke and hypothermia.

6. Hypertensive encephalopathy.

III. Drugs & Poisons:

Drugs	Poisons
• Atropine overdose. • Barbiturates, benzodiazepines. • Salicylate poisoning. • Narcotics as morphia. • Antihistamines overdose. • Theophylline overdose.	• Lead poisoning. • Kerosene poisoning. • Carbon mono-oxide poisoning. • Bango, hashish and other addicts. • Inhalation of carbon tetrachloride, gasoline or other cleaning fluids. • Organophosphorus poisoning • Rubbing alcohol sponging

IV. Psycho - neurological problems: Hysteria or functional coma: rare, recognized by exclusion.

Diagnostic Approach of a Child with Altered Consciousness:

I. History:

- Head trauma.
- Medication overdose, toxin ingestion.
- Seizures, recent illness or exposure to infection suggestive of meningitis or cerebral malaria.
- Chronic liver, renal, respiratory, metabolic diseases especially diabetes, congenital and rheumatic heart disease.
- Exposure to physical insults (sun-stroke or hypothermia).
- Failure to thrive with vomiting in metabolic and degenerative diseases of the C.N.S.
- Similar episodes in the past.
- Otitis media or ear discharge (brain abscess).

II. Mode of onset:

- Acute onset with trauma, toxins, cerebro-vascular accidents due to neurovascular malformations.
- Subacute onset with thrombosis.
- Gradual onset with progressive course with brain tumors or degenerative brain disease.

III. Family history:

- Family history of neonatal deaths may suggest inherited metabolic disorders.

IV. Clinical examination: Clinical examination of a comatose child aims at:

1. **Assessment of depth of coma:** *through GCS as mentioned before.*
2. **Detection of causes of coma:** *e.g. head trauma, hepatomegaly, heart lesion, otitis media, etc.*
3. **Early detection of signs of increased intracranial pressure:** *(life-threatening brain herniation) through examination of papillary size & reactivity, ocular movements, breathing pattern and motor response to stimuli.*

Laboratory investigations:

If the cause of coma is unknown or uncertain, a number of laboratory studies should be considered:

I. Blood examination:

- **Blood:** glucose, urea, creatinine, ammonia, bilirubin, and liver enzymes.
- **Blood gases and pH:** for metabolic disturbances.
- **Blood picture:** leukocytosis in bacterial infection, lymphocytosis in viral infection.
- **Blood culture:** in infectious causes.
- **Blood coagulation studies:** in bleeding disorders.
- **Blood film** for malaria.

II. Serum:

- **Serum electrolytes:** (Na⁺, K⁺).
- **Osmolarity:** *high in diabetic ketoacidosis.*
- **Neutralization and complement fixation studies:** *if there is possibility of viral encephalitis.*
- **Toxic screen:** *serum lead, serum salicylate, and other poisoning.*

III. Urine: *In addition to toxic screen, urine must be examined for characteristic odor, reducing substances, specific gravity, pH, ketones, glucose, RBCs, casts, and albumin.*

IV. C.S.F. examination: *bloody in subarachnoid hemorrhage, purulent in bacterial meningitis. The lumbar puncture is contraindicated if there are signs of increased intracranial pressure or if the patient is shocked.*

V. Gastric lavage: *examination of gastric aspirate is indicated if there is a possibility of poisoning.*

VI. Radiological investigation:

- **Plain x-ray:** Skull, spine, chest and heart.
- **Brain imaging:** (CT and MRI).

VII. Electro-encephalogram: *indicated in cases with unexplained stupor or coma.*

VIII. Electro-cardiogram: and Echocardiographic studies *may detect the cause of coma (e.g. embolism from chronic valvular lesion of the heart).*

Management of the comatose patient:

I. Adequacy of the child's airway, breathing, and circulation ("the ABCs"):

- The child's neck should be immobilized carefully in neutral position unless it is clear that a cervical spine injury has not occurred.
- Insert an oral airway, clear vomitus and blood from pharynx by suctioning.
- Place your patient in lateral position.
- 100% supplemental oxygen should be given initially.
- Check gag reflex early in the course of care and the airway promptly protected by intubation if this reflex is inadequate.

- Hemodynamic status then should be assessed rapidly, paying attention to heart rate, blood pressure, and peripheral perfusion (pulses, capillary refill, and skin temperature of distal extremities).
- Establish an intravenous line.
- Insert an indwelling urinary catheter. This is important for the assessment of the fluid management and for obtaining urine samples.

II. Continuous monitoring:

- The conscious level by regular estimation of GCS.
- The vital signs.
- The blood electrolytes and blood gases.
- The arterial O₂ saturation should be monitored by pulse oximetry.
- The intracranial pressure to assess cerebral perfusion (CP), (C.P. = mean arterial BP – mean intracranial pressure).
- Development of bed sores with long-standing coma.
- Prevention of corneal ulcers by covering both eyes.
- Urinary catheterization with urine retention.

III. Immediate therapeutic intervention:

1. Treatment of reversible causes of coma:

- Hypoglycemic coma: by IV D10-25W and run to give 4-6 mg glucose /kg/min and increase to keep glucose within the normal range (above 3 mmol/L).
- DKA coma: by insulin and fluid therapy.
- Narcotic overdose: Naloxone 0.5 mg IV.

2. Treat hyperthermia: by sponging with tepid water, antipyretics, and using a cooling blanket. Hypothermia requires careful re-warming of the patient.

3. **Treatment of seizures:** using diazepam IV 0.3 mg/kg/dose followed by phenytoin 10 mg/kg IV slowly. Maintenance phenytoin dose is then given 5 mg/kg divided in 2 doses.
4. **Treatment of shock:** as mentioned in chapter of shock.

IV.Prevention and urgent treatment of increased intracranial pressure:

1. Avoidance of factors that could increase ICP:

- Painful stimuli.
- Physiotherapy without sedation.
- Tracheal suctioning without sedation.
- Movements.
- Excessive fluid intake: Keep fluid at 80 ml/kg/day.
- Keep serum osmolality between 280-300 mosml/L
- Prevent hyperpyrexia.

2. Treatment of increased intracranial pressure by:

- ***Keep head in mid-position;*** elevate the head 30 degrees to augment venous drainage.
- ***Mannitol:*** 0.5 gm/kg over 20 minutes, followed by 0.25 gm/kg to be repeated as required and furosemide 1-2 mg/kg IV.
- ***Mechanical Ventillation:*** Aiming at reducing PaCO₂ between 20-25 mmHg. This will reduce brain blood flow and reduce brain edema.

Prognosis of Comatose Child:

This depends upon the following factors:

- **The etiology of the condition:** diabetic ketoacidosis has a more favorable outlook than anoxia and severe encephalitis.

- **Paralysis and placement** on the respirator.
- **Severity of the coma** (by Glasgow coma score).
- **The EEG** is also useful to estimate the potential for neurologic recovery.
- **Neurophysiologic studies** have also been used to make a prognosis for comatose children, including brain stem auditory, visual, and somatosensory evoked potentials (SEPs). Generally, the absence of all waveforms in these three modalities is associated with brain death or severe neurologic residual.

Practice Questions

(Choose one correct answer)

- 1- The most likely finding in the initial stages of septic shock is:
 - a) abnormally low blood pressure.
 - b) absent femoral pulses.
 - c) delayed capillary refill.
 - d) hyperpnea.
- 2- Which disease of the following can cause distributive shock?
 - a) cardiac tamponade.
 - b) dehydration.
 - c) early septic shock.
 - d) critical aortic stenosis.
- 3- In type I respiratory failure there is:
 - a) metabolic acidosis.
 - b) metabolic alkalosis.
 - c) respiratory acidosis.
 - d) respiratory alkalosis.
- 4- Atropine is the antidote of:
 - a) organic phosphorous.
 - b) iron.
 - c) lead.
 - d) chlorpromazine.
- 5- The diagnosis of cardiopulmonary arrest must be made rapidly in the:
 - a) absent pulse and presence of respiration.
 - b) absent respiration and presence of pulse.
 - c) absent pulse and respiration.
 - d) absent cranial reflexes.



Chapter 8 Endocrinology

Objectives:

1. Understand the causes, pathogenesis, and clinical features of congenital hypothyroidism.
2. Enumerate findings in investigations in common endocrinal problems
3. Formulate a management plan for Type I Diabetes Mellitus.
4. Understand the basics of normal puberty.
5. Describe the abnormalities in puberty.

Contents:

1. Congenital hypothyroidism
2. Type I Diabetes Mellitus
3. Short Stature
4. Puberty (normal & delayed)

Hypothyroidism

Hypothyroidism can be congenital or acquired, and both may be goitrous or non goitrous. In congenital hypothyroidism "cretinism", the disorder is believed to have been present before birth. In acquired or juvenile hypothyroidism, a previously normal child develops thyroid deficiency.

Congenital Hypothyroidism (Cretinism)

Definition:

Congenital deficiency of thyroid hormone (TH) since fetal life.

Background:

Thyroid hormone deficiency can occur because of:

- An anatomic defect in the thyroid gland,
- An inborn error of thyroid metabolism,
- Iodine deficiency.

Epidemiology:

It occurs 1 in 4000 live births worldwide.

Female: male 2:1

Mortality and morbidity:

Profound mental retardation is the most serious effect of untreated congenital hypothyroidism.

Etiology:

I- Primary Hypothyroidism (Diseases in thyroid gland)

1- non-goitrous cretinism (Thyroid dysgenesis):

- Occurs in about 90% of cases, and is due to thyroid gland dysgenesis (Aplasia, hypoplasia, or an ectopic gland).
- Most cases are sporadic, rarely are familial.
- Female to male ratio is 2:1.
- Hypoplastic thyroid may lie anywhere between the base of the tongue and the normal position of the gland in the neck.

2- Goitrous cretinism:

It occurs in about 10% of cases. It may be either transient or permanent hypothyroidism.

A- Transient hypothyroidism may be due to:

- i. Endemic iodide deficiency causing endemic goiter in the mother.
- ii. Maternal ingestion of antithyroid drugs or iodine containing drugs during pregnancy.

B- Permanent hypothyroidism (Thyroid dysmorphogenesis):

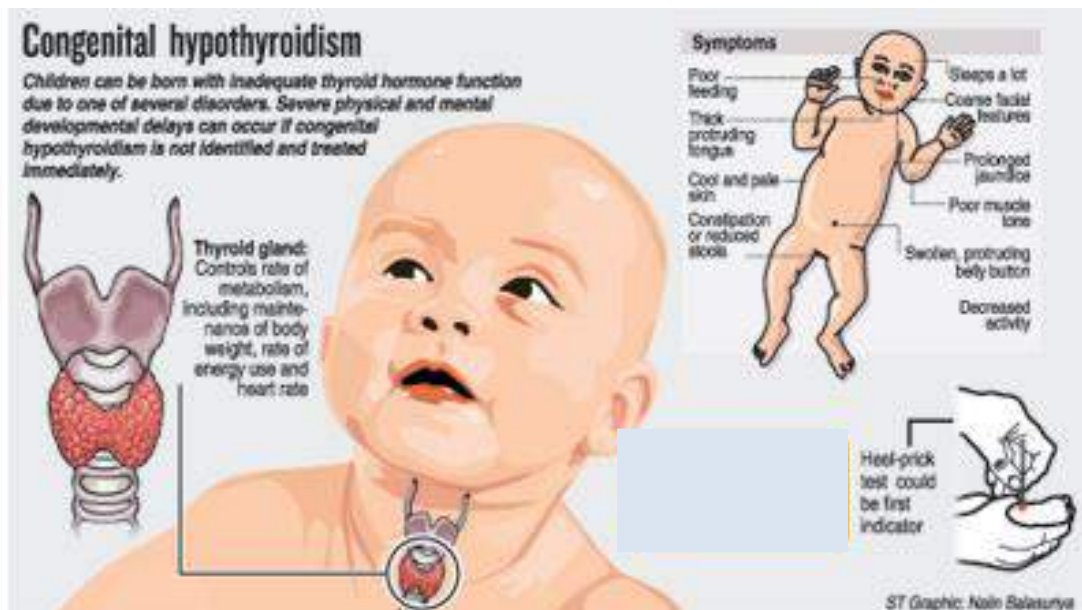
It may be caused by deficiency of any enzyme needed to synthesize thyroxine. It is one of inborn error of metabolism which is usually autosomal recessive genetic disease

II-Secondary Hypothyroidism: (Disease in Pituitary gland)

III-Tertiary Hypothyroidism: (Disease in Hypothalamus)

Clinical manifestations:

I- Presentation in neonatal period:



A. Most of the affected infants are asymptomatic at birth and hence the importance of neonatal screening for hypothyroidism. Symptoms develop weeks or months after birth. This is due to partial correction of thyroxine (T_4) deficiency by the transplacental transfer of T_4 from mother to fetus.

B. In severe cases, the early signs of congenital hypothyroidism include:

- Large-sized baby at birth.
- Prolonged physiologic jaundice owing to delayed maturation of glucuronyl transferase enzyme responsible for Bilirubin glucuronosylation.
- The infant sleeps much and cries little.
- Poor appetite and choking spells during nursing.
- Constipation.
- Cold mottled skin especially over the limbs, with or without edema or
- Myxedema.
- Wide anterior fontanel.
- Posterior fontanel is open and large.

- Coarse, and may be ugly facies.
- Goiter may be detected in some cases.
- Diagnosis at this period depends on a high degree of suspicion and serum T₄ estimation.

II- Presentation of untreated hypothyroidism during infancy and childhood:

A. Physical features:

- **Facies**: The face gradually becomes puffy, ugly, with wrinkled hairy forehead, large protruding tongue, thick lips, and small eyes with narrow palpebral fissures.
- Dry scalp hair, thick short neck with supraclavicular deposits of fat.
- Hoarse cry and voice.
- Hands broad and thick, fingers are short.
- Myxedema in eyelids, dorsum of hand and genitalia.
- Skin is pale, cold, and scaly with little perspiration.
- Short stature, mainly due to short lower limbs.
- Reduced heart rate and low body temperature.
- Delayed dentition and wide anterior fontanel.

B. Developmental retardation:

- Delayed milestones of development of variable degrees e.g., head support, social smile, sitting, standing, speech ...etc.
- Retarded and defective brain development: thyroid hormone is essential for the maturation of brain function during the first two years of life. Congenital hypothyroidism will lead to irreversible brain damage and mental retardation of varying severity if diagnosis and adequate treatment are delayed beyond the first 2-3 months of life.
- Delayed sexual maturation.

Ectopic thyroid hypoplastic tissue:

- This may provide adequate amounts of thyroxine for many months or years.
- Manifestations of inadequate formation are in the form of abnormal physical features mentioned above without affection of intelligence or learning.
- The ectopic thyroid gland may be detected sublingually or as thyroglossal duct cyst or subhyoid median thyroid.

Investigations:

It is important to establish the diagnosis and to start therapy as soon after birth as possible because the risk of brain damage increases when the treatment is delayed.

1. Neonatal screening:

- This is a major advance in early diagnosis of neonatal hypothyroidism. A drop of blood obtained by heel prick at 7th day of life is placed on filter paper and sent to a central laboratory. A serum TSH more than 20 micro units / ml (uU / ml) or T₄ less than 6 microgram / dl (ug / dl) is suggestive of hypothyroidism. The diagnosis is confirmed by repeating hormone analysis.
- Neonatal screening may miss 10 % of cases of congenital hypothyroidism, hence the importance of careful observation and critical observation.

2. Thyroid function: will show decreased T₄ (normal 5-15 ug / dl) and increased TSH (normal up to 6 uU / ml).

3. Radiological examination:

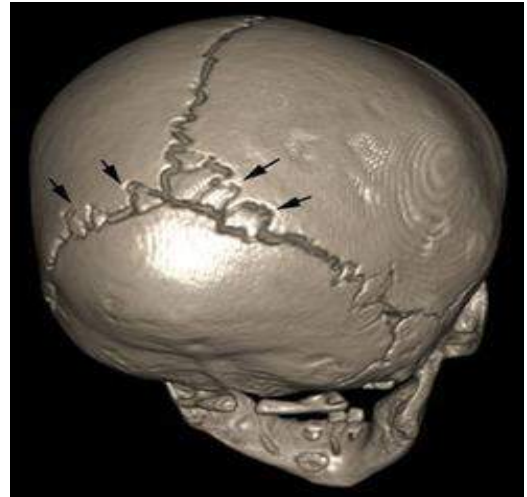
a) **Limbs:** delayed bone age and epiphyseal dysgenesis. Absent epiphyses of lower end of femur and upper end of tibia. (Epiphyses have multiple foci of ossification)



b) **Skull**: large fontanel and wide sutures, wormian (intra sutural) bones are common.

4. **ECG**: may show low voltage of P, QRS and T waves.

5. **Scintigraphic (Isotope) study**: using ^{125}I or technetium ^{99}Tc can differentiate between aplasia, ectopic thyroid (abnormal location) and defects in thyroid synthesis.



Differential Diagnosis:

I- During the first 2 months of life:

- Causes of prolonged neonatal jaundice.
- Causes of constipation.
- Causes of edema or sclerema.
- Causes of hypothermia.

II- Later on:

- Causes of developmental retardation e.g., Down syndrome.
- Causes of short stature.

Prognosis:

- 1- Early diagnosis and adequate treatment from the early weeks of life results in normal physical and mental development.
- 2- Delay in diagnosis, inadequate treatment or neglect of treatment of cases beyond the first 2-3 months of life result in variable degrees of mental retardation.
- 3- When onset of hypothyroidism occurs after 2 years of age the prognosis is much better. The IQ may be returned to pre-disease level.

Treatment:

Sodium L-thyroxine by (ELtroxin[®])

1- The dose:

The above doses should maintain serum T4 level at 12-15 µg / dL, and TSH below 5 uU / ml, and should give normal bone age.

2- Transient hypothyroidism

Infants with endemic iodine deficiency or where their mothers ingested anti-thyroid drugs may have transient hypothyroidism, and in this condition, it is advised that L-thyroxine treatment is discontinued for 3-4 weeks when the child is > 3 years old, If this results in reduction of serum T4 and marked rise of TSH, it confirms the diagnosis of permanent hypothyroidism necessitating lifelong treatment.

3- The response to treatment can be evaluated by:

Age	Dose	Comment
Neonate	10-15µg /kg/day.	The doses are given orally on the morning. Thyroxine tablet should be crushed and fed directly to the infant.
First 2 years	6-8 µg /kg/day	
Older children	4 µg /kg/day	
Adults	2 µg /kg/day	

➤ Clinical assessment:

- GIT: constipation or diarrhea,
- Pulse: Tachycardia or bradycardia
- Appetite
- Growth rate

➤ Investigations:

- serum T4 level at 12-15 µg / dL,
- TSH below 5 uU / ml,
- Should give normal bone age.

4- Follow up of the treatment: is done by:

➤ Clinical assessment

L-thyroxine overdoses → diarrhea, fever, tachycardia, excessive sweating, irritability and increased appetite

➤ Repeated measurement of plasma levels of T4 and TSH:

- 1 - At 1 month after initiation of treatment.
- 2 - Every 2 months during 1st year.
- 3 - Every 3 months between 1-3 years.
- 4 - Every 6 months until growth is complete

Acquired Hypothyroidism

Causes:

1- Goitrous:

- Hypothalamic-pituitary insufficiency (panhypopituitarism or isolated TSH deficiency).
- Iodine deficiency (endemic goiter).
- Intake of goitrogenic drugs.
- Autoimmune: Hashimoto thyroiditis after an initial stage of hyperthyroidism.

2- non-goitrous:

- Post-thyroidectomy
- Post-irradiation (e.g. radiotherapy for Hodgkin disease).

Clinical Features:

- 1- Puffiness of the eyelids
- 2- Dry, myxedematous skin
- 3- Low hair line
- 4- Yellow skin, carotenemia
(especially seen in palms of hands and soles of the feet)
- 5- Anemia refractory to hematinics
- 6- Decreased activity
- 7- Decreased school performance
- 8- Easy fatigability
- 9- Sense of coldness
- 10- Decreased appetite.
- 11- Short stature
- 12- Delayed puberty (the adolescents may not enter the puberty at all).

Hypothyroidism

Easy to diagnose and treat -- if you think of it.

slowing of mind and body

weak heartbeat

constipation

myxedema

high LDL

slow reflexes

hair thinning

depression
"schizophrenia"
irritability

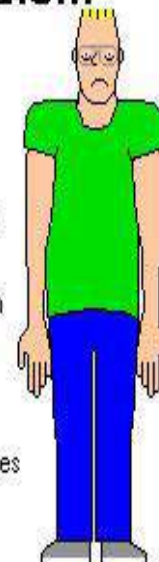
big tongue

croaky voice

dry skin

cold skin

cold intolerance



Investigations:

- 1- Decreased T₄ (normal 5-15 ug/dl) / increased TSH (normal up to 6 uU / ml).
- 2- Serum cholesterol and carotene levels are elevated, while serum vitamin A is markedly low.
- 3- Normocytic normochromic anemia,
- 4- Bradycardia with low voltage complexes (in all leads)
- 5- Radiological evidence of delayed bone age and epiphyseal dysgenesis.

Prognosis:

The prognosis of the acquired hypothyroidism depends mainly on the underlying cause. Treatment is by L- Thyroxine (See the above table for the doses).

Type 1 Diabetes Mellitus (T1DM)

Definition:

It is a metabolic endocrine disease caused by diminished insulin production and clinically characterized by polyuria, polydipsia, and weight loss, hypovolemia and glycosuria. It is also called insulin dependent diabetes mellitus (IDDM).

Features:

- Onset is usually < 25 Yrs. old
- HLA associated
- Autoimmune B cell destruction
- Insulin is deficient

Epidemiology:

Prevalence increases with age: 1/1500 by age of 5 yrs., 1-2 /1000 by school age and 3/1000 by age of 16 years. It occurs in boys and girls equally.

Etiology:

1-Type I diabetes mellitus results from gradual immunologic damage of the β -cells of the pancreatic islets.

2-The immunologic damage requires gene predisposition (HLA) and environmental factors (Viral infections, chemicals, diet, seasonality, and geographic locations).

Clinical Manifestations:

- Asymptomatic: few cases are detected by routine urine analysis.
- Mild: presents with enuresis or failure to gain weight.
- Moderate: presents with polydipsia, polyuria, polyphagia and weight loss.

- Severe cases may present with ketoacidosis, dehydration increased respiratory effort, acetone breath, mental confusion and coma.

Laboratory Manifestations:

1. Fasting glycosuria with or without ketonuria
2. Fasting plasma glucose over 126 mg/dl.
3. Random plasma glucose (RBS) over 200 mg/dL in the presence of classic symptoms of diabetes.
4. Oral glucose tolerance test (OGTT): plasma glucose after an oral glucose load is > 200 mg/dL.
5. Serum insulin and peptide C levels are reduced
6. Glycosylated hemoglobin (HbA1c) level to estimate degree of glycemic control over the previous 3 month treatment.

Complications:

1. Diabetic ketoacidosis
2. Hypoglycemic coma.
3. Hyperosmolar hyperglycemic state (HHS)
4. Infections may be frequent.
5. Stunting of growth and delayed puberty may occur in poorly controlled diabetic children.
6. Nephropathy, retinopathy and neuropathy due to narrowing of small vessels.
7. Atherosclerosis of large vessels.
8. Other complications due to insulin therapy e.g. hypoglycemia, lipid dystrophy.
9. Psychological and financial problems.

Complications are best avoided by good compliance to insulin therapy, dietetic management and achievement of good glycemic control.

Management:

Mild cases need out patient management and other cases should be hospitalized.

1- **Diet:** balanced and adequate diet for normal growth and development. Consistent timing of 3 main meals and 3 snacks between meals and before bedtime.

2- **Insulin therapy:** in established diabetes the total dose of insulin is usually 0.8-1 Unit/kg/day,

The goal of insulin regimens is to provide more physiologic insulin levels coincide with nutrient absorption and basal levels occur between meals so that there is less between meal insulin action. The basal insulin component provides baseline, between meals, or fasting insulin need. The bolus component provides insulin to cover food requirement and to correct hyperglycemia. The basal component may be provided by either rapid-acting insulin given by the basal rate using an insulin pump, or with once or twice daily injections of NPH (intermediate-acting insulin), detemir or glargine (long-acting insulin),.the bolus insulin is provided by rapid –acting insulin which may be given by injections or by the bolus function through an insulin pump

3- **Heavy exercise is avoided, but a moderate exercise is useful.** The child should have a piece of sugar or candy in his pocket and advised to ingest it if he feels hunger, weakness, sweaty or shakiness.

4- **Treatment of complications.**

Type 2 Diabetes Mellitus (T2DM)

It is known as non-insulin dependent diabetes mellitus (NIDDM)

Features:

1. Onset is usually > 25 Yrs. old.
2. Not HLA associated
3. No autoimmune B cell destruction
4. Insulin is normal or high
5. Positive Family history
6. Obesity is a risk factor.

T2 DM is common in African-Americans. Nowadays incidence is increasing due to obesity, and sedentary life. It may present $\approx 10\%$ of new cases in pediatrics.

Diabetic ketoacidosis (DKA)

Definition:

It is a state of acidemia induced by excess production of ketoacids (acetoacetic acid and beta butyric acids) due to insulin deficiency.

This condition is characterized by:

- 1- Blood glucose ≥ 300 mg/dl + Glycosuria
- 2- Increased Ketones in blood $\pm$ ketonuria
- 3- Acidosis (pH < 7.3), $\text{HCO}_3^- \leq 15$ mEq/L

The pathophysiological mechanisms of Ketoacidosis are due to:

- a. Insulin deficiency
- b. Increase counter regulatory hormones (glucagon, cortisol, catecholamines & growth hormone)
- c. Precipitating factors:
 - i. Stress (physical or psychological)
 - ii. Infection

Clinical features of ketoacidosis:

- 1- Polyuria, polydipsia, dehydration + polyphagia
- 2- Vomiting, abdominal pain (may be severe)
- 3- Altered consciousness: drowsiness $\rightarrow$ coma
- 4- Air hunger (deep rapid breathing) + acetone odor of breath
- 5- Evidence of infection may be present.

Management of diabetic ketoacidosis

I. Initial evaluation:

- A- *Careful history taking and physical examination*
- B- Laboratory investigations:
 1. Complete blood picture
 2. Serum electrolytes, ca, P, creatinine, blood urea
 3. Glucose (blood & urine) & acetone (urine only)
 4. Complete urine analysis
 5. Serum bicarbonate, PH, blood gases
 6. ECG record (signs of hypokalemia etc.)

II. Supportive measures:

- 1-Put an IV line and start normal saline infusion immediately**
- 2-Put nasogastric tube and aspirate the stomach
- 3-Put Foley catheter if the patient is anuric
- 4-Broad spectrum antibiotics for febrile patients (after obtained cultures)
- 5-Oxygen for cyanotic or shocked patients and/or with $\text{PaO}_2 < 80$ mmHg
- 6-Record all patient's data, intakes, outputs and treatments on a flow chart
- 7-Transfer patient to ICU if bicarbonate is <10 , or PH < 7 , or if severely**

ill

III- Fluid therapy:

- 1- First hour (emergency rehydration)
 - **Normal saline, 20 ml/kg over the 1st hour**
 - **Repeat if patient has not shown clinical improvement**
- 2- Next 6-12 hours (deficit + maintenance): 5-10 ml/kg/hour
 - **Start initially with normal saline**
 - Shift to glucose 5% + saline (1:1) when blood glucose drops to < 300 mg/dl
 - Potassium is added only when urine flow is satisfactory

- 3- Oral fluids (carbohydrates & electrolyte mixtures or other liquid diets) can usually be started cautiously within 24 hours and parenteral therapy may be discontinued

IV- Bicarbonate therapy:

- a. Bicarbonate therapy is indicated only if blood PH is < 7
- b. Dose: 1-2.5 mEq/kg given as IV drip over 2-3 hours, and can be repeated

V- Insulin therapy:

One of the following schedules can be used:

1- Continuous insulin infusion

- Loading dose: regular insulin, 0.1 U/kg IV
- Maintenance : regular insulin, 0.1 U/kg/hour IV

2- Intramuscular:

The intramuscular route should not be used initially in the presence of shock or contraindications such as coagulopathy

- Loading dose: regular insulin, 0.15 U/kg IV or 0.15 U/kg IM.
- Maintenance: regular insulin, 0.1 U/kg/hour IM or SC.

VI- Monitoring schedule:

1. First 6-12 hours:

- Hourly: Blood glucose, urine glucose & ketones, fluid intake and output (urine, etc.)
- Every 2 hours: Serum electrolytes.
- Every 2-4 hours: ECG (for hyperkalemia), creatinine, urea, PH and bicarbonate.

2. Next 12 hours: Laboratory studies as indicated by clinical and biochemical progress

VII- Reassessment of the dose of insulin:

1. Insulin should be given at least every 4-6 hours.
2. Adjust the dose according to rate of fall of blood glucose (no fixed schedule).

3. When patient improves, shift to 6-hourly subcutaneous insulin (Dose: 0.1-0.5 U/kg according to urine and blood glucose levels)
4. Blood glucose should be kept between 80 and 180 mg/dl.

Short Stature

The child is considered short when his/or her stature (height or length) is below the 5th percentile for age and sex (a height or length less than that of 95 % of children of the same age and sex).

I- Normal variants of short stature:

- These constitute more than 90 % of cases of short stature.
- Two types of “normal variants” are shown in the following table:

	Genetic (Familial) Short stature	Constitutional Growth Delay
Birth length	Baby is born small	Baby is born normal in size but grows slowly, so his length is less than 5 th percentile over the first 2 years
Maturation	Bone age is nearly equal to chronological age Puberty occurs at normal time	Bone age is delayed Delayed puberty and pubertal growth spurt
Family	Short parents	History of delayed puberty.
Final height	Becomes a short adult	Normal adult height and sexual development

II- Pathological Short stature may be due to:

- 1) **Primary bone disease:** skeletal dysplasia: e.g., achondroplasia,
- 2) Osteogenesis imperfecta and vitamin D resistant rickets.
- 3) **Chromosomal anomalies:** e.g., Down syndrome, Turner syndrome, and Laurence-Moon-Biedl syndrome.
- 4) **Intrauterine growth retardation:** due to maternal Infections, toxins,
- 5) Malnutrition and severe illness during pregnancy.
- 6) **Under nutrition:** PEM, Vitamin D deficiency rickets, and Mineral
- 7) deficiencies e.g., zinc, iron
- 8) **Chronic system disease:** Gastrointestinal disease, Congenital heart

9) disease, Renal disease, Pulmonary disease, Chronic infections, Collagen disease, Liver disease, Mental retardation, Blood disease

10) **Endocrine disease:** may be

A- Hyperhormonal:

- a. Cortisol excess: Cushing syndrome, and prolonged corticosteroid therapy.
- b. Androgen excess: Virilizing adrenal hyperplasia (bone age and height become markedly advanced. Premature closure of epiphysis will result in short adult height in untreated or in inadequately treated patient)

B- Hypohormonal:

- a. Hypopituitarism
- b. Hypothyroidism (congenital or acquired)
- c. Type 1 diabetes mellitus

Evaluation of short stature:

- 1- **History:** Prenatal, neonatal, and during infancy and childhood.
- 2- **Review of systems:** cardiovascular, gastrointestinal, renal, endocrine, CNS....etc.
- 3- **Measurements:** Weight, Length / height, upper / lower segment, span, Head circumference Mid-arm circumference, subcutaneous fat thickness (skin fold thickness)

A- Proportionate short stature:

1. Normal variants
2. Endocrine causes
3. Most causes of growth failure in infancy

B- Disproportionate short stature:

- With short limbs e.g., Skeletal dysplasia (achondroplasia), and Osteogenesis imperfecta

- With short trunk: in Mucopolysaccharidosis, and rickets.

4- Physical examination:

- 1- Recognition of special features of specific endocrine diseases (e.g., cretinism), or dysmorphic syndromes (e.g., Down syndrome, Turner syndrome, achondroplasia).
- 2- Measurement of blood pressure (increased in renal disease and congenital adrenal hyperplasia).
- 3- Neck: webbed neck (Turner syndrome), presence of goiter.
- 4- Heart: congenital heart disease (e.g., large VSD, Fallot's tetralogy).
- 5- Chest: bronchiectasis, asthma.
- 6- Abdomen: hepatomegaly (bilharziasis, chronic hepatitis, glycogen storage diseases).
- 7- CNS: cerebral palsy, mental retardation.
- 8- Evaluation of developmental skills.

5- Radiological studies:

- **Bone age:** It is delayed in constitutional short stature, Malnutrition, Hypothyroidism, and Hypopituitarism. It is advanced in congenital adrenal hyperplasia.
- **X ray wrist:** for diagnosis of infantile rickets.
- **Skeletal survey:** for skeletal dysplasia.

6- Echocardiography: for suspected heart disease.

7- Laboratory investigations:

- 1- Karyotyping: for the possibility of chromosomal disease.
- 2- Thyroid functions (T3, T4, TSH).
- 3- Serum Ca, P & alkaline phosphatase: for rickets and hypoparathyroidism.
- 4- Serum albumin, AST & ALT: to exclude malnutrition and hepatic disease.

- 5- Serum creatinine and electrolytes to exclude renal disease.
- 6- ESR: increased in chronic diseases e.g., T.B, chronic inflammatory bowel diseases.
- 7- Sweat chloride test: to exclude cystic fibrosis.
- 8- Serum antigliadin antibodies to exclude celiac disease.
- 9- Investigation of growth hormone secretion:
 - Performed only in short children with slow growth velocity in the absence of systemic disease.
 - Physiological test: exercise, sleep.
 - Pharmacological test: clonidine, glucagon, L dopa, insulin.

Treatment:

- 1- Treatment of the underlying disease process if possible.
- 2- Growth hormone for children with growth hormone deficiency.
- 3- Replacement of other hormonal deficiencies e.g. thyroid hormone.

Normal Puberty

Definition

Puberty is a process leading to physical and sexual maturation that involves the development of secondary sexual characteristics as well as growth, changes in body composition and psychosocial maturation. Normal puberty begins between 8 and 14 years of age in girls and between 9 and 14 years of age in boys

Normal Development

Two processes contribute to the physical manifestations of puberty: adrenarche and gonadarche.

1] Adrenarche:

It is maturation of adrenal gland which ready to secrete dehydroepiandrosterone (DHEA) and its sulphate. Adrenarche normally occurs between six and eight years of age. It is accompanied by changes in pilosebaceous units, a transient growth spurt and the appearance of axillary and pubic hair in some children, but no sexual development.

2] Gonadarche:

Gonadarche is initiated by the macroneurons of the hypothalamus that secrete Gonadotropin-releasing hormone (GnRH) in a critical pulsatile pattern that regulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary. This pulsatile secretion of Gonadotropin is responsible for enlargement of the gonads and secretion of sex hormones.

Stages of Puberty

1- Girls begin puberty with:

- Appearance of secondary sexual characters:
- Breast buds (10-11yr)
- Skeletal growth (usually the peak height velocity precedes menarche)
- The arrival of pubic hair, then axillary hair

- Appearance of primary sexual character.
- The interval to menarche is usually 2-2.5 years.

2- In boys puberty begin with

- Appearance of secondary sexual characters:
- Testicular enlargement.
- Thinning and pigmentation of the scrotum.
- The appearance of pubic hair then axillary hair.
- Enlargement of the penis and spermatarche (primary sexual character).
- Skeletal and muscle growth are late events in male puberty.

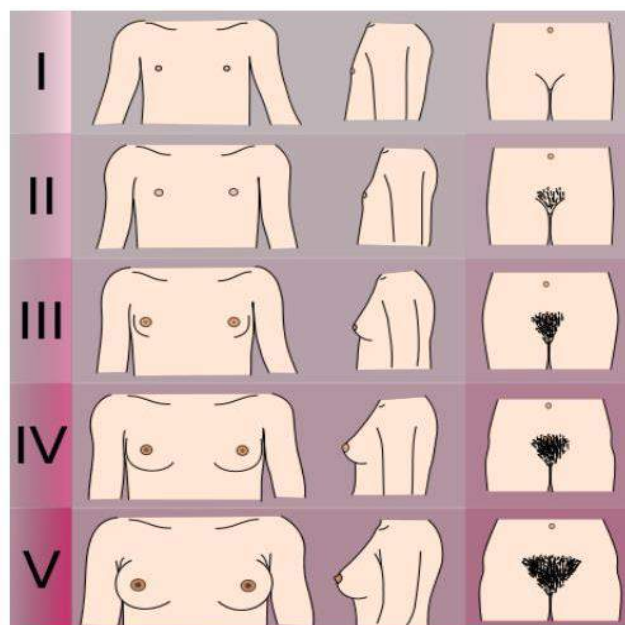
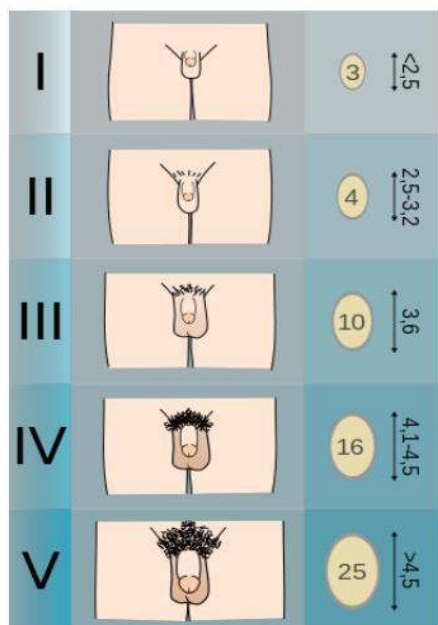
Factor affecting puberty

- 1- **Osseous maturation:** the onset of puberty is more closely correlated with osseous maturation than with chronological age.
- 2- **Race:** black girls have early menarche than white
- 3- **Environmental factors:** e. g., climate.
- 4- **Nutrition and general health:** good nutrition and general health leads to early pubertal changes.
- 5- **Body weight and composition:** obese girls tend to have early menarche. The condition is variable in boys
- 6- **Genetic factors:** familial

Disorders of Puberty:

May be either delayed puberty or early puberty (precocious puberty)

Sex Maturity Stages (Tanner's Stages)



A- For Girls:

Tanner stage	Pubic hair	Breast
1	Preadolescent	Preadolescent
2	Sparse, straight, lightly pigmented,	Breast and papilla elevated as small mound
3	Increase in amount, start to curl, darker	Breast and areola enlarged
4	Coarse, curly, abundant but less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

B- For Boys:

Tanner stage	Pubic hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Sparse, straight, lightly pigmented	Slight enlargement	Enlarged scrotum, pink
3	Increase in amount, start to curl, darker	Longer	larger
4	Coarse, curly, abundant but less than adult	Larger glans and breadth	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

Delayed Puberty

Definition:

In girls, delayed puberty is defined as lack of any breast development by 14 years of age or when more than five years pass between initial growth of breast tissue and menarche. In boys, delayed puberty is defined as no testicular enlargement by 14 years of age or the passing of five years between the initial and complete development of the genitalia.

Causes of delayed puberty

- 1- Constitutional delay (the commonest cause)
- 2- Gonadotropin deficiency (low plasma levels of LH and FSH)
- 3- Primary gonadal failure
- 4- Hypopituitarism due to tumor, infection, idiopathic (panhypopituitarism)
- 5- Chronic illness, malignancy, chronic infection, chronic debilitating disease.
- 6- Chromosomal abnormalities: Turner syndrome (45, XO), and Klinefelter syndrome (47, XXY).
- 7- Miscellaneous condition: anorexia nervosa, extreme athletic persons, idiopathic, malnutrition.

Practice Questions**(Choose one correct answer)**

- 1- Hyperglycemia is present when fasting blood sugar exceeds:
 - a) 126 mg/dL.
 - b) 180 mg/dL.
 - c) 110 mg/dL.
 - d) 140 mg/dL.

- 2- Insulin infusion for DKA treatment should be started usually:
 - a) simultaneously with IVF.
 - b) half an hour after IVF.
 - c) one hour after IVF.
 - d) half an hour before IVF.

- 3- Thyroxine deficiency causes all of the following EXCEPT:
 - a) hypercholesterolemia.
 - b) accelerated bone age.
 - c) epiphyseal dysgenesis.
 - d) low voltage ECG.

- 4- Adrenarche is maturation of adrenal gland to secrete :
 - a) dihydroepiandrosterone.
 - b) gonadotropin-releasing hormone.
 - c) follicle-stimulating hormone.
 - d) luteinizing hormone.

- 5- Pathological short stature may be due to :
 - a) Turner syndrome.
 - b) Kwashiorkor.
 - c) Achondroplasia.
 - d) all of the above.



Chapter 9

Neonatology

Objectives:

1. Classify newborns according to gestational age and weight.
2. Understand indications and steps of neonatal resuscitation.
3. Define prematurity and common problems associated.
4. Enumerate birth injuries, causes and management.
5. Understand different neonatal disorders, clinical picture, diagnosis, and management.

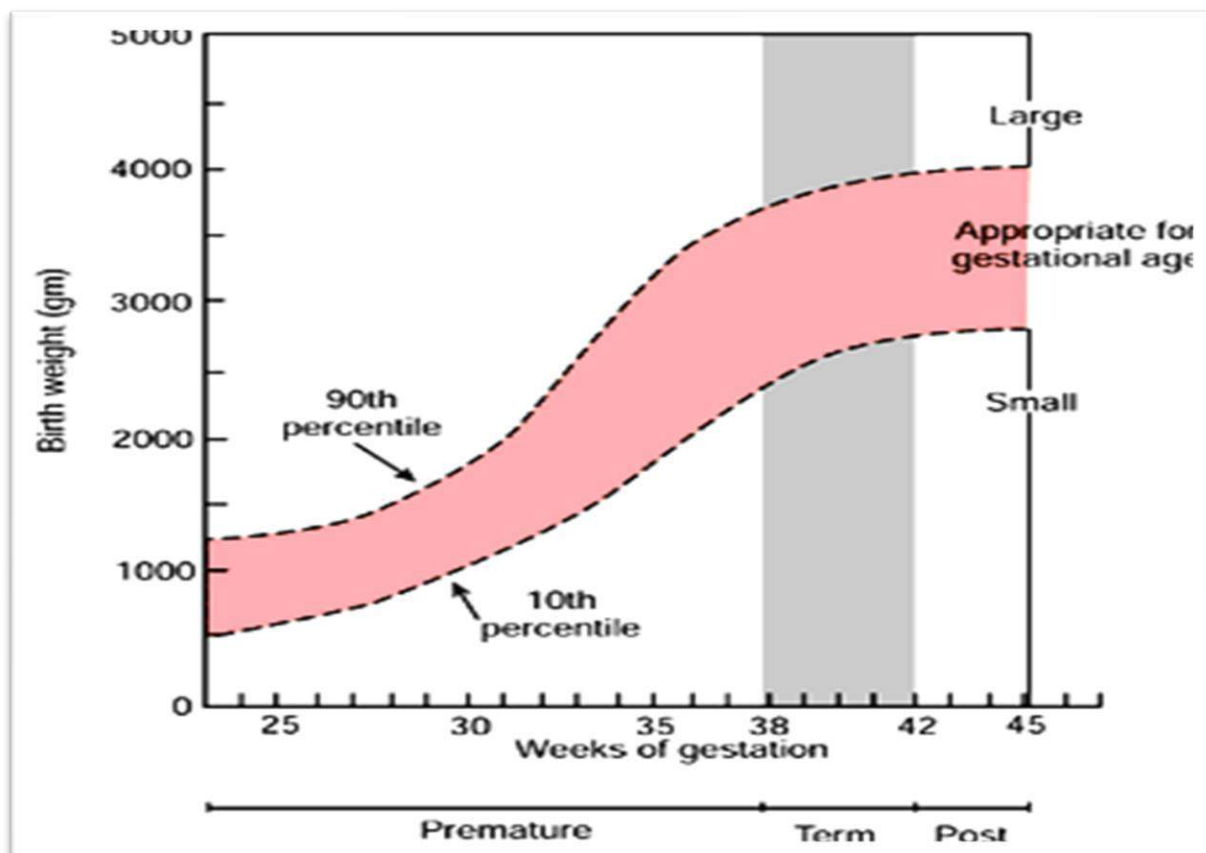
Contents:

1. Definitions.
2. Neonatal resuscitation.
3. Prematurity.
4. Birth injuries.
5. Neonatal Disorders:
 - Neonatal Respiratory distress.
 - Neonatal Hyperbilirubinemia.
 - Neonatal Metabolic Disturbances (IDM).
 - Neonatal Hematological Disorders.
 - Neonatal sepsis.
 - Neonatal seizures.

Definitions

Newborn	First 4 weeks of life.
Live birth	Newborn that shows signs of life (movements, any respiratory effort & heartbeat or pulsating umbilical cord).
Still birth	Born died ≥ 24 weeks pregnancy.
Abortion	Born died < 24 weeks pregnancy.
<i>According to gestational age:</i>	
Preterm	Live born < 37 weeks pregnancy.
Full-term	Live born 37-42 weeks pregnancy.
Post-term	Live born > 42 weeks pregnancy.
<i>According to birth weight for gestational age:</i>	
Gestational age	the age of an embryo or fetus (or newborn infant) from the first day of the woman's last menstrual period (LMP).
Appropriate for gestational age (AGA)	Baby weighting <u>between the 10th and 90th</u> percentile for expected for his gestational age.
Small for gestational age (SGA)	Babies weighting <u>below 10th</u> percentile for expected for his gestational age.

Large for gestational age (LGA)	Babies weighting <u>above the 90th</u> percentile for expected for his gestational age.
<i>According to birthweight:</i>	
Low birth weight (LBW)	Babies weighting <u>1500-2500 gm</u> at birth.
Very low birth Weight (VLBW)	Babies weighting <u>1000-1500 gm</u> at birth.
Extremely low birthweight (ELBW)	Babies weighting less <u>than 1000 gm</u> at birth.



Birthweight for gestational age

Neonatal resuscitation

Definition:

Neonatal resuscitation is a procedure applied to neonates who fail to spontaneously establish respiration.

Goals of resuscitation:

1. Minimizing immediate heat loss.
2. Establishing normal respiration and lung expansion
3. Increasing arterial PO₂
4. Supporting adequate cardiac output

Which newborn needs resuscitation?

All newborn babies require some sort of resuscitation, only 10% of them require some assistance to begin breathing after birth and only 1 % requires extensive resuscitative measures to survive.

Physiology of asphyxia-Apnea:

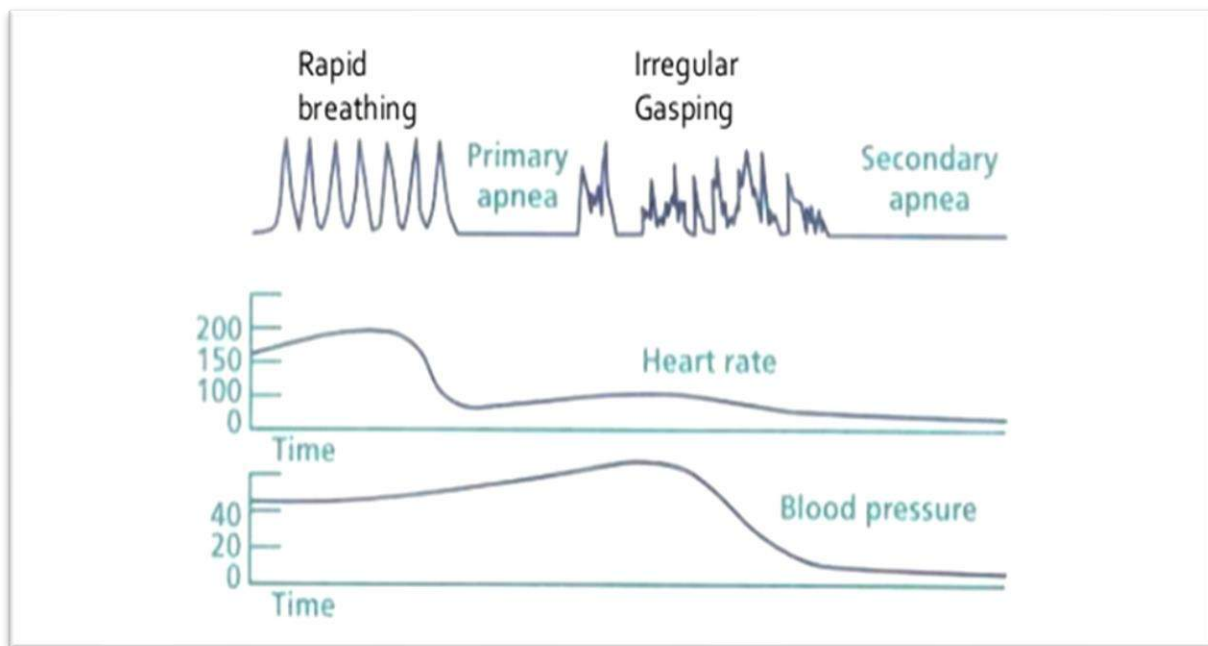
When a fetus or infant is deprived of oxygen (either in utero or following delivery) they undergo a well-defined sequence of events:

I. Primary apnea:

- Initial period of rapid breathing occurs. If the asphyxia continues, the respiratory movements cease, and the infant enters a period of apnea known as primary apnea, during which:
 - The heart rate begins to fall, but blood pressure is maintained.
 - Exposure to oxygen and stimulation in most instances will induce respirations.

II. Secondary apnea:

- If the asphyxia continues the infant develops deep gasping respiration, The respirations become weaker and weaker until the infant takes a last gasp and enters a period of apnea called secondary apnea, during which:
 - The heart rate continues to fall, and the blood pressure begins to fall.
 - The infant now is unresponsive to stimulation, and artificial ventilation with oxygen (positive- pressure ventilation) must be initiated at once.



Apgar Score:

The Apgar score is a practical method for assessing a neonate after birth.

Sign	0	1	2
Heart rate	Absent	Below 100 b/min	Over 100 b/min
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexions of extremities	Active motion
Response to nasal catheter	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, but extremities blue	Completely pink

Interpretation of Apgar score: (done at 1 and 5 minutes)

- **0-3:** Severe hypoxia.
- **4-6:** Mild to moderate hypoxia.
- **7-10:** No hypoxia.

The Apgar score is an objective method to assess the newborn's condition and response to resuscitation. However, resuscitation must be initiated before the 1-minute score is assigned. Therefore, the Apgar score is NOT used to determine the need for resuscitation, what resuscitation steps are necessary, or when to use them.

Before delivery of the baby the resuscitation team should do:

- Antenatal counselling.
- Team briefing.
- Equipment check.

The resuscitation flow diagram (Follows A-B-C-D approach)**Three questions (assessment) must be answered:**

- Term gestation?
- Good muscle tone?
- Crying or breathing?
 - *If the answer to all 3 of these questions is “YES,” the baby does not need resuscitation and should not be separated from the mother and receive routine care:*
 - Covered with dry linen to maintain temperature.
 - The baby should be dried.
 - Clear airway, if necessary
 - Observation of breathing, activity, and color.

- *If the answer to any of these assessment questions is “NO,” the infant should receive one or more of the following steps in sequence (30 sec for each step).*

I. Initial stabilization and evaluation:

- The Golden Minute **(60-second)** mark for completing the initial assessment, initial steps, re-evaluating, and beginning ventilation (if required)

1. Provide warm and maintain normal temperature:

- Radiant warmer.
- Plastic wrap with a cap.
- Thermal mattress.
- Warmed humidified gases.
- Increased room temperature to 26.

2. Positioning: (open airway)

- Supine.
- Put rolled towel under shoulders (neck is some extension (sniffing position) NOT flexed, NOT over extended.

3. Clear airway: (only if necessary)

- Suction of mouth before nose (to avoid aspiration).
- Suction should be limited to 5 seconds at a time.
- Using bulb syringe.

4. Dry thoroughly:

- Dry the baby then remove the wet towel (2 towels).

5. Tactile stimulation: (Flicking or slapping the sole & gentle rubbing the back).

II. Evaluation:

1. Respiratory effort.

2. Heart rate:

- Assessment of heart rate remains critical during the first minute of resuscitation and the use of a 3-lead ECG may be reasonable
- Because providers may not assess heart rate accurately by auscultation or palpation, and pulse oximetry may underestimate heart rate

3. Assessment of oxygen need and administration of oxygen:

- It is recommended that pulse oximetry be used when resuscitation can be anticipated, when PPV is administered, when central cyanosis persists beyond the first 5 to 10 minutes of life, or when supplementary oxygen is administered.
- **Term infants:** start resuscitation with 21% O₂
- **Preterm infants:** should be initiated with low oxygen (21% to 30%) and the oxygen titrated to achieve preductal oxygen saturation using blender.

III. After evaluation:

- If HR is less than 100 bpm, or if newborn is apneic or gasping, begin positive-pressure ventilation (PPV).
- If HR is more than 100 bpm and respirations are laboured, consider CPAP, especially for preterm newborns.

1. Positive pressure ventilation: (using bag-mask or endotracheal intubation)

➤ **Indications:**

- Apnea/gasping.
- Heart rate below 100 bpm, even if breathing.
- Persistent central cyanosis below target saturation, despite free-flow oxygen increased to 100%.

➤ **Technique of PPV:**

*Breathe..... Two..... Three..... Breathe.....Two.....Three
squeeze.....release.....squeeze.....release.....*



- Start at a rate of 40 to 60 breaths per minute.
- Start with oxygen concentration 21%, The oxygen concentration used during resuscitation is guided using a pulse oximeter that measures the baby's oxygen saturation.
- The most important indicator of successful PPV is a rising heart rate.
- 2 separate assessments of the baby's heart rate response to PPV.
- First Heart Rate Assessment: after 15 seconds of PPV.

➤ **Heart rate is increasing:**

- Continue PPV and do second assessment of the heart rate after another 15 seconds.

➤ **Heart rate is not increasing:**

- *Chest IS moving* → Continue PPV that moves the chest→ second assessment of the heart rate after another 15 seconds of PPV.
- *Chest is NOT moving* → Perform the ventilation corrective steps→ second assessment of the heart rate after another 15 seconds of PPV.

➤ **Second Heart Rate Assessment** (After 30 sec of PPV):

- *HR < 60 bpm*: Start chest compression and ETT.
- *2-HR (60:100 bpm) and improving*: Continue PPV and stop chest compressions.
- *3- HR (60:100 bpm) and not improving*: Consider pneumothorax or hypovolemia.
- *4- HR above 100 bpm*: Stop PPV unless baby is apneic.

2. **Chest compression:**

➤ **Indications:**

- HR < 60 bpm, despite 30 sec of effective PPV.

➤ **Site:**

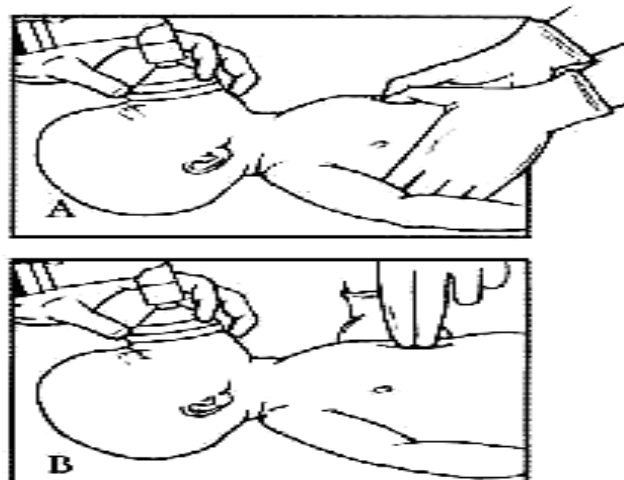
- Lower third of sternum (between xiphoid and a line between the nipples).

➤ **Depth:**

- 1/3 AP diameter of the chest.

➤ **Technique:**

- *2 thumbs technique*: **BETTER**.
- *2 fingers technique*: **ALTERNATIVE**, if there is:
 - Discrepancy - big baby and small rescuer's hands
 - While umbilical vein being inserted.
 - While umbilical line being accessed for drugs



➤ **Rate of chest compression:**

- One cycle: 3 compressions: 1 ventilation.
- One & two & three & breathe and.... in 2 seconds.
- 90:30 = 120 event per minute.

➤ **Intubation is strongly recommended when chest compressions begin to help ensure effective ventilation.**

➤ **Increase FiO₂ to 100% once you begin compressions.**

3. Drugs:

a. Epinephrine:

➤ **Indication:**

When HR is below 60 bpm after 30sec of effective PPV & another 60 sec of coordinated chest compressions and effective ventilation.

➤ **Recommended concentration:**

- 1:10,000 = 0.1mg/ml

➤ **Recommended route:**

- IV (consider endotracheal route ONLY while IV access is obtained)

➤ **Recommended dose:**

- IV: 0.1 to 0.3 ml/kg followed by 1ml saline flush.
- Endotracheal: 0.5 to 1 ml/kg followed by few PPV.
- Recommended rate: As quickly as possible.

➤ **Results:** (check HR after 1 min of IV or longer if endotracheal).

- HR above 60 bpm: stop chest compression & continue PPV.
- HR below 60 bpm: repeat and increase dose every 3:5 minutes.

b. Volume expanders:

➤ **Indication:** (not routine)

- When baby is not responding to resuscitation (HR is below 60 bpm after Epinephrine).

- Baby is in shock (pale, weak pulse, decrease HR).
- History of fetal blood loss (vaginal bleeding, placenta previa).
- **Recommended solutions:** ringer lactate, **Normal Saline** or O negative blood.
- **Recommended route:** IV (umbilical vein).
- **Recommended dose:** 10ml/kg.
- **Recommended rate:** 5:10 min by syringe.

Resuscitation if meconium stained amniotic fluid (MSAF):

- If an infant is born through meconium-stained amniotic fluid and presents non vigorous the infant should be placed under a radiant warmer and PPV should be initiated if needed.
- Definition of **vigorous baby**:
 1. Heart rate > 100
 2. Good respiration.
 3. Good muscle tone.
- Routine intubation for tracheal suction is no longer suggested because there is insufficient evidence to continue this recommendation.
- Appropriate intervention to support ventilation and oxygenation should be initiated as indicated for each individual infant.
- This may include intubation and suction if the airway is obstructed.

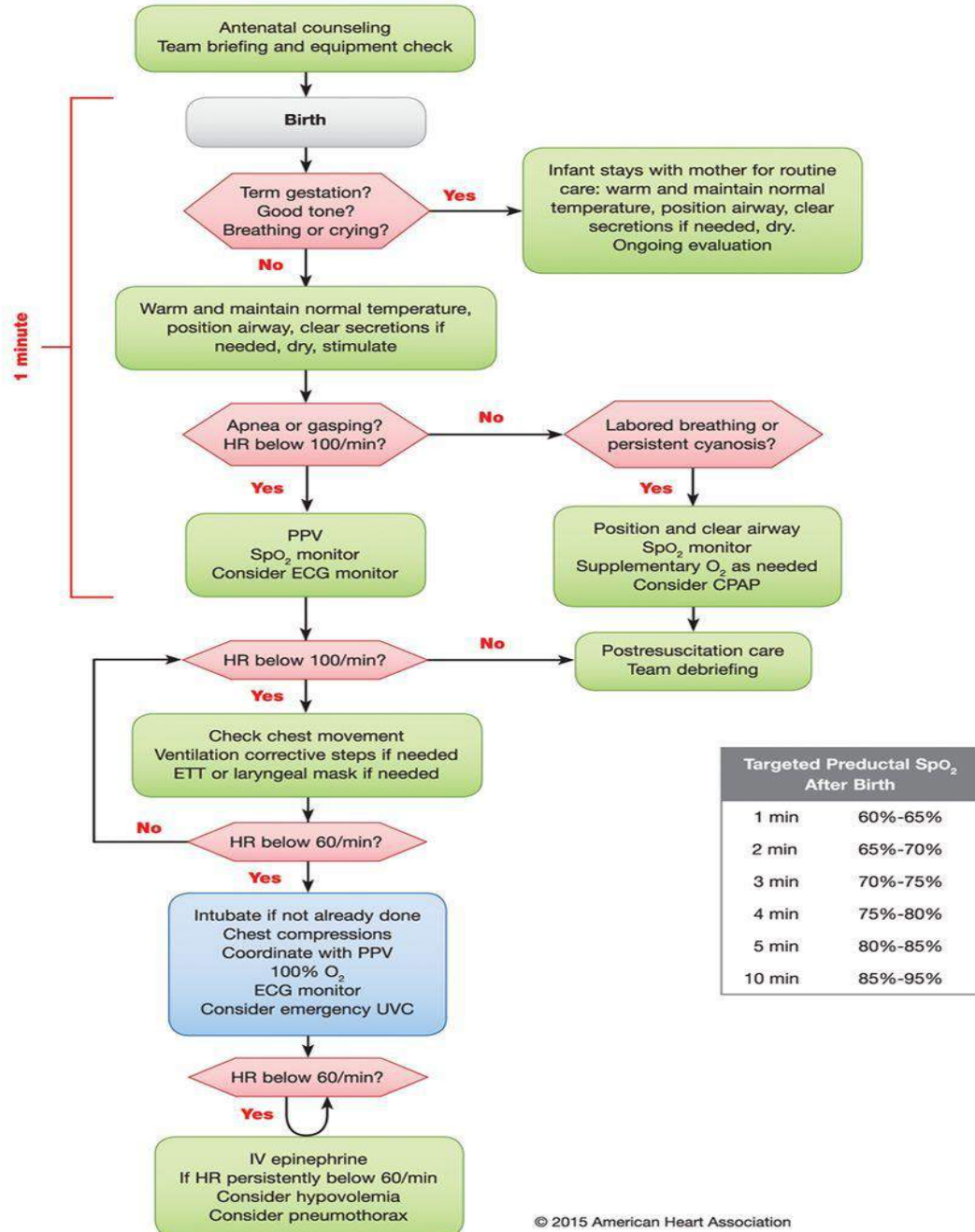
Ethical issues:

- **When you do not resuscitate (DNR)?**
 - Gestational age is < **23** weeks or birth weight is < **400 gm**.
 - Confirmed lethal genetic disorder (**Trisomy 13, 18**) or malformation.
 - **Anencephaly**.

• Discontinuation of resuscitation:

- Asystole after 10 min of complete resuscitation.

Neonatal Resuscitation Algorithm—2015 Update



Resuscitation flow diagram

(Updated according to American Academy of Pediatrics (AAP) guidelines, 2015)

Prematurity

Definition:

A live born infant who is delivered before **37 completed** weeks of gestation calculated from the first day of the last menstrual period.

Etiology

- Idiopathic (unknown): most cases.
- Fetal Factors: e.g., twins, congenital infections.
- Maternal Factors: e.g., infection, malnutrition, systemic illness.
- Obstetric factors: e.g. polyhydramnios, uterine malformations, vaginal bleeding, and premature rupture of membranes (PROM).

Physical characteristics:

I. Anthropometric measurements:

- Birth weight: < 2500 gm.
- Birth length: < 47 cm.
- Birth head circumference: < 33 cm.
- Chest circumference :< 30 cm.
- The head is relatively large to the body size but the neck and extremities are relatively short.

II. Signs of physical immaturity:

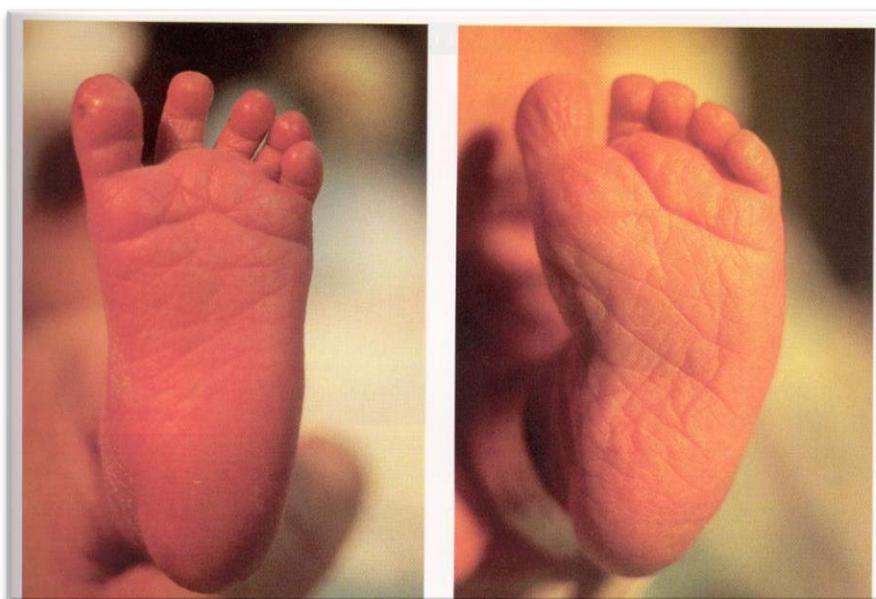
- **Cry:** poor crying with poor suckling.
- **Behavior:** hypoactive and sleeps more.
- **Skin:**
 - Thin, smooth and red skin.
 - Little subcutaneous fat: triangular face and loose skin over limbs.
 - Abundant lanugo hair that may cover the whole body.

- Frequent occurrence of edema hands and feet



Abundant lanugo hair

- **Chest:** *Irregular respiration with periodic spells of apnea(weak respiratory muscles).*
- **Abdomen:** *prominent with thin wall and visible peristalsis.*
- **Breast:** *not palpable nodule, with diminished areola and nipple formation.*
- **Ear:** *soft, easily folded with absent cartilage.*
- **Plantar Surface:** *creases don't exceed anterior 2/3 of the sole.*

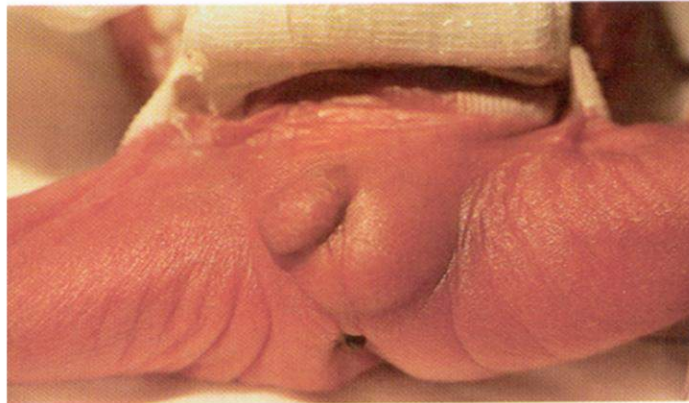


Anterior 2/3 (32 weeks)

Entire foot (36 weeks)

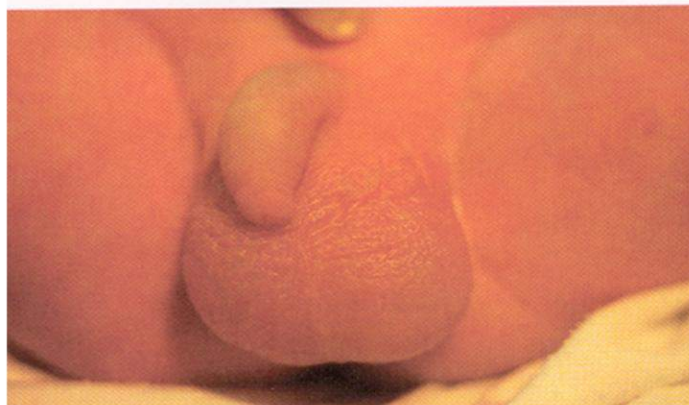
• Genitalia:

- **Male:** light colored, smooth scrotum with absent rugae, and undescended testes.
- **Female:** widely separated labia majora with prominent labia minora and clitoris.



Genitalia

FIGURE 1-44. Male at 28 weeks' gestation: testes high in scrotum



Genitalia

FIGURE 1-45. Male at 32 weeks' gestation: testes descending, some scrotal rugae



III. Signs of neuromuscular immaturity:

- **Posture:** *Limp hypotonic (frog position)*
- **Heel to ear maneuver:** *heels can be brought easily by the side of the ears.*
- **Popliteal angle:** *wide*
- **Arm recoil:** *diminished.*
- **Square window:** *wide.*
- **Scarf sign:** *arms can round easily around the neck, elbow can cross midline.*



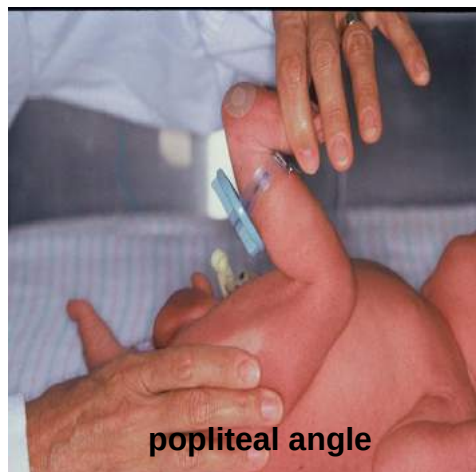
Square window



Scarf sign



Heel to ear maneuver



popliteal angle

Modified New Ballard score: used for estimation of gestational age.

Physical Maturity

	-1	0	1	2	3	4	5																												
Skin	sticky friable transparent	gelatinous red, translucent	smooth pink, visible veins	superficial peeling &/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled																												
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald	Maturity Rating <table><tr><th>Score</th><th>weeks</th></tr><tr><td>-10</td><td>20</td></tr><tr><td>-5</td><td>22</td></tr><tr><td>0</td><td>24</td></tr><tr><td>5</td><td>26</td></tr><tr><td>10</td><td>28</td></tr><tr><td>15</td><td>30</td></tr><tr><td>20</td><td>32</td></tr><tr><td>25</td><td>34</td></tr><tr><td>30</td><td>36</td></tr><tr><td>35</td><td>38</td></tr><tr><td>40</td><td>40</td></tr><tr><td>45</td><td>42</td></tr><tr><td>50</td><td>44</td></tr></table>	Score	weeks	-10	20	-5	22	0	24	5	26	10	28	15	30	20	32	25	34	30	36	35	38	40	40	45	42	50	44
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Plantar Surface	heel-toe 40-50 mm: -1 < 40 mm: -2	>50mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole																													
Breast	imperceptible	barely perceptible	flat areola no bud	stippled areola 1-2mm bud	raised areola 3-4mm bud	full areola 5-10mm bud																													
Eye/Ear	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. Curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff																													
Genitals male	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae																													
Genitals female	clitoris prominent labia flat	prominent clitoris small labia minora	prominent clitoris enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora																													

Neuromuscular Maturity

	-1	0	1	2	3	4	5
Posture							
Square Window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm Recoil		180°	140°-180°	110°-140°	90°-110°	<90°	
Popliteal Angle	180°	160°	140°	120°	100°	90°	<90°
Scarf Sign							
Heel to Ear							

Complications of prematurity:

I. Respiratory:

- **Respiratory distress syndrome (RDS)**: due to surfactant deficiency.
- **Apnea of prematurity**: due to immaturity of respiratory center.

II. Cardiovascular:

- **Patent ductus arteriosus (PDA)**: that may result in heart failure.
- **Hypotension and bradycardia**: due to hypovolaemia or cardiac dysfunction.

III. Hematological:

- **Bleeding tendency**: due to increased vascular fragility with diminished coagulation factors.
- **Anemia of prematurity**: due to iron and folic acid deficiency.

IV. Neurologic:

- Intracranial hemorrhage.
- Hypoxia-ischemic encephalopathy.

V. Gastrointestinal:

- Necrotizing enterocolitis (NEC).
- Poor suckling, swallowing, digestion and absorption.
- Decreased stores of vitamins and minerals.

VI. Renal:

- More prone to dehydration and acidosis: due to decreased capacity to concentrate urine.

VII. Metabolic:

- More prone to hypocalcaemia and hypoglycemia.

VIII. Hypothermia: due to

- Large surface area: that leads to excess heat loss.
- Low subcutaneous fat.
- Immature heat regulating centre.

IX. Immunologic:

- **More prone to infection:** due to deficiencies in both humoral and cellular immune response.

Long-term problems of prematurity:**I. Developmental disability:**

- Major handicaps (cerebral palsy, mental retardation)
- Sensory Impairments (hearing loss, visual impairment)
- Minimal cerebral dysfunction (language disorders, learning disability, hyperactivity, attention deficits, behavior disorders)

II. Retinopathy of prematurity (ROP).**III. Chronic lung disease:** bronchopulmonary dysplasia (BPD).**IV. Poor growth.****V. Increased risk of congenital anomalies.****VI. Increased risk of child abuse and neglect.****VII. Increased risk of post-neonatal illness and rehospitalization.****Management of the premature infant:****I. Immediate postnatal management:**

- Resuscitation and stabilization: Adequate oxygen delivery and maintenance of proper temperature control are important.

II. Neonatal management

- **Thermal regulation:** this requires either an overhead radiant warmer or a closed incubator.
- **Oxygen therapy** and assisted ventilation.
- **Fluid and electrolyte therapy:** to compensate for potentially high insensible water loss.
- **Nutrition:** may require gavage feeding or parenteral which may be due to poor sucking and swallowing and feeding intolerance.
- **Infection:** Broad spectrum antibiotics should be begun when suspicion of infection is strong.
- **Immunization:** Routine immunization should be given on the regular schedule at standard doses.

Birth Injuries

I. Neurological Birth Injuries:

1. Cranial Injuries:

➤ **Extracranial injuries:**

- Caput succedaneum.
- Cephalhematoma.
- Fracture skull.
- Subconjunctival hemorrhage.
- Abrasion, ecchymosis.

➤ **Intracranial injuries:** Intracranial hemorrhage.

2. Spine and Spinal Cord Injuries:

- **Vertebrae:** fractures and dislocations.
- **Spinal cord:** Hemorrhage, edema and transection.

3. Peripheral Nerve Injuries:

- Facial nerve palsy.
- Brachial birth palsy.
- Phrenic nerve palsy.

II. Non-Neurological Birth Injuries:

1. Visceral injuries:

- Rupture liver with subcapsular hematoma
- Rupture spleen with subcapsular hematoma
- Adrenal hemorrhage

2. Sternocleidomastoid injury:

- Sternomastoid hematoma (tumor).

3. Bone injuries:

- Clavicle fracture
- Extremities: Fractures, dislocation.

▪ **Caput succedaneum and cephalhematoma:**

	Caput Succedaneum	Cephalhematoma
Site	- Subcutaneous extraperiosteal edema. - Over presenting part.	- Sub-periosteal blood collection. - Any bone (commonly parietal bone)
Extent	- Diffuse (cross suture line)	- Localized (doesn't cross suture line)
Consistency	- Soft	- Firm
Association	- Ecchymosis of skin	- Anemia, jaundice and skull fracture
Onset	- At birth	- Few hours after birth
Fate	- Resolve spontaneously within few days	- Resolve spontaneously within 2:3 weeks. - Infection or calcification rarely occur.
Treatment	- NO	- Observation. - Treat: - Anemia (blood transfusion). - Jaundice (phototherapy). - Infection (antibiotic). - No aspiration: due risk of infection (except if infection occurs)



▪ ***Intracranial Hemorrhage(ICH):***

➤ **Causes:**

- Birth trauma e.g., forceps.
- Birth asphyxia.
- Congenital vascular anomalies.
- Bleeding disorders.
- Spontaneous: especially in preterm.

➤ **Types:**

- Extradural.
- Subdural.
- Subarachnoid.
- Intracerebral.
- Intraventricular.

➤ **Clinical Presentation:**

- **Onset:** may present at birth or later on.
- Asymptomatic.

- **symptoms:**

- Lethargy.
- Poor feeding and suckling.
- Diminished or absent Moro reflex.
- Bulging anterior fontanelle.
- Pallor
- Irritability and seizures.
- Irregular respiration with frequent episodes of apnea and cyanosis.
- Ocular palsy and other cranial nerve affections.

➤ **Diagnosis:**

I. History of traumatic delivery.

II. Clinical manifestations.

III. Investigations:

- a. Cranial ultrasonography.
- b. CT scan or MRI.
- c. Lumber puncture:
 - Exclude CNS infection.
 - Diagnose subarachnoid hemorrhage (hemorrhagic CSF).

➤ **Management:**

I. Supportive treatment:

- Incubator care.
- Minimal handling of the baby.
- Oxygen supply.
- Vitamin K: 1-5 mg I.M help arrest of bleeding.

II. Symptomatic treatment:

- Convulsion: Phenobarbital (3:8mg/kg/Day).
- Anemia: Fresh blood transfusion (10 ml/kg).

III. Surgical treatment:

- Subdural hemorrhage.
- Post-hemorrhagic hydrocephalus:
 - Serial lumbar Punctures.
 - Shunt operation.

▪ Brachial Palsy:**➤ Etiology:**

- Traction on the head in cephalic presentation.
- Traction on the shoulders in breach presentation.

**Erb's Palsy****Klumpke's Paralysis**

	Erb's palsy	Klumpke's palsy
Incidence	- Common	- Rare
Injury	- C5,C6	- C7,C8, T1
Deformity	- Adduction at the shoulder. - Internal rotation of the upper arm. - Pronation of the forearm. - Outward direction of the palm of the hand. (waiter's tip posture)	- Paralysis of all intrinsic muscles of the hand. (Claw hands)
Reflexes	- Moro reflex: absent - Grasp reflex: present	- Moro reflex: present - Grasp reflex: absent
Association	- Impaired sensation on the outer side of the arm. - Phrenic nerve palsy (C3,C4,C5)	- Horner syndrome: injury to sympathetic fibers of T1. - (Ptosis, miosis, anhidrosis, enophthalmos)
Prognosis	- Favorable	- Less favorable
Treatment	- Relaxation of the paralyzed muscles in opposite position: ○ Abduction at the shoulder. ○ External rotation of arm ○ Supination of the forearm. (Holding of the wrist to the head of the bed) - Physiotherapy after 2 weeks. - Neuroplasty (nerve graft) - If no response after 3:6 months	- Relaxation of the paralyzed muscles in opposite position: (Holding pad of cotton in the fist) - Physiotherapy. - Neuroplasty.

- **Injury of the visceral organs:**

- 1. **The Liver or spleen:**

- **Clinically:**

- a. The infant usually appears normal for the first 1-3 days.
 - b. Manifestations of blood loss: severe pallor up to shock (if ruptured capsule into peritoneal cavity).
 - c. Abdominal distension.

- **Diagnosis:** abdominal ultrasonography is diagnostic.

- **Treatment:**

- a. Blood transfusion in marked anemia or shock.
 - b. Surgical repair may be required.

- 2. **The Adrenal Gland:**

- **Clinically:**

- a. Pallor Profound shock
 - b. Flank mass, 90% are unilateral, mainly on right side.
 - c. Adrenal insufficiency (vomiting, shock)

- **Diagnosis:** abdominal ultrasonography is diagnostic.

- **Treatment:**

- a. Blood transfusion in marked anemia or shock.
 - b. Treatment of acute adrenal failure (fluid, steroid).

Neonatal Respiratory Distress

The normal newborn breathes **40-60** breath /minute.

Clinical signs of respiratory distress:

- Grade I: tachypnea.
- Grade II: retractions.
- Grade III: grunting.
- Grade IV: central cyanosis.

Respiratory Distress Scoring System (Downes' score)

Score	0	1	
Respiratory rate	60	60: 80	80 or apnea
Retractions	None	Mild	Severe
Grunting	None	Audible with stethoscope	Audible without Stethoscope
Cyanosis	None	Cyanosis in room air	Cyanosis in 40% O ₂
Air entry	Clear	Delayed or decreased	Barely audible

➤ Interpretation of downes' score:

- **4** = Clinical respiratory distress; monitor clinically and with arterial blood gases.
- **8** = Impending respiratory failure; is an indication for ventilatory support.

Causes neonatal respiratory distress:

I. Pulmonary causes:

1. Airway:

- **Nasal:** choanal atresia.
- **Oral:** Hypoplasia of the mandible, Macroglossia.
- **Laryngeal:** Laryngomalacia, laryngeal stenosis and cord paralysis.
- **Tracheal:** tracheomalacia, tracheal stenosis, tracheo- oesophageal fistula.
- **Bronchial:** bronchial stenosis.

2. Lung:

- Respiratory distress syndrome (**RDS**).
- Transient Tachypnea of the newborn (**TTN**).
- Meconium aspiration syndrome (**MAS**).
- Neonatal pneumonia.
- Lung collapse, cyst, congenital lobar emphysema.
- Broncho-pulmonary dysplasia (**BPD**).

3. Pleura:

- Pneumothorax.
- Pleural effusion.

II. Extra-pulmonary causes:

1. Cardiac causes:

- PDA (patent ductus arteriosus).
- PFC (Persistent fetal circulation).
- Heart failure.

2. Hematological causes:

- Severe anaemia.
- Polycythaemia.

3. Metabolic:

- Hypoglycemia.
- Hypothermia.
- Metabolic acidosis.

4. Cerebral causes:

- Intracranial Hemorrhage (**ICH**).
- Hypoxic-ischemic encephalopathy (**HIE**).
- Meningitis, *Manifested by:*
 - Shallow, irregular respiration, apnea and cyanosis.
 - Bulging anterior fontanelle, disturbed consciousness, and seizures.

Respiratory Distress Syndrome (RDS)

Hyaline Membrane Disease

Definition:

Syndrome of respiratory distress occurs almost always in **preterm** infants due to lung **surfactant deficiency**.

Incidence:

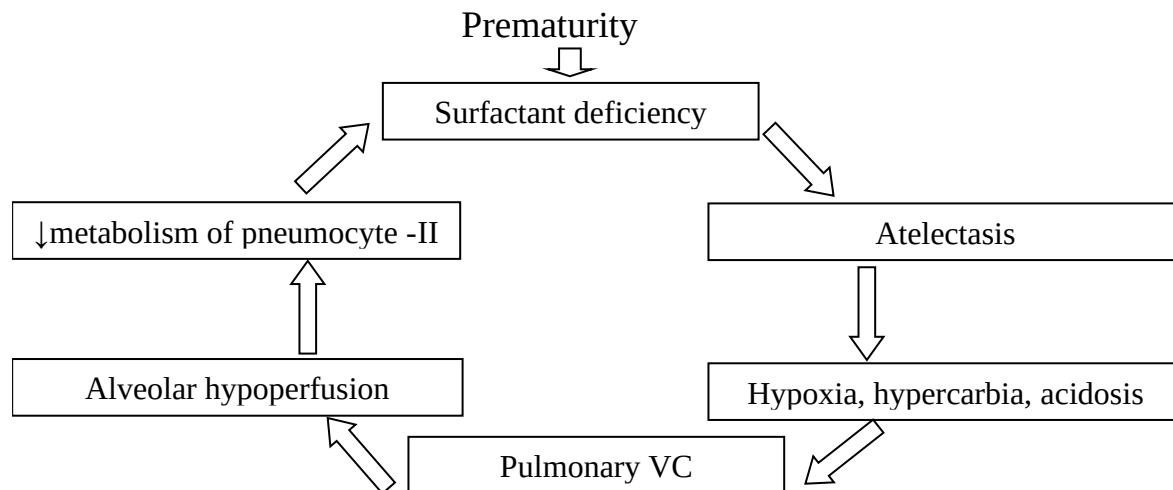
- Incidence and severity of RDS are related inversely to the gestational age.
- Commonest cause of neonatal death.

Lung surfactant:

- **Produced by:** type II pneumocytes start at 20 weeks and become mature at 35 weeks of gestation.
- **Composition:** mixture of phospholipids and surfactant proteins.
- **Function:** It lower the surface tension of the fluid lining alveoli leading to:
 - During inspiration: facilitate good expansion of alveoli.
 - At the end of expiration: prevent collapse of alveoli.

Pathophysiology:

- **Surfactant deficiency** → *increased surface tension of fluid lining alveoli (diminished lung compliance) → diffuse alveolar atelectasis → increase work of breathing and impaired gas exchange → hypoxia, hypercarbia and acidosis.*
- **Hypoxia** → *pulmonary vessels vasoconstriction → alveolar hypoperfusion → decreased metabolism of type II pneumocyte → more surfactant deficiency.*



Risk factors:

Increased risk of RDS	Decreased risk of RDS
• Prematurity: (most important). • IDM. • Cesarean section. • Perinatal asphyxia. • Others: - Second twin. - Male sex. - RDS in sibling.	• Use of antenatal steroid. • Maternal hypertension. • Premature rupture of membrane. • Maternal narcotic addiction.

Clinical manifestations:

- **Onset:** shortly after birth or within few hours after birth (2:6 hours).
- **Signs of respiratory distress:**
 - **Grade I:** tachypnea and working alae nasi
 - **Grade II:** retractions (intercostal and subcostal)

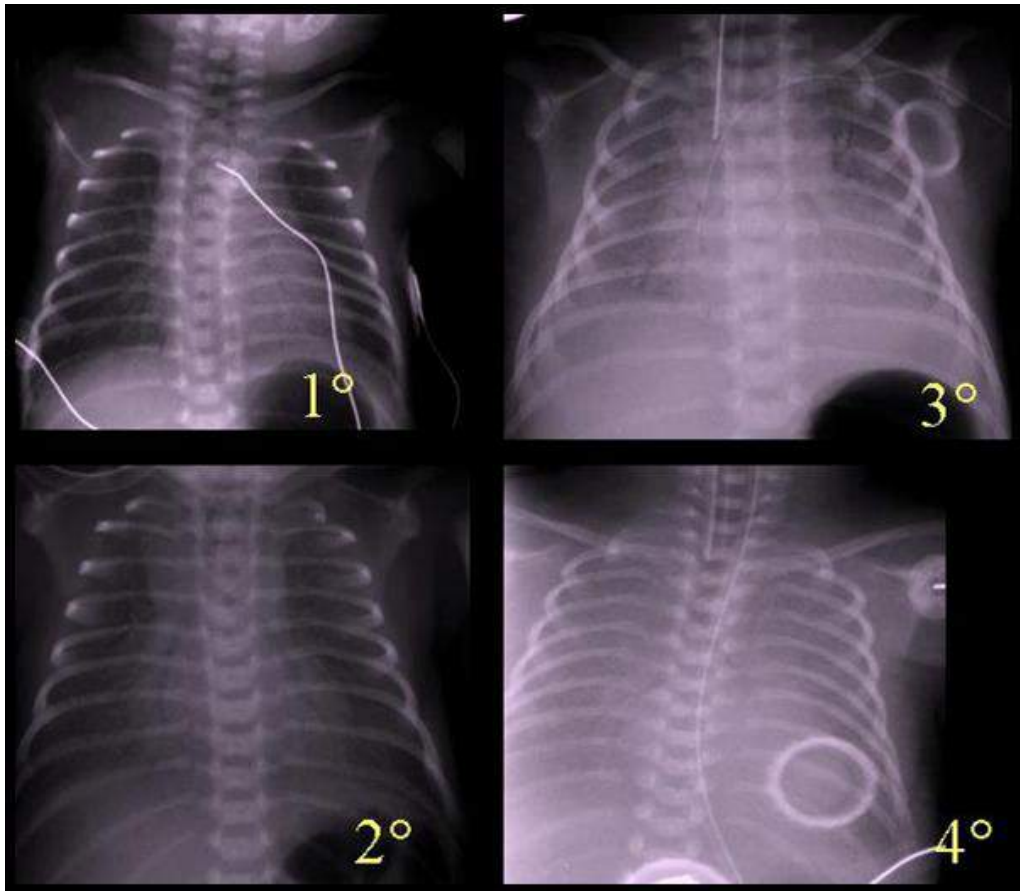
- **Grade III:** grunting.
- **Grade IV:** central cyanosis.
- **Course:** progressive course
 - **Mild:** gradual improvement after 3 days (reappearance of surfactant).
 - **Severe:** complications or death.

Investigations:

I. Chest X-ray:

- **Stage 1:** *fine reticulogranular mottling*
- **Stage 2:** *ground glass appearance, air bronchogram, decreased lung volume*
- **Stage 3:** *diffuse opacity, but can be differentiated from borders of diaphragm and heart.*

- **Stage 4:** *White lung cannot be differentiated from borders of diaphragm and heart.*



II. **Blood gases:** respiratory and metabolic acidosis with hypoxia.

III. **Echocardiography:** to exclude PDA.

IV. **Sepsis workup:** to exclude sepsis.

Prevention:

- Avoid risk factors e.g., prematurity.
- Antenatal steroid therapy:
 - **Indications:** pregnant women < 34 weeks who are at risk for preterm delivery.
 - **Mechanism:** steroid enhances surfactant production.
 - **Dose:** betamethasone 12 mg /IM, two doses 24 hours apart.

Treatment:

I. Supportive treatment:



- **Incubator care.**
- **Support circulation:** IV. Fluids, plasma, dopamine.
- **Support nutrition:** oral or parenteral feeding.
- **Antibiotic administration:** Start antibiotics after obtaining blood cultures; discontinue antibiotics after 3-5 days if blood cultures are negative. (Because it is difficult to differentiate from neonatal sepsis)
- **Respiratory support:** oxygen therapy by
 - *Incubator oxygen.*
 - *Head box.*
 - *Nasal cannula.*
 - *Continuous positive airway pressure (CPAP):* It keeps the alveoli open at the end of expiration.
 - *Mechanical ventilation:*

Indications of mechanical ventilation:

- $PO_2 < 50$ mm, $PCO_2 > 60$ mmHg, < 7.20 , despite using 100% oxygen
- Frequent apnea.
- Marked retractions.

- Cyanosis.

II. Specific treatment (surfactant therapy):

- **4 ml/kg/dose** via endotracheal tube.
- **Side effects**: apnea, bradycardia, and pneumothorax



Complications:

I. Acute:

1. **Air leak syndromes** (pneumothorax, pneumomediastinum,...).



2. **Infections.**
3. **Intracranial hemorrhage.**

4. **PDA** with increasing left-to-right shunt may complicate the course of RDS.
5. **Heart failure.**
6. **Pulmonary hemorrhage:** especially following surfactant therapy.

II. Chronic

1. **Bronchopulmonary dysplasia (BPD).**
2. **Retinopathy of prematurity (ROP).**
3. **Neurologic impairment.**
4. **Familial psychopathology**

Transient Tachypnea Of The Newborn (TTN)

Definition:

Self-limited respiratory distress that affects mainly full-term infants.

Etiology:

Delayed clearance of fetal lung fluid.

Risk factors:

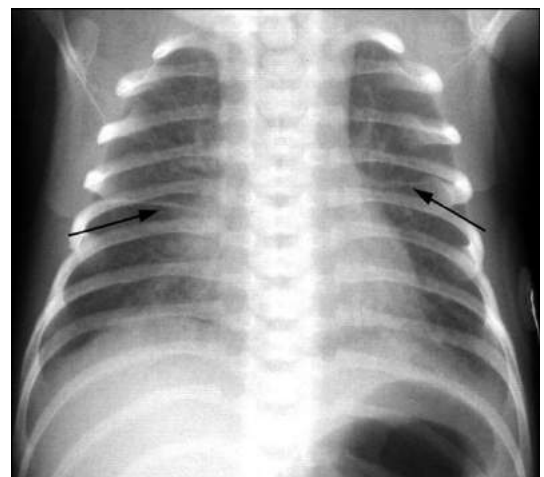
- Caesarian section.
- Maternal diabetes.
- Perinatal asphyxia.
- Excess maternal analgesia.

Clinical manifestations: (diagnosis by exclusion or retrograde)

- **Onset:** usually within few hours after birth.
- **Respiratory distress** mainly tachypnea may exceed 100 cycle/min, retraction, grunting are variable, but cyanosis in extreme cases is rare.
- **Resolves** over 2:3 days.

Chest x-ray:

- Increased bronchovascular markings.
- Hyperinflation of the lung.
- Fluid in fissure and costophrenic angle.



Treatment:

- Incubator care.
- Respiratory support (oxygen therapy).

Meconium Aspiration Syndrome (MAS)

Definition:

Disease causing respiratory distress that affects mainly post-term infants or infant exposed to intrauterine hypoxia.

Mechanism:

Intrauterine hypoxia → relaxation of anal sphincter → passage of meconium → meconium-stained amniotic fluid → if meconium is aspirated in lung:

- Complete airway obstruction → atelectasis.
- Partial airway obstruction → air trapping → pneumothorax.
- Chemical pneumonitis and secondary bacterial infection.

Clinical manifestations:

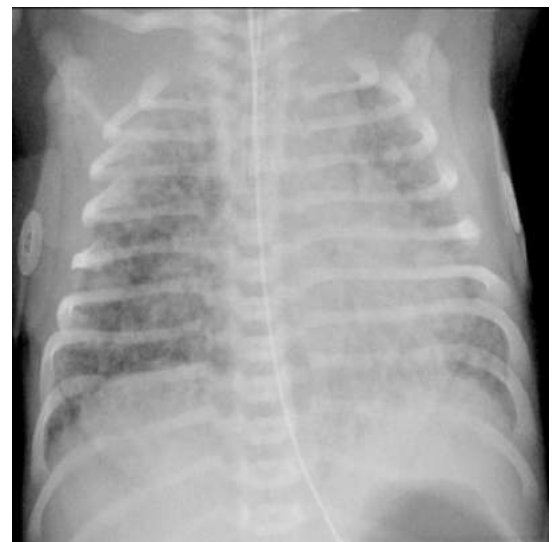
- History of post-term delivery or intrauterine hypoxia.
- Meconium stained amniotic fluid.
- Meconium stained skin, umbilical cord and nails.
- Variable grades of respiratory distress, grunting and cyanosis is common.

Chest x-ray:

- Patchy coarse infiltrates.
- Hyperinflation of the lung.
- Pneumothorax or atelectasis may be seen.

Treatment:

- Incubator care.
- Respiratory support (oxygen therapy).



Congenital Diaphragmatic Hernia (CDH)

Definition:

Defect in the diaphragm between the peritoneum and pleura, allowing intestine to herniate in the pleural space.

Clinical manifestations:

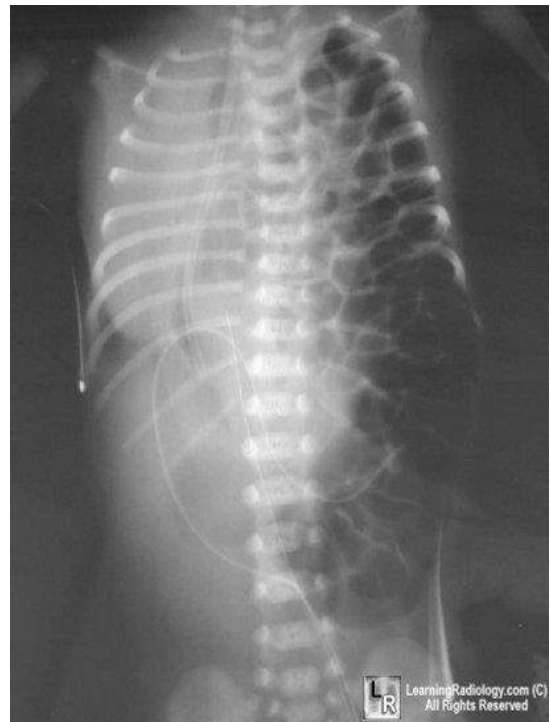
- Significant respiratory distress after birth.
- Scaphoid abdomen.
- Decreased air entry on one side of the chest.
- Intestinal sounds may be heard on the chest.

Diagnosis:

- **Antenatal ultrasound.**
- **Chest X ray:**
 - Bowel gas pattern in one hemithorax.
 - Mediastinal shift.
 - Compression of contralateral lung.

Treatment:

- Surgical repair.



Esophageal Atresia

Definition:

The esophagus ends blindly, and in 85% of cases the distal esophagus communicates with trachea by fistula (distal tracheoesophageal fistula).

Clinical manifestations:

- Polyhydramnios.
- Respiratory distress after birth.
- Excessive frothy secretions.
- Coughing, choking and cyanosis.
- Chest is full of secretions.

Diagnosis:

- **Failure to pass Ryle in esophagus with resistance.**
- **Chest X ray:**
 - Ryle coil in the upper esophagus.
 - Pulmonary infiltrates.
 - Gas in GIT means presence of fistula

Treatment:

- Surgical repair



Neonatal Hyperbilirubinemia

Definition:

- Yellowish discoloration of skin, mucous membrane and sclera due to increased serum bilirubin.
- Jaundice appears clinically when serum bilirubin $>5\text{mg/dl}$ in newborn, while $>2\text{mg/dl}$ in older children and adults.
- It occurs in about 60% of full-term and 80% of preterm during the first week of life.

Bilirubin metabolism:

- **Production:**

Bilirubin is produced by:

- Hemolysis of old RBCs in reticuloendothelial system(mainly).
- Other sources of heme (myoglobin and cytochromes)

- **Transport:**

- Bilirubin is bound to serum albumin and called unconjugated (indirect) bilirubin.

- **Uptake:**

- Bilirubin is bound to ligandins Z and Y proteins for transport to the endoplasmic reticulum for conjugation.

- **Conjugation:**

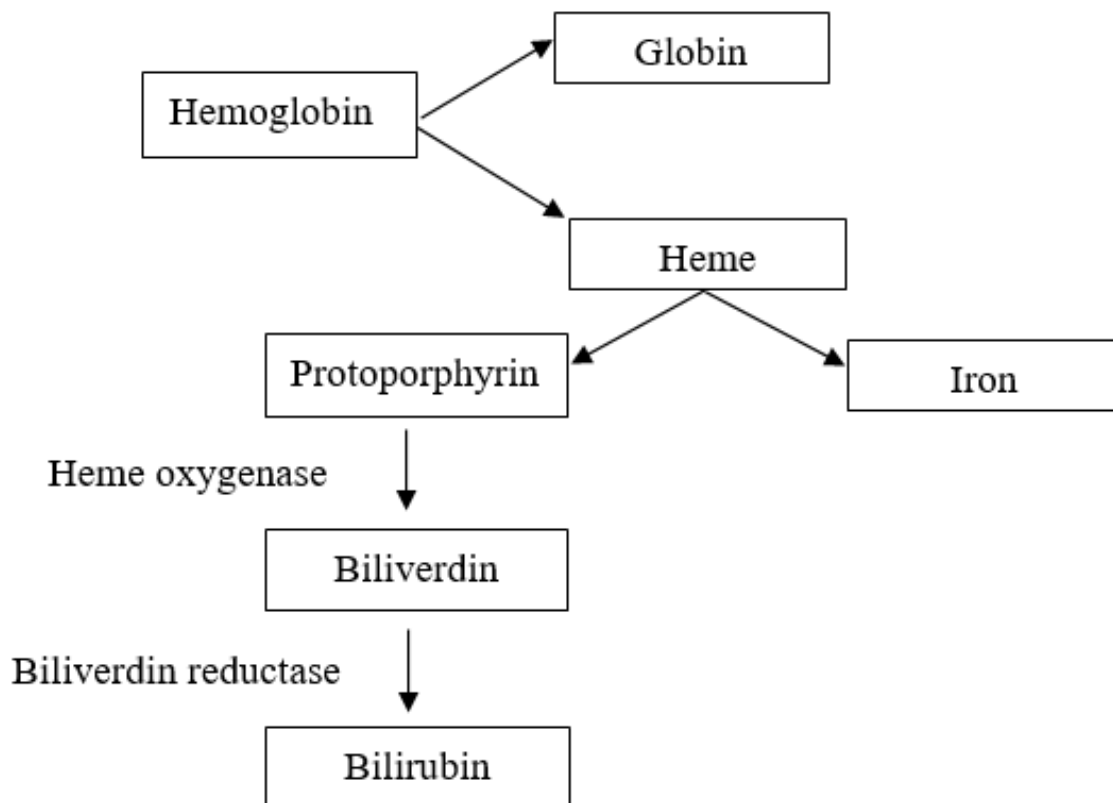
- It is conjugated by glucuronyl transferase enzyme with glucuronic acid to form conjugated (direct) bilirubin.
- Conjugated bilirubin is water soluble and can be excreted in kidney to urine.

- **Excretion:**

- Conjugated bilirubin is excreted in the bile into the intestine.

- **In intestine:**

- Some is deconjugated by glucuronidase enzyme in the intestine into unconjugated bilirubin which will be reabsorbed to:
 - Liver (entero-hepatic circulation).
 - Kidney (urobilinogen) and excreted in urine.
- Some is converted by intestinal bacteria in the intestine into stercobilinogen (colorless) which will be oxidized inside as well as outside the intestine giving rise to stercobilin (brown in color) and excreted in the feces.



Hyperbilirubinemia either:

- Unconjugated hyperbilirubinemia (Physiological or pathological).
- Conjugated hyperbilirubinemia.

I. Unconjugated hyperbilirubinemia:

1. Physiological jaundice:

It is the most common cause of jaundice in neonates.

- **Mechanisms:**

- *Bilirubin production:*

Increased due to:

- Large RBCs volume.
- Short life span of RBCs.
- Increased entero-hepatic circulation.

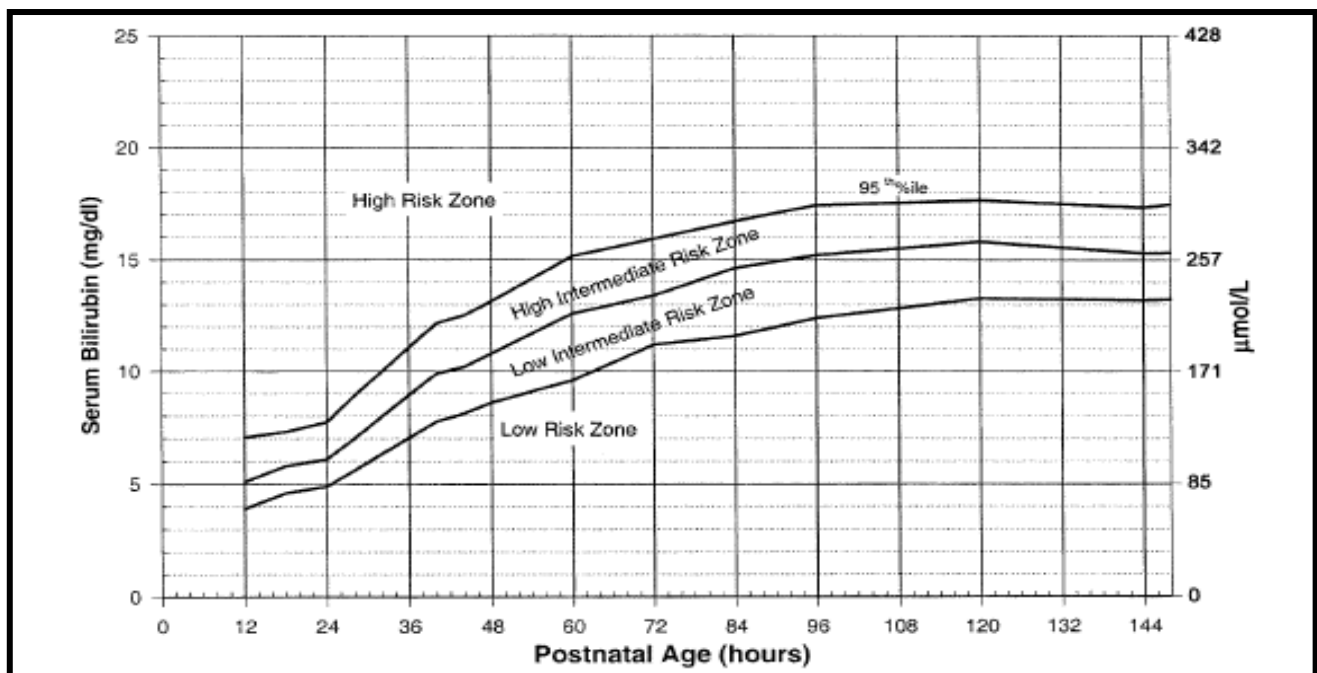
- *Uptake of bilirubin by the liver:* Defective.

- *Conjugation:* Defective.

- *Excretion into bile:* Defective.

- **Exclusion criteria for physiologic jaundice:**

- Total serum bilirubin level > **95th** percentile for age in hours based on nomogram for hour- specific serum bilirubin concentration.
- Bilirubin level increasing at a rate >5 mg/dl/day, or >**0.2**mg/dl/h.
- Jaundice in the **first 24 hours** of life.
- Conjugated bilirubin >**2** mg/dl or > **20%** of the TSB.
- Clinical jaundice persisting > **2** weeks in full-term.



2. Pathological jaundice:

a. *Common causes:*

- Hemolytic anemia (Rh and ABO incompatibility).
- Breast milk jaundice.
- Neonatal infection (congenital or acquired)
- Increased RBCs content (polycythaemia, cephalhematoma, twin-twin transfusion)

b. *B-Rare causes:*

- Congenital haemolytic anaemia: G6PD deficiency, hereditary spherocytosis.
- Endocrine disorders: Maternal diabetes, hypothyroidism.
- Other disorders: Down syndrome.
- Glucuronyl transferase defect:
 - *Congenital:* Grigler-Najjar syndrome (type I, II), Gilbert syndrome.
 - *Acquired:* Lucey-Driscoll syndrome.
- Metabolic disorders: Galactosemia.

- Increased entero-hepatic circulation: ileus, intestinal obstruction.
- Drugs: Aspirin, sulphonamides, and furosemide.

a. Rh incompatibility:

- **Pathogenesis:**

- If Rh-ve mother get pregnant to an Rh +ve fetus.
- Leakage of fetal RBCs across the placenta into the maternal circulation.
- Sensitization and formation of IgG antibodies against fetal antigens.
- Antibodies can cross the placenta and induce destruction of fetal RBCs.
- First baby is not affected unless the mother was previously sensitized from previous mismatched blood transfusion or abortion or amniocentesis.

- **Clinical manifestations:** according to degree of haemolysis; Ranging from mild jaundice and anemia to hydrops fetalis in severe form.

- **Prevention: (*Anti-D gammaglobulin*)**

- Given to Rh negative pregnant mother within 3 days after delivery.
- The standard dose of 300 µg I.M.

b. ABO incompatibility:

- If mother group is O and baby group is A or B.
- Antigens present on the surface of RBCs react with antibodies in the plasma causing hemolysis.
- First baby is affected.

c. Jaundice associated Breast milk:

	Breast feeding(failure)jaundice	Breast milk jaundice
Incidence	13%	2:4%
Onset	First 3:4 days after birth	After 1 week
Etiology	• ↓ milk intake(starvation) • Glucose intake (↓caloric intake) • Stool stasis & ↑ entero-hepatic circulation	Unknown may be: • Pregnanediol in breast milk. • ↑ Fatty acids in breast milk. • Glucuronidase in breast milk → ↑ entero-hepatic circulation
Bilirubin level	< 12 mg/dl	May reach 10:30 mg/dl
Treatment	Frequent breast feeding	Interruption or cessation of breast milk for 24:48 hours

• Investigations:

- Total and direct bilirubin.
- Maternal & infant blood group & Rh.
- Complete blood picture and reticulocytic count.
- Direct Coomb's test.
- Of the cause: Sepsis work up, G6PD screening, liver function test, thyroid function test.

- **Management of unconjugated hyperbilirubinemia:**

- I. **Phototherapy:**

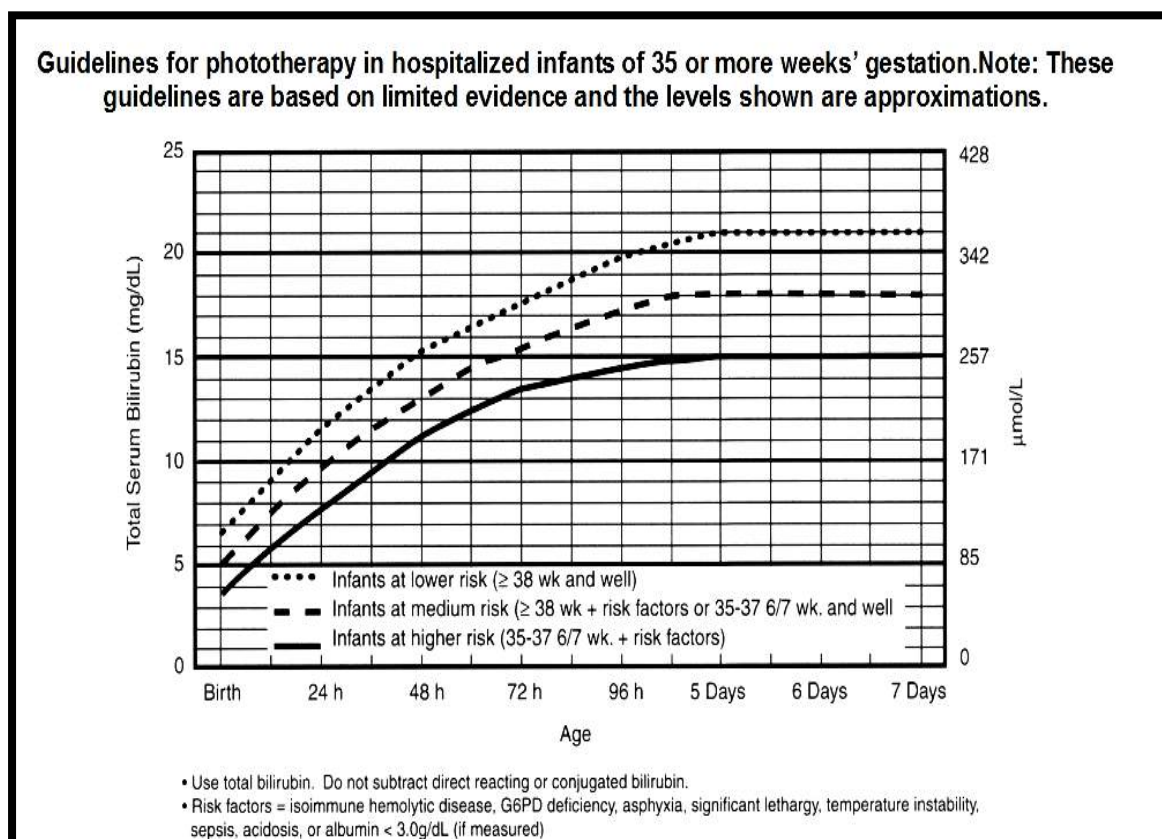
- **Mechanism:**

Exposure to the light with wavelength ranging from **425:475 nm** will convert **insoluble** unconjugated bilirubin to non-toxic **soluble** isomers by:

- *Photo-configuration.*
- *Photo-structural isomerization:* forming lumirubin.
- *Photo-oxidation:* more slowly.
- These products can be excreted in bile and urine.

- **Indications:**

When exceed the level for phototherapy on the **phototherapy chart**.



➤ **Technique:**

- The infant should be naked except for genitalia and the eyes.
- Distance between the infant's skin and the light source no greater than 50 cm.
- Continuous exposure and interrupted only by feeding.
- Change position of baby every 2 hours, check temperature every 4:6 hours, and the weight daily.
- Skin colour is not a guide to hyperbilirubinemia in infants under phototherapy.



➤ **Side effects:**

1. **Dehydration:** due to insensible water loss.
2. **Diarrhoea.** (Due to increased bile and indirect bilirubin in bowel)
3. **Hyperthermia.**
4. **Genital and retinal damage.**
5. **Skin rash and photosensitivity.**
6. **Bronzed-baby syndrome:** due to exposure to **conjugated** bilirubin to phototherapy.
7. **Loss of maternal infant bond.**
8. **Rebound hyperbilirubinemia.**
9. **Hypocalcaemia:** may occur especially in preterm, due to decreased secretion of parathyroid hormone

II. Exchange transfusion:

➤ Mechanism:

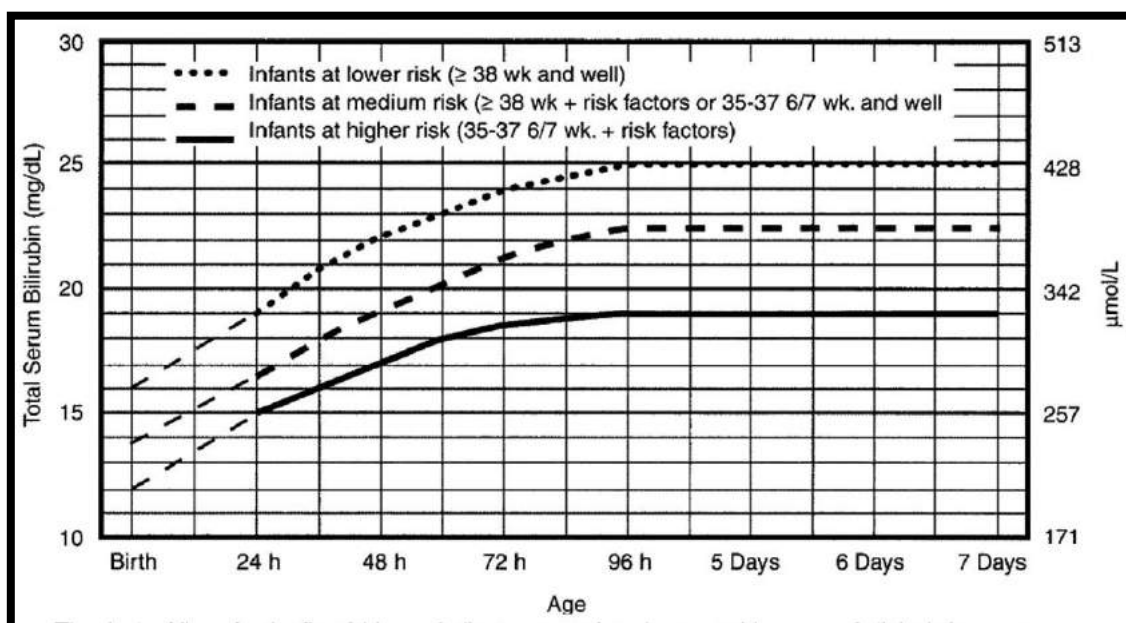
- Remove excess bilirubin.
- Remove antibodies from circulation.
- Correct the anaemia.

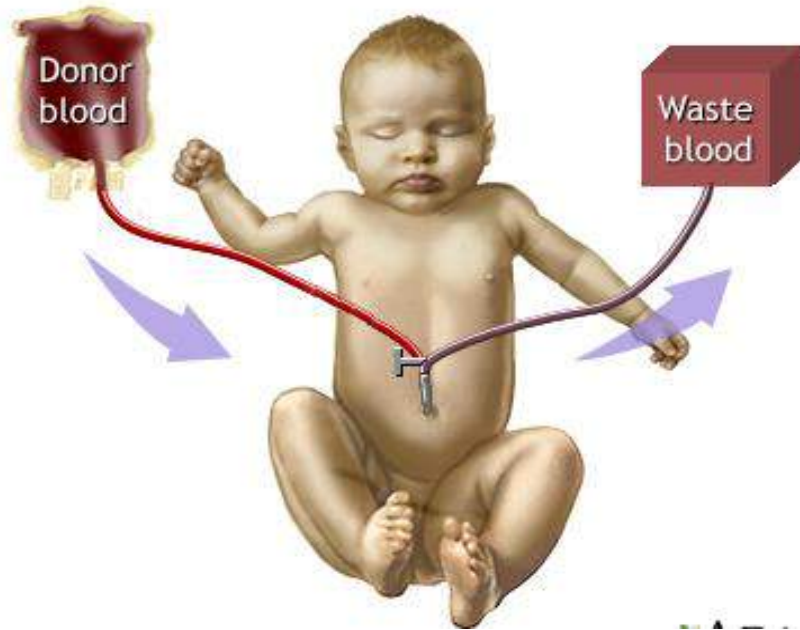
➤ Indications:

1. Failure of phototherapy to prevent rise in bilirubin to toxic levels.
2. When exceed the level for exchange transfusion on the exchange transfusion chart.

➤ Technique:

- *Volume of blood:* double blood volume is needed ($2 \times 85 \times \text{body weight}$).
- *Type of blood:*
 - a. In Rh incompatibility: Rh-ve, same group of the infant.
 - b. In ABO incompatibility: O group, same Rh of the infant.
 - c. Other causes: infants blood group after cross matching
- ***Whole blood should be fresh (<3 days), warm, washed, irradiated, and filtered.***





➤ **Side effects:**

1. ***Umbilical catheterization:*** Embolization, thrombosis, infarction.
2. ***Cardiac:*** Heart failure, arrhythmia or arrest.
3. ***Hematological:*** Thrombocytopenia, anemia
4. ***Electrolyte disturbances:***(hypocalcemia, hypoglycemia,hyperkalemia)
5. ***Infections:*** HIV, CMV, Hepatitis
6. ***Graft- versus-host disease.***

III. Other therapies:

• **IVIG:**

- **Indications:** ABO & Rh incompatibility.
- **Mechanism:** occupy Fc receptors in RES, preventing the hemolysis of antibody coated RBCs.
- **Dose:** 0.5:1 gm/kg/dose (can be repeated in 12 hours).

Bilirubin encephalopathy

Definition:

Neurological syndrome due to deposition of unconjugated bilirubin in the brain, mainly basal ganglia.

Risk factors:

1. Bilirubin level: differ according to gestational age and postnatal age.
2. Duration of exposure to high bilirubin.
3. Factors increase free bilirubin: (hyopalbuminemia, drugs e.g sulfa)
4. Factors increase permeability of blood brain barrier (**BBB**) e.g., (Prematurity, hypoxia)

Clinical manifestations:

I. Acute bilirubin encephalopathy:

- **Phase I:** (1:2 days)
 - Hypotonia, poor feeding, irritability, seizures.
- **Phase II:** (3:7 days)
 - Hypertonia, opisthotonos, retrocollis, fever.
- **Phase III:** (after 1 week)
 - Hypertonia and may die or survive with apparent recovery for 2:3 months.

II. Chronic phase (kernicterus):

- Choreoathetoid CP but may be spastic.

Prevention: (more important than therapy)

- Avoid risk factors.
- Proper management of hyperbilirubinemia.

Treatment:

- **If suspected (acute):** immediate exchange transfusion.
- **If established (CP):** only supportive treatment of CP.

Infant Of Diabetic Mother (IDM)

Pathophysiology:

- Maternal hyperglycemia → fetal hyperglycemia → fetal **hyperinsulinemia** leads to **Macrosomia** secondary to:
 - Increase hepatic uptake of glucose and glycogen synthesis.
 - Increase fat synthesis.
 - Increase protein synthesis.
- **After birth:** interruption of maternal glucose infusion to the neonate, while hyperinsulinemia is going on → **hypoglycemia**.

Clinical presentation:

I. During pregnancy:

- Polyhydramnios.
- Abortion, stillbirth.

II. At birth:

- Preterm delivery.
- Obstructed labor.
- Birth injuries.



III. After birth:

1. Metabolic and electrolyte complications:

- **Hypoglycemia:**
 - **Definition:** blood glucose less than 50 mg/dl.
 - **Mechanism:** see pathophysiology.
 - **Clinical picture:**
 - Asymptomatic.
 - Symptomatic: lethargy, hypotonia, apnea, tachypnea, jitteriness, seizures.
- **Hypocalcemia:** due to transient immaturity of parathyroid gland.
- **Hypomagnesemia.**

2. Hematological complications:

- **Polycythemia:**
 - Venous blood haematocrit > 65%
 - Due to placental insufficiency and hypoxia which lead to increased erythropoietin level and erythropoiesis
- **Hyperbilirubinemia:** due to polycythemia.

3. Cardiac complication:

- Transient hypertrophic cardiomyopathy (Most common).
- Other congenital heart diseases e.g. VSD, ASD, TGA.
- May present with heart failure.

4. Respiratory complications:

respiratory distress may be due to:

- Respiratory distress syndrome (RDS) because fetal hyperinsulinemia decrease lung surfactant.

- Transient tachypnea of newborn.
- Hypoglycemia.
- Polycythemia.
- Heart failure.
- Cerebral edema due to birth trauma or asphyxia.

5. GIT complications:

- **Small left colon syndrome:** presented by generalized abdominal distension due to failure to pass meconium.

6. Renal complications:

- Renal vein thrombosis presented by flank mass and hematuria.

7. Cerebral complications:

- Cerebral edema due to birth trauma or asphyxia.

8. Congenital malformations:

- Neural tube defects (anencephaly, encephalocele, meningomyelocele)
- Skeletal anomalies (caudal regression syndrome).
- Renal anomalies (renal agenesis, hydronephrosis).
- Cardiac anomalies.

Management:

- **Proper control of maternal diabetes in periconception and during pregnancy.**
- **Assessment of fetal well-being.**
- **Resuscitation and post-natal care.**
- **Screening for and management of neonatal hypoglycemia:**
 - **Early feeding** (1st hour) of IDM is essential to prevent hypoglycemia.

- **Glucose screening** should continue until **12 hours** of age for infants born to mothers with diabetes and who maintain plasma glucose concentrations > 40 mg/dl, and for **24:48 hours**, if **hypoglycemia**.
- **Hypoglycemia should be treated**, even in asymptomatic infants, by frequent feeding and/or intravenous infusion of glucose.
- **Intravenous therapy:**
 - **Bolus:** (200 mg glucose/ kg = 2 ml/kg) glucose **10%** IV.
 - **Maintenance:** continuous IV infusion of glucose **10%** at a rate of **4:8** mg/kg/min
 - The goal is to maintain plasma glucose concentration between 40: 50 mg/dl.
- **Treatment of complications** e.g. hypocalcemia, hypomagnesemia and hyperbilirubinemia.

Neonatal Hematological Disorders

Physiological Anemia in the Neonate:

- Normal hemoglobin level in term infants at birth is 14:20g/dl.
- A “physiologic” decrease in hemoglobin is noticed:
 - At 8-12 wk in term infants (hemoglobin, 9-11 g/dl).
 - At 6 wk in premature infants (hemoglobin, 7-10 g/dl).

Etiology:

- **In utero:** fetal O₂ saturation is low and erythropoietin level is high, resulting in stimulation of erythropoiesis, so that Normal hemoglobin level in term infants at birth is 14:20g/dl.
- **After birth:** O₂ saturation is high; erythropoietin level is low, leading to decrease of erythropoiesis, so that hemoglobin level is decreased to its nadir.

No treatment is required (It is physiological anemia).

Pathological Anemia in the Neonate:

➤ Etiology:

I. Blood loss:

➤ Prenatal:

- Placenta previa.
- Feto-maternal hemorrhage.
- Twin to twin transfusion.

➤ Natal:

- Birth injuries (ICH)

➤ Postnatal:

- Hemorrhagic disease of the newborn.

- Frequent blood sampling for investigations.

II. Hemolysis:

- Hemolytic disease of the newborn.

III. Decreased production of RBCs:

- Congenital pure red cell anemia.
- Congenital infection (rubella).
- Congenital leukemia.

➤ **Clinical Presentation:**

I. Acute blood loss:

- Acute pallor, shock and anemic heart failure (tachypnea, tachycardia, hepatomegaly)

II. Chronic blood loss:

- Gradual Pallor, poor weight gain, poor feeding, decreased activity, apnea, and if severe, heart failure.

➤ **Diagnosis:**

	Blood loss	Hemolysis	Decreased production
Hemoglobin, Hematocrit value	↓	↓	↓
Reticulocyte	Normal or ↑	↑	↓
Bilirubin	Normal	↑	Normal

➤ **Investigations:**

- CBC, blood indices.
- Reticulocytic count.

- Comb's test.
- Serum bilirubin.

➤ **Treatment:**

I. Blood transfusion:

(Packed RBCs or Whole blood in case of acute blood loss (hemorrhage))

- **Criteria:**
 - Blood should be **fresh** (less than 3 days).
 - **Tests** for (CMV, HIV, Hepatitis B and C antibodies)
 - **Irradiated** blood (in case of immune compromised infant)
- **Volume**
 - 10-20 ml/kg.

II. Treatment of underlying cause:

Hemorrhage In The Newborn Infant:

I. Deficient clotting factors:

1. **Transient**: (hemorrhagic disease of the newborn).
2. **Associated with other diseases**: DIC, and significant liver disease.
3. **Inherited**: (Classic hemophilia (F8 deficiency)).

II. Platelet problems:

1. **Thrombocytopenia**: *decreased platelet count.*
2. **Thrombasthenia**: *decreased platelet function.*

III. Vascular problems: *Hypoxia, acidosis.*

IV. Fibrinolysis: DIC.

Hemorrhagic Disease of the Newborn(HDN)

• Definition:

Transient coagulation disorder due to transient deficiency of vitamin K-dependent clotting factors (II, VII, IX, X).

• Etiology and types:

	Early-onset	Classic	Late-onset
Onset	1 st day	2:7 days	2 weeks :6 months
Causes	• Maternal drugs that inhibit Vit K synthesis: - Anticonvulsants. - Anticoagulants. - Anti-tuberculous drugs.	• Decreased intake: breast milk is poor in vit K • Immaturity of the liver • Decreased vit K stores: common in preterm	• Absence of bacterial intestinal flora (that form vitamin K): Total parenteral nutrition. • Broad spectrum antibiotics. • Malabsorption: Biliary atresia. • Cystic fibrosis.
Incidence	Very rare	2% of neonate not given Vitamin K at birth	Dependent on cause

• Clinical picture:

- Haemorrhagic anaemia (pallor, up to shock)
- Site: GIT, Ear, Nose, Throat, Intracranial, Circumcision, Injection site.

- **Investigations:**

- **PT, PTT, and clotting time**: prolonged.
- **Levels of factors** 2, 7, 9, 10: reduced.
- **Bleeding time**: normal.
- **CBC**: to assess Hb level, platelet count is normal.

- **Prevention:**

- **Vitamin K1**: 1mg, IM at birth.

- **Treatment:**

- I. **Vitamin K1**:

- I.V. infusion of 1-5 mg (stop bleeding within a few hours).

- II. **Fresh frozen plasma**:

- 10 ml/ kg, indicated when:
 - Ineffective vit K therapy.
 - Serious bleeding.
 - Premature.
 - Liver disease.

- III. **Whole blood transfusion**: in case of marked hemorrhage.

- **Differential Diagnosis:**

- 1. **Causes of hemorrhage in newborn.**

- 2. **Swallowed blood syndrome**:

- **Cause**: swallowing of maternal blood during delivery or from fissured nipple.
 - **Clinical picture**: Blood vomiting or stools are passed during the 2nd or 3rd day of life.
 - **Differential diagnosis**: It may be confused with hemorrhage from GIT of the newborn.

➤ **Diagnosis:** (**Apt test** = *Alkali denaturation test*)

- *Used to* differentiate neonatal blood from maternal blood found in a newborn's stool or vomitus.
- *Method:* addition of alkali to blood sample from newborn's stool or vomitus.
- *Results:*
 - **Infant blood (HbF):** resist denaturation by alkali, stay **(pink)**.
 - **Maternal blood (HbA):** it forms hematin, turns **(yellow)**.



Neonatal Sepsis

Definition:

- **Clinical** syndrome characterized by **systemic** signs and symptoms of infection with **evidence** of bacteremia.
- The single most important cause of **neonatal deaths** in the community.

Etiology:

	Early- onset sepsis	Late- onset sepsis
Onset	In the 1st week usually before 3rd day	After the 1 st week
Risk factors	• Prematurity. • Low birth weight. • Prolonged rupture of membranes. • Chorioamnionitis. • Maternal fever. • Maternal UTI.	• Prematurity. • Hospitalization. • Invasive procedures: - Umbilical catheterization - Endotracheal intubation. - Mechanical ventilation
Organisms	• Group B streptococci (GBS). • E. coli. • Listeria monocytogenes. • Others: klebsiella, H. influenza.	• Staphylococcus Aureus. • Klebsiella. • Pseudomonas. • H.influenza. • Viral or candida.
Manifestations	Multisystem	Multisystem or focal

Clinical features:

Nonspecific and can simulate other diseases, so a high index of suspicion is needed for early diagnosis

I. General:

- Not doing well.
- Lethargy.
- Poor feeding.
- Poor temperature control (hypothermia is more common than fever)
- Scleroderma (hardening of the skin).

II. Gastrointestinal manifestations:

- Abdominal distension.
- Anorexia, vomiting, diarrhoea.
- Necrotizing enterocolitis (NEC).
- Hepatomegaly.

III. Respiratory manifestations:

- Tachypnea and flaring.
- Retractions.
- Grunting.
- Cyanosis and apnea.

IV. Cardiovascular manifestations:

- Tachycardia and arrhythmias.
- Hypotension.
- Pallor, cyanosis, and mottling.
- Cold skin.



V. Central nervous system manifestations:

- Irritability.
- Tremors, seizures.
- Hyporeflexia.
- Abnormal Moro reflex.
- Full or tense fontanel.

VI. Hematological manifestations:

- Jaundice.
- Pallor.
- Splenomegaly.
- Petechiae, purpura.
- Bleeding and DIC.

Investigations:

I. Hematological signs:

1. **Leucopenia:** (total leucocyte count < 5000 per mm^3)
2. **Neutropenia:**
 - Is more predictive of neonatal sepsis than neutrophilia.
 - Absolute neutrophil count (ANC) is < 1800 per mm^3 .
 - Immature neutrophils (Band cells + myelocytes + metamyelocytes) to total neutrophils ratio (I/T) > 0.20 means that immature neutrophils are over 20 percent of the total neutrophils because bone marrow pushes even the premature cells into circulation, to fight infection.
3. **Thrombocytopenia:** Platelet count $< 100,000$ per mm^3 .

II. Acute phase reactants:

- **C-reactive protein:** is often elevated neonatal sepsis.

III. Direct method Isolation of microorganisms:

- From blood, urine, stool, CSF, pleural fluid, or pus culture is diagnostic.

IV. Imaging:

- CXR, cranial sonar, CT and MRI may be needed.

Treatment:

I. Antibiotic therapy:

- Antibiotic therapy should start immediately once diagnosis is suspected and after samples for cultures are obtained.
- Initial therapy (broad spectrum) consisted of:
 - A combination of ampicillin and gentamicin is recommended for treatment of sepsis and pneumonia.
 - Cefotaxime with aminoglycoside is recommended for treatment of suspected meningitis.
 - Choice according to culture and sensitivity is the best.
- The duration of antibiotic therapy:
 - 14 days therapy is required for sepsis or pneumonia.
 - 21 days therapy is required for osteomyelitis and meningitis.

II. Supportive care

- **Incubator care.**
- **Respiratory support:** oxygen therapy, mechanical ventilation.
- **Circulatory support:** I.V. fluid, fresh plasma transfusion, packed RBCs transfusion and dopamine infusion.
- **Nutrition support:** enteral or parenteral nutrition.

Neonatal Seizures

Etiology:

I. Central nervous system: (Commonest)

- Hypoxic-ischemic encephalopathy (HIE)
- Intracranial Hemorrhage.
- CNS infections e.g., meningitis, encephalitis.
- CNS malformation e.g., cerebral agenesis.

II. Metabolic:

- Hypoglycemia.
- Hypocalcemia.
- Hypomagnesaemia.
- Hyponatremia and hypernatremia.
- Inborn error of metabolism e.g., vitamin B6 deficiency, organic acidemia, hyperammonemia.

III. Others:

- Local anesthesia during labor.
- Drug withdrawal e.g., maternal narcotics.
- Familial.
- Fifth-day fits.

IV. Unknown causes

Clinical manifestation and classification:

I. Subtle seizures: (50%) most common

- **Eye:** Staring, blinking, eye deviation, eye opening.
- **Mouth:** Sucking, mouthing, lip smacking.
- **Limbs:** Limb posturing, swimming, pedalling.
- **Apnea:** Associated with initial tachycardia and desaturation.
- **Rhythmic changes in vital signs:** Tachycardia , hypertension.

II. Tonic seizures: (5%)

- Sustained rigid posture of the body.
- May be focal or generalized.

III. Clonic seizures: (25:30%)

- Rapid alternating contraction and relaxation of the muscles.
- May be:
 - Focal.
 - Multifocal: migrating from limb to limb.
 - Rarely generalized.

IV. Myoclonic seizures: (15:20%)

- Sudden, fast, shock like, non- rhythmic movement of group of muscle.

“N.B.”: Generalised tonic-clonic seizures are rare in the first month of life and not seen in the preterm infant.

Differential diagnosis:

	Jitteriness	Seizures
Provocation	By stretching the limb	Spontaneous
Movement pattern	Tremors	Clonic
Abnormal eye movement	Absent	Present
Cessation with passive flexion	Stop	Continue
EEG	Normal	abnormal

Investigation:

- **Screen for** blood glucose, electrolytes (Ca, Mg, and Na).
- **Screen for sepsis:** CBC, blood culture, lumbar puncture.
- **Metabolic screen:** serum ammonia, lactate, urine organic acids.
- **Screen by cranial ultrasound,** consider CT, MRI.
- **EEG:**
 - To determine whether the paralyzed infant is having seizures.
 - To determine whether infant with subtle signs is having seizures.
 - Interictal EEG is of some value in estimating prognosis.

Prognosis:

EEG Background	Neurologic Sequelae (%)
Normal	≤10%
Severe abnormalities	≥90%
Moderate abnormalities	Approx. 50%

Treatment:

- **Stabilize vital signs:** (Airway, Breathing, Circulation)
- Treatment of the underlying cause (if known) for example:
 - **Hypoglycemia:** glucose 10%, I.V, 2 ml/kg.
 - **Hypocalcemia:** calcium gluconate 10%, slow I.V 2 ml/kg.
- **Anticonvulsant therapy:**
 - **Phenobarbitone:** (drug of choice)
 - *Loading dose:* 20 mg/kg slow I.V.
 - *Maintenance dose:* 3:8 mg/kg/day.
 - **Phenytoin** (is added, if no response to phenobarbitone)
 - *Loading dose:* 20 mg/kg slow I.V.
 - *Maintenance dose:* 3:8 mg/kg/day.
 - **Midazolam:** is given If no response to previous lines.
 - **Pyridoxine therapeutic trial:** 50mg I.V.; if pyridoxine deficiency is suspected.

Neonatal Screening

-

I. Biochemical screening	• This is performed on all infants between days 3-7. Blood spots, usually from a heel prick, are placed on a card, commonly screened disease include: - Congenital hypothyroidism. - Phenylketonuria. - Congenital Adrenal Hyperplasia - Galactosemia - Sickle cell disease. - Thalassemia - Cystic fibrosis
II. Hearing screening	• To detect congenital hearing loss for all newborns.

Practice Questions

(Choose one correct answer)

- 1- Regarding drugs given in neonatal resuscitation, which of the following is true:
 - a) adrenaline increases heart rate and force of contraction.
 - b) sodium bicarbonate is given with prolonged cardiac arrest.
 - c) naloxone is given only when there is history of maternal intake of narcotics.
 - d) all of the above
- 2- Assessment of a neonate at birth includes a search for:
 - a) imperforate anus.
 - b) nasal choanal atresia.
 - c) cranial sutures and fontanel.
 - d) all of the above.
- 3- At birth normal heart rate is:
 - a) 60-80/ minute.
 - b) 70-120 / minute.
 - c) 80-110 / minute.
 - d) 110-150 / minute.
- 4- Unconjugated hyperbilirubinemia occurs in all of the following EXCEPT:
 - a) physiological jaundice.
 - b) Rh incompatibility.
 - c) breast milk jaundice.
 - d) biliary atresia.
- 5- The investigation that should be done to diagnose the cause of jaundice in a 24-hour old baby is:
 - a) full blood picture.
 - b) Coomb's test.
 - c) G6PD enzyme assay.
 - d) all of the above.
- 6- Direct hyperbilirubinemia is applied to which of the following:
 - a) direct bilirubin is more than 5% of the total serum bilirubin.
 - b) direct bilirubin is more than 15% of the total serum bilirubin.
 - c) direct bilirubin is more than 20% of the total serum bilirubin.
 - d) direct bilirubin is more than 25% of the total serum bilirubin.



Chapter 10

Gastrointestinal Disorders

Objectives:

1. Formulate a management plan for a child presented with vomiting.
2. Understand different disorders of the oral cavity.
3. Discuss the causes, pathogenesis, and clinical features of pyloric stenosis
4. Demonstrate the general approach to a patient with acute diarrhea:
5. Classify malabsorptive syndromes, and common childhood malignancies.

Contents:

1. **Vomiting.**
2. **Stomatitis.**
3. **Gastroesophageal reflux.**
4. **Hypertrophic pyloric stenosis.**
5. **Malabsorption syndromes.**
6. **Constipation.**
7. **Diarrheal disorders.**

Evaluation of the Child with Vomiting

Causes of Vomiting and Regurgitation	
GASTROINTESTINAL TRACT DISORDERS	
Esophagus	Intestine and colon
Gastroesophageal reflux	Atresia and stenosis
Hiatal hernia	Meconium ileus
Esophagitis	Malrotation, volvulus
Esophageal atresia, stenosis	Duplication
Congenital vascular rings, webs	Intussusception
Foreign body	Foreign body
Periesophageal mass	Gastroenteritis, infections
Stomach	Soy or cow's milk protein intolerance
Hypertrophic pyloric stenosis	Gluten enteropathy
Pylorospasm	Appendicitis
Diaphragmatic hernia	Inflammatory bowel disease
Peptic disease and gastritis	Other abdominal organs
Duodenum	Hepatitis
Annular pancreas	Gallstones
Duodenitis and ulcer	Pancreatitis
Duodenal stenosis/atresia	
Malrotation and mesenteric bands	
EXTRAGASTROINTESTINAL TRACT DISORDERS	
Sepsis	Subdural effusion
Pneumonia	Hydrocephalus
Otitis media	Brain tumor
Urinary tract infection	Intoxications
Meningitis	Inborn errors
Rumination	Uremia

Diagnosis:

- A complete history, physical examination, and description of the vomitus.
- Erect abdominal X ray if there is bilious emesis.
- An upper gastrointestinal (GI) series is essential to rule out anatomic causes.
- A urinalysis and culture in urinary tract infection or urinary obstruction.
- Serum electrolyte abnormalities, which may interfere with GIT motor function.
- CT scan brain for increased intracranial pressure.
- X ray chest, or sinuses based on data from the history or physical examination.
- Viral and bacterial gastroenteritis are associated with diarrhea.
- Gallbladder disease is suspected if the family is suggestive of hemolytic disorders, hypercholesterolemia, or other conditions promoting gallstones.
- Mucus and blood in the stool suggests intussusception or bacterial or toxic colitis.

Treatment:

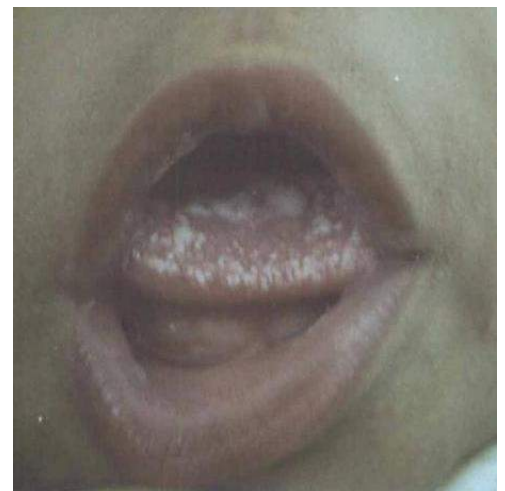
- 1- Treatment of the cause.
- 2- Antiemetic as metoclopramide 0.3-.5 mg/kg/d divided 8-12 hourly.
- 3- Correction of any resulting dehydration or electrolyte abnormality.

Some Disorders of Gastro-intestinal Tract

(I) Stomatitis

Oropharyngeal Candidiasis

- Oropharyngeal infection with *Candida albicans* (thrush, moniliasis).
- Infants and children following myelosuppressive or prolonged antibiotic therapy.
- The lesions appear as white plaques on the oropharyngeal mucosa, which can be removed leaving

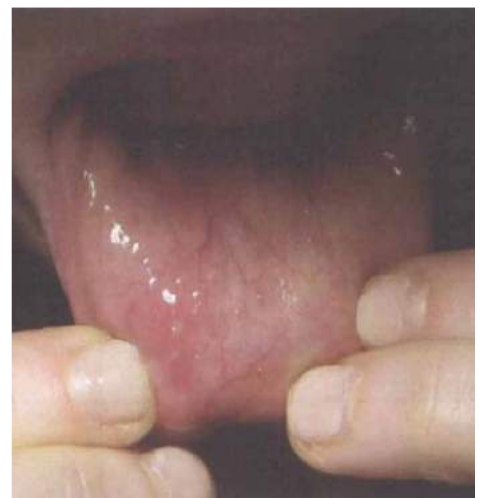


inflamed surface that may bleed.

- The diagnosis is confirmed by direct microscopic examination and culture of scrapings from lesions.
- It is usually self-limited in the healthy newborn infant, but treatment with nystatin, 100,000 iu/day divided into 4 doses, will hasten recovery and reduce the risk of spreading to other infants. Persistent infections should be treated with fluconazole therapy.

Aphthous Ulcers

- Occurs in 20% of the population and is usually recurrent.
- Their etiology is unclear, but infectious causes, have been implicated.
- Clinically, they are characterized by well-circumscribed, ulcerative lesions with a white necrotic base surrounded by a red halo. The lesions last 10 to 14 days and heal without scarring.
- Treated by readily available over-the-counter palliative therapies.



Herpetic Gingivostomatitis

- Incubation period is 1 wk.
- The symptoms usually regress within 2 wk without scarring.
- Fluids should be encouraged to prevent dehydration.
- Treated by analgesics and anesthetic rinses in addition to gentian violet paint.
- Caution should be exercised to prevent infection of the eyes.



Geographic Tongue

- The condition has no known cause and no treatment is indicated.
- Geographic tongue (migratory glossitis) is a benign and asymptomatic lesion and is characterized by one or more smooth, bright-red patches, often showing a yellow, gray, or white membranous margin on the dorsum of an otherwise normally roughened tongue.



(II) Gastroesophageal reflux

It is the most common esophageal disorder in children of all ages.

Definition:

Gastroesophageal reflux is the return of gastric contents into the esophagus. Physiologically, gastroesophageal reflux episodes do occur in all people but only occasionally and for short durations, without pathological changes in esophageal mucosa or respiratory tract.

The pathologic gastroesophageal reflux disease is diagnosed either by:

- Demonstrating an abnormal quantity of reflux
(Increased frequency or duration of episodes compared to asymptomatic individuals).
- Demonstrating that detrimental effects (such as malnutrition, esophagitis, or respiratory disease) have resulted from reflux.



Epidemiology:

- Physiologic regurgitant reflux is extremely common in infants, disappearing during the first year or so of life.
- Pathogenic reflux is more common in infants 1- 4 months than in older children. It tends to resolve during the first 2 y of life. No sex predilection was observed.
- Provocative factors include obesity, exposure to smoke, respiratory disease, or supine positioning.
- Children particularly likely to have pathogenic reflux include neurologically-impaired children; those requiring gastrostomy feedings; those who have cystic fibrosis, bronchopulmonary dysplasia, or repaired esophageal atresia.

Pathogenesis:

- The lower esophageal sphincter dysfunction.
- Increased gastric volume and delayed gastric emptying.
- Increased abdominal pressure as in obesity or tight clothing, coughing, and straining.
- Delayed physiologic clearance of regurgitated fluids from the lower esophagus.

Clinical picture:

SYMPTOMS AND SIGNS:

In infants:

- Regurgitation (especially postprandially),.
- Signs of esophagitis (irritability, arching, choking, gagging, food refusal).
- Failure to thrive.
- Respiratory (extraesophageal) presentations are obstructive apnea, stridor or lower airway disease.
- These symptoms resolve spontaneously in the majority by 12 to 24 months.

In older children:

- Regurgitation with heart burn extending during the preschool years.
- Abdominal and chest pain supervene during later childhood.
- Children may present with bizarre neck contortions called “Sandifer syndrome”.
- Airway manifestations in older children include asthma, laryngitis or sinusitis. Recurrent or chronic aspiration pneumonia.
- Esophagitis may manifest as iron-deficient anemia or hematemesis.
- Dysphagia due to an esophageal stricture may be the first manifestation of esophageal damage due to reflux.

DIAGNOSIS:

Thorough history and physical examination enforced by suitable diagnostic tests to exclude other differential diagnoses of chronic vomiting such as:

- Milk and other food allergies.
- Pyloric stenosis.
- Intestinal obstruction (especially malrotation with intermittent volvulus).
- Infections and inflammations.
- Inborn errors of metabolism.
- Urinary tract infections and hydronephrosis.
- Increased intracranial pressure.
- Psychogenic as rumination, and bulimia.

Diagnostic methods more related to reflux are:

1-Monitoring of the pH of the distal esophagus using special probe is the "gold standard" for diagnosing reflux.

2- Scintigraphic monitoring for reflux using swallow of technetium 99m sulfur colloid followed by one hour of scintigraphic studies.

3-Barium meal is less sensitive in diagnosis of gastroesophageal reflux but helps to exclude other anatomical abnormalities e.g. hiatus hernia.

4- Endoscopy of the upper gastrointestinal tract may demonstrate visible esophagitis in the form of erosions or ulcerations are clear signs of esophagitis. This can be confirmed by biopsy.

5- Bronchoscopy demonstrating ingested material in the airway.

Treatment:

1- Conservative antireflux measures as:

- Seated or prone positioning,
- Elevation of the head of bed.
- Thickening of feeds with rice cereal added to milk formula,
- Giving "small, frequent feedings."
- Fasting before bed.
- Avoidance of obesity and tight clothing, and foods or unnecessary drugs

2- Prokinetic agent as metoclopramide or domperidone if pathogenic reflux is documented.

3- Acid-reducing therapy as cimetidine or ranitidine is added if there is esophagitis.

4- Sucralfate as a mucosal protective agent may be added in severe cases.

5- Surgical management (Nissen fundoplication) for serious unresponsive manifestations persisting beyond 18 to 24 mo of age. Also in children who have neurologic deficits or peptic strictures or who receive gastrostomy tube feedings are very likely to require surgical treatment for reflux.

(III) Hypertrophic Pyloric Stenosis

- Hypertrophic pyloric stenosis occurs in approximately 3 in 1,000 infants.
- More common in whites than in blacks.
- Males (especially firstborns) are 4 times as often affected as females.
- Pyloric stenosis develops in about 20% of the male and 10% of the female descendants of a mother who had pyloric stenosis.
- The incidence is increased in infants with type B and O blood groups.
- More common in offspring of affected parents.

- May be associated with other congenital defects, as tracheoesophageal fistula.

Etiology:

- The cause of pyloric stenosis is unknown.
- Pyloric stenosis is usually not present at birth.
- May be due to abnormal muscle innervation or, elevated serum prostaglandins.

Clinical Manifestations:

- Non-bilious vomiting which is usually projectile, occurring immediately after feeding.
- Emesis may follow each feeding, or it may be intermittent.
- After vomiting, the infant is hungry and wants to feed again.
- The vomiting usually starts after 1-3 wk of age, but sometimes at the 5th month.
- Progressive course, and as vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to hypochloremic metabolic alkalosis and potassium deficiency. Finally there is chronic malnutrition and severe dehydration.

Diagnosis:

- Palpable pyloric mass, which is firm, movable, approximately 2 cm in length, olive shaped, hard, best palpated from the left side, and located above and to the right of the umbilicus below the liver edge. It is easier to palpate just after vomiting.
- After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen.



Investigations:

- Ultrasound examination:

Confirms the diagnosis in the infants with suspected disease but no pyloric mass on physical examination.

Ultrasonography has a sensitivity of approximately 95%.

Criteria for diagnosis include:

Pyloric thickness greater than 4 mm or an overall pyloric length greater than 14 mm.

- Barium studies:

Performed in questionable cases, **they demonstrate:**

- Elongated pyloric channel.
- Bulge of the pyloric muscle into the antrum (shoulder sign).
- Parallel streaks of barium seen in the narrowed channel, “double tract sign”.

Differential Diagnosis:

- Infants hyper-reactive to external stimuli,
- Those fed by inexperienced or anxious caretakers
- Inadequate maternal-infant bonding relationship
- Gastroesophageal reflux
- Hiatal hernia,
- Adrenal insufficiency
- Inborn errors of metabolism
- Vomiting with diarrhea suggests gastroenteritis
- Pyloric membrane or pyloric duplication
- Duodenal stenosis

Treatment:

- The preoperative correction of the fluid, acid-base, and electrolyte losses.
- Nasogastric suction.
- The surgical procedure is the Ramstedt pyloromyotomy.

- Feedings can be initiated within 12–24 hr after surgery and full oral intake within 36–48 hr of the surgery.
- Persistent vomiting after operation suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction.
- Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.
- Conservative medical therapy (small frequent feedings, atropine) has been attempted in the past but is associated with slow improvement and a higher mortality.

(IV) Malabsorptive syndromes

These disorders are conditions that cause insufficient assimilation of ingested nutrients as a result either of maldigestion or of malabsorption

They are divided into:

1- Generalized malabsorption:

These children have disorders that cause generalized defects in assimilation of nutrients and tend to present with:

- a) Abdominal distention.
- b) Passage of pale, foul-smelling, bulky stools.
- c) Muscle wasting; poor weight gain or weight loss, and stunted growth.

Mechanisms:

- Distortion of normal anatomy of GIT affecting food mixing with digestive juices.
- Decrease of digestive juices (bile, pancreatic or intestinal).
- Impairment and atrophy of intestinal absorptive surface.

Most important causes are:

- **Exocrine pancreatic defects:**

Cystic fibrosis, chronic pancreatitis, chronic protein-calorie malnutrition.

- **Liver and biliary tree:**

Biliary atresia and other cholestatic states as neonatal hepatitis.

- **Intestinal anatomic defects:**

Massive intestinal resection, Stagnant loop syndrome.

- **Chronic infection:**

Giardiasis, immune deficiency.

- **Intestinal mucosal disease:**

Celiac disease, tropical sprue, dietary protein intolerance (cow milk, soya).

2- Selective malabsorption:

These are congenital disorders affecting individual intestinal digestive enzymes or transport processes. Some of these disorders may present as early as the 1st wk of neonatal life and can be life threatening. The clinical features of these disorders typically differ from those of the generalized malabsorption syndromes. Some even present without gastrointestinal symptoms.

Clinical Manifestations of generalized malabsorption:

- Congenital disorders may cause diarrhea and malabsorption from birth (e.g. glucose-galactose transport defect, and congenital chloride diarrhea)
- In some disorders, the symptoms may not present until the introduction of a new food (e.g. gluten in gluten-sensitive enteropathy, lactose in congenital lactase deficiency).
- There is an initial decrease in weight followed by a deceleration in height velocity.
- Signs of chronic malnutrition, vitamin and mineral deficiencies follow such as: lethargy decreased subcutaneous fat, muscle wasting, edema, clubbing, depigmentation of skin and hair, hemorrhagic tendency, eczema, and follicular hyperkeratosis. Patients may also present with cheilosis, stomatitis, glossitis, and diffuse abdominal pain.

Diagnosis:

- 1) A careful history should cover:
 - The time of onset of symptoms
 - The relation to diet (symptoms appear with every re-introduction of substance and improve with its withdrawal)

- Frequency, looseness, and quantity of stool.
- 2) Clinical examination for above signs of malnutrition and various deficiencies.
- 3) Inspection of stools (bulky, pale creamy color and foul odor of fatty acids)
- 4) Microscopic detection of excessive fat droplets stained by Sudan III.
- 5) Determination of 72-hour stool fat. Excretion of more than 7% of the total fat intake is abnormal.
- 6) D-xylose test which is administered in a dose of 5 g orally then the following 5-hour urinary D-xylose excretion is measured.
- 7) Appropriate radiological and endoscopic examination of the intestine with biopsy to determine the cause of malabsorption.

Treatment:

Treatment of the cause and supplementation of sufficient food and various deficient vitamins and minerals with follow up.

(V) Constipation

Definition:

It is defined as a hard stool passed with difficulty every 3 days or more

Mechanisms:

Constipation may arise from

1- Defective filling of the rectum:

(Ineffective colonic peristalsis as hypothyroidism, or bowel obstruction)

2- Defective emptying of the rectum:

(Defective defecation reflex due to weak muscles, spinal cord lesions, or pain induced sphincteric spasm)

CAUSES:

- **Non-organic:** (Functional) due to habitual delay in defecation.

- **Organic causes of constipation:**

- **Intestinal**

Hirschsprung disease, anal–rectal stenosis, stricture, volvulus.

- **Drugs**

Narcotics, antidepressants, vincristine.

- **Metabolic**

Dehydration, Cystic fibrosis, Hypothyroidism, Hypokalemia, Hypercalcemia

- **Neuromuscular**

Psychomotor retardation, absent or weak abdominal muscles, muscle dystrophy, Spinal cord lesions (tumors, spina bifida)

- **Psychiatric**

Anorexia nervosa

Treatment of constipation:

- Treat the cause in organic constipation.
- Increased intake of fluids.
- High-residue foods such as bran, whole wheat, fruits, and vegetables.
- Establishment of regular bowel habit, BY Sitting on the toilet 10–15 min after each meal. Rewards for compliance should be offered.
- Stool softener as
 - Barley malt extract, 1–2 tsp added to feedings 2-3 times daily,
 - Polyethylene glycol solution (1 g/kg/d),
 - Lactulose (5-15 ml daily added to orange juice).
 - Mineral oil such as paraffin oil (2–3 mL/kg/d),
 - Milk of magnesia (1–2 mL/kg/d).
- Cathartics such as extract of senna fruit can be used for short periods.
- Fleet enemas or glycerol suppositories are used only temporarily to relieve stool impaction if present.

(VI) Diarrheal Diseases

ACUTE DIARRHEA

Definitions:

- ❖ **Diarrhea** is defined as an increase in the frequency and/or fluidity of the stools relative to the previous habit of the same individual.
- ❖ **Acute Diarrhea** is diarrheal attack of duration less than 14 days.
- ❖ **Persistent diarrhea** defines diarrheal episode that starts acutely but lasts for 14 days or more (but no specific underlying pathology).
- ❖ **Chronic diarrhea** refers to recurrent or long lasting diarrhea (for more than 2-4 weeks) due to a major specific underlying pathology for which diarrhea is just a symptom. Examples are chronic diarrhea due to a secretory tumor, gluten sensitivity, endocrinopathy or immunodeficiency syndrome.
- ❖ **Gastroenteritis** is diarrhea due to intestinal infectious agent.

Epidemiology:

- The Egyptian child under 5 years on the average suffers from 3 to 5 diarrheal episodes per year.
- Diarrhea is the first cause of infant mortality in Egypt.
- Diarrhea is more prevalent in:
 - a- Children in highly contaminated environments.
 - b- Low socioeconomic status.
 - c- Poor water supply and bad sanitary facilities.
 - d- Non breast fed infants.

Diarrhea and malnutrition:

- Diarrhea occurring in malnourished children tends to be more severe, and is more likely to persist due to low immunity and poor healing.
- Infants with persistent diarrhea suffer growth failure or actual weight loss during a diarrheal episode due to poor intake and intolerance to food.

Etiology:

1. Intestinal infections:

Oral ingestion is the primary route of infection, although rotavirus appears to be transmitted by respiratory or mucous membrane contact as well.

- **Viruses:** They are responsible for 50-70% of diarrheal cases e.g. Rotavirus and Norwalk virus.
- **Bacteria:** Most common are E.coli, Shigella, Salmonella, Vibrio cholera and Staphylococcus aureus.
- **Protozoa:** such as Entameba histolytica, Giardia lamblia, Cryptosporidium
- **Helminths:** as Ascaris and Ankylostoma.
- **Fungi:** as Candida albicans.

2. Extraintestinal infections (parenteral diarrhea):

This includes otitis media, pneumonia and urinary tract infections. Diarrhea may be due to toxic effect or associated enteric infection.

3. Non-infectious diarrhea:

- 1) **Dietetic factors:** such as overfeeding, underfeeding, food allergy or intolerance. Also over concentrated formula.
- 2) **Malnutrition:** may be due to associated alteration of intestinal mucosa and motility in addition to changes in intestinal flora.
- 3) **Drugs:** direct villus damage e.g. streptomycin and neomycin, alteration of intestinal flora e.g. ampicillin or osmotic load e.g. Mg containing purgatives.

- 4) Environmental factors: such as hot weather and high humidity.
- 5) Psychologic factors: such as anxiety
- 6) Chronic diarrhea may be due to secretory neoplasm (neuroblastoma), malabsorption (cystic fibrosis, celiac disease), endocrinopathy (thyrotoxicosis), anatomical defect (Hirschsprung's disease) or immunodeficiency syndrome.

Mechanisms of diarrhea:

i. Secretory diarrhea:

- Increased secretion by viral invasion, bacterial toxins, and parasites as giardia.

ii. Invasive diarrhea:

- Due to bacterial or parasitic invasion of mucosa with inflammatory response.

iii. Osmotic diarrhea:

- Lactose, drugs as Mg salts.

Pathogenesis:

1 - Viral diarrhea:

- The virus invades the villus tips (absorptive cells).
- These cells are then renewed by cells coming from the crypts.
- Crypt cells are poorly absorptive resulting in less absorption of sodium, chlorides and glucose.
- So, diarrhea will be watery with high solute content (secretory).

2 - Bacterial diarrhea:

- Enterotoxigenic bacteria: where bacteria adhere to the mucosa and elaborate toxins that inhibit the absorption of sodium and glucose and stimulate the secretion of chlorides (secretory diarrhea).

- Enteroinvasive bacteria: which invade the mucosa and destroy the infected cells and elicit an inflammatory response causing hyperemia and exudation so, pus cells and RBCs can be found in the stools (dysenteric diarrhea).

3 - Parasitic diarrhea:

- *Entamoeba histolytica* colonize the colon causing inflammation, invasion and ulceration (dysenteric).
- *Giardia lamblia* causes irritation and absorptive dysfunction of mucosal cells (secretory).

Clinical picture:

History should be taken for:

- Age and residence: which may help to suggest a probable etiologic agent (e.g. salmonella prevails in younger infants).
- Duration of diarrhea, stool consistency and frequency and associated vomiting, abdominal pain or fever.
- Type of feeding of the patient and any recent changes in diet, e.g. food allergy or contamination.
- Recent contact with a diarrhea case (infection).
- Recent intake of drugs e.g. antibiotics or osmotically active substances.
- Recent travel to infected areas, or sharing infected food.
- Socioeconomic status and degree of hygiene practiced.
- Associated parenteral infections e.g. otitis media.

Clinical examination should include:

- Assessment of the degree and type of dehydration.
- Assessment of nutritional status by appropriate anthropometric measurements and clinical signs.
- Systemic examination for sites of parenteral infections and for complications.

DEHYDRATION

Definition:

It is an abnormal state of body water and electrolytes in which there is diminution of extracellular and/or intracellular fluid volume.

- It can occur due to decreased fluid intake e.g. coma or increased fluid losses from the body e.g. diarrhea and vomiting.
- The degree and type of dehydration depends on the amount and type of losses (in stools, vomits, urine, and insensible losses) versus the amount and type of fluids taken during the same period.
- Provided the pre-illness body weight of the patient is known, dehydration is designated as no signs of dehydration if there is loss of less than 5% of body weight, some dehydration if 5-10% body weight was lost and severe dehydration if more than 10% of body weight was lost.

Types of dehydration:

Dehydration may be hypertonic, hypotonic or isotonic according to relative net losses of water and electrolytes (particularly sodium) from the body.

1 - Isotonic (Isonatremic) Dehydration:

- It is the most common type of dehydration (more than two thirds of the cases).
- The serum level of sodium is maintained within the normal limits (130-150 mEq/L) due to equivalent losses of water and electrolytes, balanced with intake and helped by renal compensation.
- There are no major water shifts between extracellular and intracellular compartments of body fluid.
- Different signs of dehydration are presented without discrepancy.

2 - Hypertonic (hypernatremic) dehydration:

- There is more loss of water than electrolytes or more intakes of electrolytes than water.
- Serum sodium is elevated above 150 mEq/L.
- Hypertonic dehydration occurs in 5-15% of dehydrated cases especially the young infants due to their renal immaturity and decreased renal ability to conserve water.
- Water shifts from inside the cell to the extracellular fluid where sodium concentration and hence osmolarity is high.
- Cellular dehydration occurs and this accounts for most of clinical manifestations of this type of dehydration.
- The child becomes very thirsty, irritable or drowsy, with very dry tongue and may proceed to convulsions. However the skin elasticity is relatively preserved giving the texture known as doughy skin.
- It is the most serious type of dehydration with mortality 5-10 times higher than that of other types of dehydration.
- It is associated with higher morbidity and complications such as intracranial hemorrhage, dural sinus occlusion, cerebral vein thrombosis, subdural effusion, renal tubular necrosis, skin gangrene or DIC.

3 - Hypotonic (Hyponatremic) Dehydration:

- There is more loss of electrolytes than water or more intake of water than electrolytes.
- Hypotonic dehydration constitutes 5-15% of dehydrated cases.
- Serum sodium falls below 130 mEq/L i.e. extracellular fluid becomes hypotonic.
- In attempt to compensate, water shifts from extracellular to intracellular compartment due to osmotic gradient with resulting cellular edema.

- This accounts for clinical manifestations of this type. The child appears weak, hypotonic with drowsiness or delirium. There is severe loss of skin turgor, while the tongue (representing intracellular compartment status) remains moist.
- In severe cases brain edema with convulsions and coma may occur.

Associated acid-base and electrolyte disturbances:

1. Metabolic acidosis: It occurs due to:

- i. Loss of bicarbonates in the stools.
 - ii. Formation and absorption of organic acids due to incomplete breakdown of carbohydrates in the bowels.
 - iii. Starvation leads to ketone body formation.
 - iv. Accumulation of acidic metabolites in the blood due to severe dehydration oliguria and prerenal failure.
- Plasma bicarbonate is decreased (normally 22-28 mEq/L).
 - Clinically there is hyperpnoea or rapid deep respiration.
 - It is an emergency necessitating IV infusion of sodium bicarbonate.

2 – Hypokalemia (serum potassium less than 3.5 mEq/L) :

- Potassium is lost from stools and vomits.
- It can occur also during correction of acidosis by bicarbonate where potassium is shifted from the extracellular to the intracellular fluid.
- During infusion of potassium poor fluid.
- There is hypotonia and abdominal wall distension
- ECG shows depressed ST segment, low or inverted T wave and prolonged QT interval.
- Treated by adding potassium chloride to the infusion and oral intake potassium for several days thereafter.

3 – Hyperkalemia (serum potassium more than 5.5 mEq/L):

- It may result from oliguria or anuria of severe dehydration.
- Following administration of large amount of potassium before restoration of renal function.
- Clinically there is restlessness, parasthesia, muscle weakness or paralysis and cardiac arrhythmia.
- ECG shows peaked T wave, short QT interval; latter on there is prolonged PR interval, wide QRS complex and ventricular fibrillation.

4 - Tetany:

- This may be due to hypocalcemia e.g. due to decreased calcium intake, excessive losses or due to excessive infusion of alkali during correction of acidosis (which decreases ionised calcium and called post-acidotic tetany). Tetany can also occur due to hypomagnesemia.
- Clinically, there is characteritic carpopedal spasm, with adduction of thumb, flexion of the wrist and metacarpophalangeal joints and extension of interphalangeal joints. In the feet, there is planter flexion of all toes. In severe cases, there may be laryngeal spasm or generalised convulsions.

Management of acute diarrhea

Prevention:

- 1) Exclusive breastfeeding during the first 4-6 months and continued breastfeeding for 2 years. Breastfeeding reduces the incidence and severity of acute infantile diarrhea due to sterility, antibodies, phagocytic cells and nutritional value.
- 2) Improved weaning practices by giving nutritious suitable food and avoiding contamination of feeds.
- 3) Use of clean water for drinking and preparation of infant feeds.
- 4) Hand washing.
- 5) Use of latrines and safe disposal of infant stools.
- 6) Vaccination against infectious diseases that predispose to diarrhea such as measles.

General approach to a patient with acute diarrhea:

Rapid determining and managing the fluid losses, dehydration and electrolyte abnormalities in addition to proper feeding and specific treatment of infectious diarrhea by proper antimicrobial or antiparasitic.

Treatment plans:

Physical signs of dehydration should be familiar to every physician (table 2).

Table (2): Assessment of diarrheal dehydration

Clinical aspect	No dehydration	Some dehydration	Severe dehydration
General condition	Well, alert	*Restless, irritable*	*Lethargic, unconscious,
Thirst	Drinks	*Drinks eagerly*	floppy*
Skin pinch	Returns quickly	*Returns slowly*	*Drinks poorly or unable to do*
Eyes	Normal	Sunken	*Returns very slowly*
Tears	Present	Absent	Very sunken
Mouth & tongue	Moist	Dry	Absent
			Very dry

To have some or severe dehydration the patient should have two or more related signs of dehydration with at least one *key sign*

Plan A for treatment at home

This plan is applied to the infants having acute diarrhea with no dehydration.

The three rules for treating such patients at home are:

- Giving the patient more fluids than usual.
- Giving the patient plenty of foods (more than usual).
- Identifying warning signs of dehydration by the caregiver in order to take the patient back to the doctor.

1. Giving the patient more fluids:

- Oral rehydration is safe and effective and is the preferred route for prevention of dehydration in plan A and treatment of cases with some dehydration in plan B.
- The standard ORS containing glucose and electrolytes revolutionized the treatment of diarrhea associated dehydration.
- The co-transport between sodium and glucose in the small intestine made possible the rehydration across the intestinal mucosa even when sodium absorption is decreased by bacterial toxins or viral infection. After using oral rehydration in the developing countries, the diarrhea associated infant mortality has been decreased by about 1 million deaths annually.

The WHO standard solution contains the following ions (mmol/L):

1. Sodium 90
 2. Potassium 20
 3. Bicarbonate 30
 4. Chloride 80.
 5. Glucose 111.
- The standard WHO solution can be used along with extra amounts (similar volume) of plain water, breast milk or low-salt drinks during the course of diarrhea.
 - A maximum of 200 ml/kg/day of this solution should not be exceeded.
 - The ORS should be properly prepared by dissolving the components of the packet in 200 ml of clean water and completely stir it until no residual powder is left in the bottom of the glass.

- Amount of ORS intake during plan A:

Age of the patient	< 6 months	6-24 months	2-10 years
ORS for every motion	50 ml	100 ml	100-200 ml
ORS for every vomit	25 ml	50 ml	50-100 ml

Modified ORS:

- Solutions with lower sodium are more suitable for hydration of mild diarrheal cases and for maintenance of hydration after the initial sitting.
- Recent work suggested that the substitution of rice powder or other cereals for glucose in ORS could enhance fluid absorption.
- Amino acids were also suggested to be added to ORS to enhance solute absorption through their co-transport with sodium.
- Zinc salts also can be added for their beneficial effects of diarrhea and to help fluid absorption and reduce the risk of hypernatremia.

Table (3): Problems encountered during oral rehydration therapy

Difficulty	Possible solution
The child vomits frequently	- Explain that more fluid is kept than vomited - Wait for 10 min., then resume more slowly
The child refuses to drink	- Encourage the child - Give some plain water - Re-assess as he may be already hydrated
The mother believes that no food should be given during diarrhea	- Discuss with her how food is essential for intestinal healing, child's growth and general health.

The mother is disappointed as no prescription of drugs were given

- Explain that diarrhea is self-limiting
- Explain that drugs may be toxic & delay cure
- Explain that fluids treat and prevent dehydration which is the main problem of diarrhea

2. Giving the child plenty of food to prevent malnutrition:

- Continue breast-feeding frequently.
- If the child is not breast fed, give the usual milk in the same full concentration as before.
- If the child is 6 months or more, and is already taking solid foods: give cereal or starchy food mixed if possible with beans, vegetables or meat. Add 1-2 teaspoonfuls of vegetable oil to each serving.
- Give fresh fruit juice or meshed banana to supply potassium.
- Offer at least 6 feeds per 24 hours.
- After diarrhea has stopped, continue to give an extra-meal for further two weeks.

3. Taking the child back to the doctor:

The mother should return to rehydration center once any of the warning signs appears.

Table (3): Warning signs of dehydration**The mother is instructed to come for advice if:**

1. The baby did not become well within 3 days
2. Developed any of the following:
 - Marked thirst
 - Fever
 - Repeated vomiting
 - Eating or drinking poorly
 - Many watery stools
 - Lethargy
 - Blood in the stools

Treatment Plan B

- It is used for treatment of patients with some dehydration at health center or rehydration unit.
- First, the doctor estimates the amount of ORS required for the child (75 ml/kg).
- This amount is given to the child during 4 hours that he stays in the rehydration unit.
- Initially 5 ml is offered every 5-10 minutes to avoid vomiting then the rate is increased gradually according to tolerance and the body weight gain is observed every 1-2 hour.
- The mother is taught how to prepare and administer ORS.
- The child is repeatedly observed and monitored for body weight gain and disappearance of signs of dehydration as the process of rehydration progresses until full rehydration.
- The mother is instructed to continue treatment at home as in plan A.

- Nasogastric administration of ORS is resorted to whenever the oral route has failed to rehydrate a child due to repeated vomiting, refusal, the baby is too sleepy to drink or the mother is too tired to give the ORS by mouth while the child is not severely dehydrated. Also, it is used when IV fluids are indicated but there is lack of facilities or during transfer of the patient to hospital.

Treatment Plan C

- It is used for treatment of severe dehydration in the hospital.
- The intravenous fluids are started immediately.
- If shock is present: start with Ringer's lactate solution 20 ml/kg to be given within the first 30 minutes. If no response, give plasma or blood transfusion 10-20 ml/kg within 30 minutes. Airway clearance, warmth, oxygen, and elevation of lower limbs are also done to manage the shock.
- If not shocked, or after correction of shock, start polyelectrolyte solution containing (in mmol/L) sodium 90, potassium 15, chloride 65, acetate 40, and glucose 111). 100 ml/kg of this solution is given within the next 6 hours to correct severe dehydration.
- The patient is reassessed after 6 hours and we choose the appropriate plan A, B or C to continue the treatment.
- Intravenous rehydration is mandatory in severe dehydration (with impending cardiovascular collapse) or when oral rehydration is impossible (coma, intractable vomiting, or inability to drink, severe abdominal distension with absent bowel sounds).
- Oral fluids and breast-feeding should be initiated as soon as the patient can drink and be given simultaneously with IV fluids until the total fluids administered have replenished the calculated deficit, after which the IV fluids can be discontinued.

Feeding during diarrhea:

- Current recommendations no longer include withdrawing food or milk. Human milk should be continued with the frequency of breast feeding increased.
- In case of non-breast fed babies, full strength milks are resumed immediately after full rehydration in smaller more frequent feeds (e.g. 5-8 feeds), diluted if possible with cereals or other foods (not by water).
- Lactose free milks are not needed routinely in acute diarrhea as the incidence of significant lactose malabsorption is quite small (about 1 in 75 cases or 1.3%).
- Other well-tolerated foods can be given according to situation but the general rule is to give more food during diarrhea. Inadequate feeding during diarrhea, particularly in malnourished babies may increase the potential risk for the diarrhea becoming persistent, due to slower regeneration of the brush border when the intraluminal nutrients are absent.

Role of antibiotics and antiparasitic agents:

- Most diarrheal cases are due to viruses.
- Even great number of bacterial diarrheas is self-limited.
- Antimicrobials and anti-parasitics are not needed as a routine in the management of acute diarrhea.

Indications of antibiotics and antiparasitics in acute diarrhea:

- Malnourished patients with potential infection and low immunity.
- Cases with toxic appearance and high fever indicating blood spread of infection.
- Cases with extra-intestinal infections requiring antibiotic treatment as otitis media or urinary tract infections (parenteral diarrhea).

- Dysenteric diarrhea (mucus and blood in stools) and bacteriologically proven cases of shigella, cholera and some cases of E coli. The antibiotic is preferably given according to culture and sensitivity testing.
- Cases with parasitic infestation should receive proper anti-parasitic treatment.

Commonly used antibiotics and anti-parasitics:

❖ **Shigella:**

Co-trimoxazole 48 mg/kg/d, Ampicillin 100 mg/kg/day preferably (Ampicillin-sulbactam); or Nalidixic acid 55 mg/kg/day for 7 days. Third generation cephalosporin (cefotaxime 50-100 mg/kg/d) can also be used.

❖ **Cholera:**

Ampicillin 100 mg/kg /d for 7 days

❖ **E coli:**

Ampicillin 100 mg /kg /d or cefotaxime 50-100 mg/kg/d

❖ **Giardia:**

Metronidazole 15 mg /kg /d for 10 days.

❖ **Amoeba:**

Metronidazole 25 mg/kg/d for 10 days.

Diloxanide 10-20 mg /kg /d for 10 days.

Symptomatic treatment:

There is no evidence that any of the antidiarrheal drugs has beneficial effects on the course or outcome of acute diarrhea.

These agents should no longer be used as they may mask the problem, others may increase fluid or nutrient losses and many of them have toxic effects.

These agents include 3 groups:

1. **Adsorbents:** as Pectin, Kaolin, Smectite and Bismuth subsalicylates. These agents adsorb toxins but adsorb as well solutes and nutrients increasing their stool losses.
2. **Antisecretory drugs:** as chlorpromazine and acetyl salicylic acid. These drugs have narrow safety margin with toxic doses are near therapeutic levels. Racecadotril is still under trial.
3. **Antimotility drugs:** as loperamide (Imodium) and diphenoxylate (Lomotil). These drugs may cause bowel stagnation with increased toxin absorption and possibly paralytic ileus.

Laboratory investigations:

1. For non-inflammatory diarrhea of 3-5 day duration responds to simple rehydration therapy and appropriate dietary management alone without the need for investigations.
2. Laboratory assessment is reserved for cases:
 - Who have fever or visible blood in the stools.
 - After treatment failure for 3-5 days.
 - With history of recent antibiotic use, debilitating disease as malnutrition, contact with ill person, consumption of possibly contaminated food or attendance in child care center.

These investigations include:

- Stool examination for leucocytes and RBCs.
- Stool culture for Shigella, and Salmonella.
- Stool examination for Giardia, Entameba or Cryptosporidium.
- Intestinal biopsy may be indicated in cases of chronic diarrhea.

- Investigations used for assessment of the hydration, acid-base status may be required such as serum electrolytes, pH, bicarbonates, urea and creatinine.
- Stool pH and reducing substance help in diagnosing disaccharide intolerance.
- Urine analysis and culture may be requested to exclude urinary tract infections.

Complications of acute diarrhea:

1. Dehydration

2. Metabolic acidosis

3. Shock.

4. Electrolyte disturbances: Hypokalemia, hypernatremia, hyponatremia, and hypocalcaemia.

5. Infections: Bronchopneumonia, pyogenic arthritis, peritonitis, meningitis, and bacteremia or septicemia.

6. CNS disturbances:

- Encephalopathy due to thrombosis of cerebral vessels, hypernatremia, hyponatremia, shock or febrile.
- Meningoencephalitis.
- Convulsions.

7. Renal complications: Thrombosis of renal veins, renal cortical necrosis, and uremia.

8. Gastrointestinal complications:

- Intussusception.
- Rectal prolapse.

- Paralytic ileus.
- Persistent diarrhea.

9. Disseminated intravascular coagulopathy due to severe dehydration, shock, acidosis and toxemia.

10. Failure to thrive and malnutrition.

Persistent Diarrhea

The term persistent diarrhea describes an episode of acute gastroenteritis that persists for **14 days or longer**.

Clinical importance:

- In developing countries, persistent diarrhea accounts for 10-20 % of all episodes of gastroenteritis but causes 30% to 50% of the diarrhea-associated deaths.
- Mortality among patients of persistent diarrhea may reach 15% in developing countries.

Pathophysiologic mechanisms:

In most cases the initial infectious agent is no longer isolated from the stool.

With severe continuous diarrhea **significant intestinal mucosal injury** occurs and leads to:

- Intolerance to food stuffs:

- ☐ Lactose and monosaccharide intolerance.
- ☐ Fat malabsorption (50%).
- ☐ Mild protein malabsorption.

- Cow milk protein allergy (due to passage of macromolecules through damaged intestinal barriers) that perpetuates chronic intestinal injury.

- Persistent infection: some cases may suffer from intestinal infection with *Shigella* or *Salmonella* with continuous intestinal invasion and inflammation.

- Bile acid deconjugation occurs by bacterial overgrowth. These deconjugated bile acids are intestinal secretagogues and cause direct mucosal intestinal injury contributing to persistent diarrhea.

Risk factors:**Related to the patient:**

1. Low birth weight.
2. Younger infants < 6 months.
3. Non-breast fed.
4. Malnourished,
5. Immunocompromised.
6. Vitamin A deficiency.

Related to the diarrhea attack:

1. Infants recently introduced to new protein or contaminated formula feeds
2. After severe or invasive diarrhea e.g. Shigella, invasive E coli.
3. Diarrhea due to Giardia, E histolytica or Cryptosporidium.
4. Past history of an episode of persistent diarrhea.

Related to faulty management:

1. Prior broad spectrum antibiotic use.
2. Drug induced damage to the enterocyte brush border with low levels of disaccharidases e.g. streptomycin, neomycin.
3. Prolonged use of I.V. rather than oral rehydration.
4. Stopping or inadequate feeding during acute diarrhea.

Treatment of persistent diarrhea:**❖ Proper attention to nutrition using:**

1. Lactose-free formula (milk based or Soya based) in cases with lactose intolerance.
2. Cow-milk protein free diets for cow milk protein allergy: e.g.
 - Comminuted chicken-rice formula.

- Lentil-rice formula.
- Chickpea-rice formula.
- 3. Elemental diet formula.
- 4. Total Parenteral Alimentation.
- ❖ **Rehydration** and electrolyte therapy.
- ❖ **Treatment of specific cause if present.**
- ❖ **Bowel cocktail** of cholestyramine, metronidazole and oral non-absorbable antibiotic as oral gentamicin in cases with bacterial overgrowth of the upper bowel.

Practice Questions

(Choose one correct answer)

- 1- Which of the following has not been implicated as a viral cause of gastroenteritis :
 - a) Adenovirus.
 - b) Rotavirus.
 - c) Astrovirus.
 - d) E-coli.

- 2- Which of the following is not suggestive of pyloric stenosis :
 - a) constant hunger even after vomiting.
 - b) visible gastric peristalsis.
 - c) hypochloremic metabolic alkalosis with low plasma potassium.
 - d) bile-stained vomiting.

- 3- What is the complication of acute diarrhea which requires surgical consultation :
 - a) Hirschsprung disease.
 - b) dehydration.
 - c) Celiac disease.
 - d) intussusception.

- 4- Which of the following is an organic cause of constipation :
 - a) hypothyroidism.
 - b) hypercalcemia.
 - c) Hirschsprung disease.
 - d) all of the above.

- 5- Which of the following is not a clinical feature of dehydration in an infant?
 - a) increased skin turgor.
 - b) dry mucous membrane.
 - c) absent tears.
 - d) sunken fontanelle and eye.



Chapter 10 Hepatology

Objectives:

1. Understand the aetiology, clinical picture, and different presentations of acute hepatitis.
2. Classify different causes of cholestasis in infants and children.
3. Correlates between the clinical presentations and the special nature of each hematological disorder.
4. Understand the pathogenesis of chronic liver disease in pediatrics
5. Recognise the clinical features of chronic liver disease
6. Formulate a management plan for liver diseases in pediatrics.

Contents:

1. Acute Hepatitis.
2. Cholestasis in Infants and Children
3. Liver Cirrhosis.
4. Portal Hypertension (PH).
5. Ascites.
6. Causes of hepatomegaly in children.

Acute Hepatitis

Hepatitis is a non-specific clinical syndrome of variable severity due to inflammation & necrosis of hepatic parenchyma. **Causes may be:** infective, toxic, autoimmune, genetically determined, ischemic or cryptogenic.

Acute Viral Hepatitis

Viral hepatitis is mostly caused by:

- Hepatotropic viruses (A, B, C, D & E).
- Non-hepatotoxic: Herpes viruses, CMV, EBV, HIV, rubella, mumps & enteroviruses

Hepatitis A

Etiology and epidemiology:

Causative organism	Hepatitis A virus (HAV) is a non-enveloped, single-stranded RNA virus. Only one serotype has been recognized. It is excreted in stool & bile
Route of spread	Fecal-oral.
Source	Case only, HAV causes only acute hepatitis with no carrier state.
Mode of transmission	Transmission by close personal contact and by contaminated food & water. Infection in late pregnancy has not been shown to affect the newborn infant.
Infectivity period	Late in the incubation period & within 2 weeks of clinical onset of hepatitis.

Pathogenesis:

HAV is mildly cytopathic and the major hepatic injury is due to cell-mediated (cytotoxic T-lymphocytes) immune responses.

Clinical picture:

- Incubation period: from 20-40 days.
- Most children have an asymptomatic subclinical infection.
- Symptomatic infection has **2 phases**:

A. Pre-icteric phases: Fever, Anorexia, Hepatomegaly, Malaise (FAHM) + nausea, vomiting, abdominal discomfort, diarrhea.

B. Icteric phases:

- Jaundice, dark urine & pale stool.
- All symptoms regress & sometimes pruritus occurs.
- Liver is enlarged and tender. Splenomegaly occurs in 20-30% of cases.
- Jaundice may persist for only a few days but fades in the second week.
- Rarely it may persist for months (cholestatic hepatitis).
- Recurrence of cholestasis may also occur (relapsing hepatitis).
- Complete recovery is the rule.

Diagnosis:

1. **History:** Exposure to jaundiced person in family, school or nurseries
2. **Clinical examination.**
3. **Laboratory investigations:**

A-Biochemical:

- Serum biphasic bilirubin level rises.
- ALT & AST levels are elevated several folds the normal values.
- PT to assess the extent of liver injury.

B-Serological:

- IgM anti-HAV antibodies appear in serum at onset of symptoms & disappear after 2 months.
- IgG anti-HAV antibodies appear during convalescence & persist for many years.

Complications:**A. Fulminant hepatic failure (FHF):**

The most serious complication.

Incidence: 0.5% of cases within 8 weeks of onset of symptoms.

Clinical features:

- a. Rapid progression of symptoms.
- b. Deepening of jaundice.
- c. Reduction of liver size.
- d. Development of ascites.
- e. Neuro-psychiatric changes (Aggressive behavior, encephalopathy).

Laboratory findings:

- a. Prolongation of prothrombin time (not responding to Vit. K).
- b. Falling of serum albumin.
- c. Raised serum ammonia.

B. Aplastic anemia:

- i. Is a very rare complication it is transient but may be fatal.
- ii. It is due to bone marrow depression.
- iii. Death is usually due to sepsis infection due to depressed immunity.

C. Cholestasis:

The patient becomes intensely pruritic and jaundiced. It is due to hepatocyte edema which may cause element of obstruction.

D. Relapsing (biphasic) hepatitis:**Treatment:**

1. Most children are managed at home except if liver cell failure is suspected.
2. There is no specific therapy for acute viral hepatitis.
3. Balanced diet with low fat intake should be given.

Prevention:

- **General measures:** Hygienic measures: hand washing & sterilization.
- **Immunoprophylaxis:**

Passive: Human immune serum globulin (ISG): Before exposure (travelers to endemic areas) or after exposure (household & close contacts); Dose: 0.02 ml/kg within 2 weeks of exposure.

Active: Highly immunogenic, formaldehyde inactivated HAV vaccine given to high-risk children and travelers to endemic areas.

Dose: children over 2 years: 3-dose regimen (0, 1, 6 months interval) I.M.

Hepatitis B

Etiology and epidemiology:

Causative organism	Hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus. HBV is composed of 3 antigens: surface (HBsAg), core (HBcAg) and envelope (HbeAg).
Route of spread	HBV has been found in almost all body secretions, but only blood, serum, semen and vaginal secretions have been shown to be infectious. HBV is transmitted parenterally by needle and intravenous equipment, perinatally, unscreened blood products and sexually.
Source	HBsAg positive family member or other close contacts, drug abusers, homosexuals, hemodialysis patients. Blood products, particularly clotting factor concentrates. Medical personnel and institutionalized children are susceptible.

Mode of transmission	<u>Perinatal transmission:</u> From infected HBsAg positive mother to infants (10-40%) during delivery. Risk of infection increases to 70-90% if the mother is also HbeAg positive. Chronic hepatitis and chronic carrier state develop in >90% of infected infants. <u>Parenteral:</u> In patient receiving transfusion of contaminated blood or blood products, renal dialysis, dental care and through contaminated syringes and needles. <u>Child to child transmission:</u> It may occur through biting of insects, ear perforation, drooling and shared chewing gums. Although HBV was detected in breast milk of infected mother there is no role of breast milk to transmit the infection.

Clinical picture:

Incubation period: 30-180 days (mean 90 days). Many cases are asymptomatic. Symptomatic cases with jaundice occur in 25% of patients.

A. **Prodromal phase:** lasts for 2-3 weeks

- FAHM + nausea.
- Serum sickness-like illness: in a few children
- Fever, abdominal pain, arthralgia, pruritic urticarial or maculopapular skin rash.
- Papular acrodermatitis: erythematous papular eruption on face and extremities and lymphadenopathy.

B. **Icteric phase:**

- lasts from 4-6 weeks. Jaundice, hepatomegaly and splenomegaly.

Laboratory investigations:

- Anticore antibodies appear in the serum after 4 weeks and followed by antisurface antibodies (HBs Ab).

Complications:

1- **Fulminant hepatitis:**

It occurs more frequently with HBV than other viruses (1%). Risk increases when there is co-infection or super infection with hepatitis D virus. Mortality is 70%.

2- Chronic hepatitis:

This develops in >90% of neonates and 10-20% in older children.

Types: chronic persistent and chronic active hepatitis. Chronic hepatitis may progress to cirrhosis and hepatocellular carcinoma.

Treatment:

- 1- Supportive treatment.
- 2- Interferon- α -2b is useful for treatment of children with recent HBV infection and active viral replication (25-40% recovery rate). However, it is less successful in children with long-standing HBV infection.
- 3- Liver transplantation is used in end stage liver failure (ESLF) caused by HBV infection.

Prevention:

A. General measures:

- Screening for HBV of blood and plasma-derived products.
- Use of disposable needles, sterilization of equipments and safe handling of all clinical specimens.

B. Immunoprophylaxis:

a) Passive:

- Hepatitis B immune globulin (HBIG) containing high titers of anti-HBs given at a dose of 0.04-0.06 ml/kg as early as possible or after exposure for household and sexual contacts and perinatal exposure.

b) Active:

- Recombinant yeast-derived vaccines (Recombivax HB, Engerix B). A highly immunogenic effective and safe vaccine.
- **Indications:** Universal infant immunization and Children.
- **Dose:** three IM dose (initial injection, repeated 1 and 6 months later).
- Neonates of HBs Ag-positive mother should receive HBIG (0.5 ml) + HB vaccine (5ug) IM within 12 hours of birth and repeated at 1 and 6 months.

Prognosis:

- i. Recovery may be complete.
- ii. The child may remain as an asymptomatic carrier.
- iii. Or chronic patient for months or years.

Hepatitis C

Etiology and epidemiology:

Causative organism	HCV is a small, lipid-enveloped single stranded RNA virus
Route of spread	Parenteral.
Source	HCV positive patient, drug abusers, hemodialysis. Contaminated blood products, particularly clotting factor concentrates. Medical personnel and institutionalized children are susceptible.
Mode of transmission	i) Intravenous drug use 40%. ii) Transfusion of blood and blood products 10%. iii) Occupational and sexual exposure 10%. v) Perinatal transmission is uncommon. N.B. Breast-feeding does not transmit HCV.

Clinical picture:

Incubation period: 2 weeks - 6 months (average 7 weeks). Most cases are symptomatic, Jaundice occurs in 20% of those infected. Acute HCV is usually mild, and course is more indolent:

1. **Preicteric phase:** (FAHM) + nausea, vomiting and abdominal pain.
2. **Icteric phase:** jaundice and dark urine.

Laboratory investigations:

- **Serum transaminases:** SGPT and SGOT are moderately elevated and fluctuate for long time.
- **Serologic tests:** Detection of anti-HCV: by enzyme -linked immunoassay (ELISA-2) and recombinant immuno Blot assay (RIBA) (confirmatory) / Positive by 2-4 weeks post infection.
- **Detection and quantitative measurement** of HCV RNA: by polymerase chain reaction (PCR) positive by 1-3 weeks after exposure.

Complications:

1. **Fulminant hepatitis:** rare - mortality 90%.
2. **Chronic hepatitis:** occurs in 70% of cases. Half of those cases develop cirrhosis.
3. **Hepatocellular carcinoma** may occur.
4. **Extrahepatic complications:** Aplastic anemia, pancreatitis and glomerulonephritis.

Prevention:

- **Screening** of blood donors for Anti HCV, Use of disposable needles, and sterilization of equipments and safe handling of all clinical specimens.
- **Immunoprophylaxis:** Neither passive nor active immunization against HCV is

currently available.

- Children with HCV and their household contacts should be **vaccinated against hepatitis A and B virus** to prevent worsening or catching of liver disease. There is no need to prevent children with HCV infection from attending daycare.
- **Breastfeeding** is not contraindicated for mothers with HCV infection.

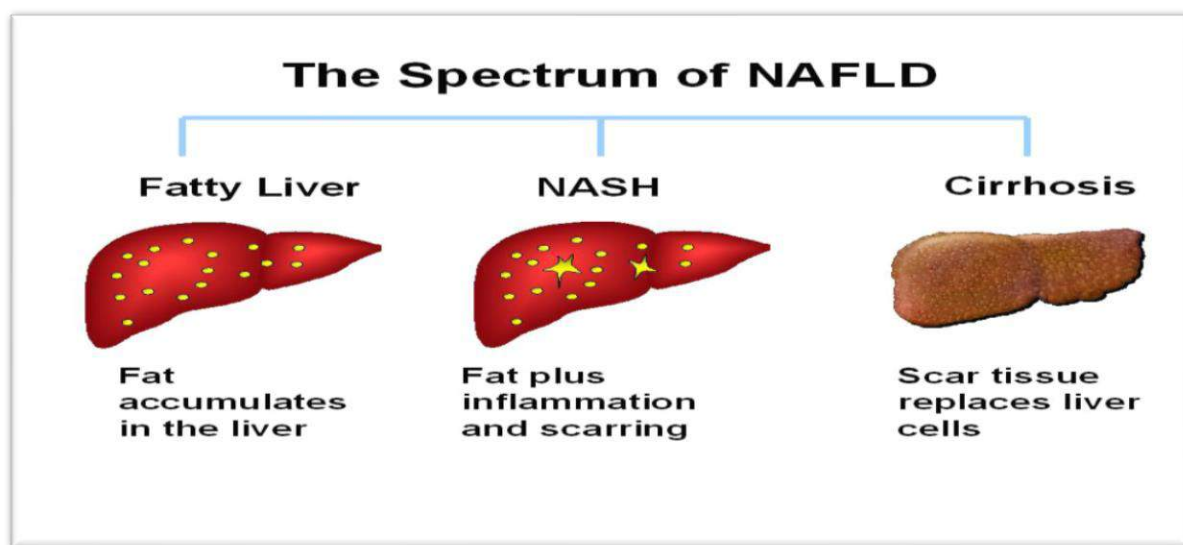
Treatment:

- The antiviral therapy (peginterferon–ribavirin) is considered of historical interest nowadays due development of oral new treatment options that include several potent oral directly-acting antiviral drugs (DAAs) such as (sofosbuvir/daclatasvir, sofosbuvir /ledipasvir or sofosbuvir/velpatasvir combined oral therapy ± ribavirin) with great success in adults.
- Recently (on April 7, 2017), the U.S. Food and Drug Administration (FDA) approved the first DAAs for children that included sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni) to treat HCV in children and adolescents aged 12 years and older or weighing at least 35 kilograms. The adult fixed-dose of ledipasvir [90 mg] /sofosbuvir [400mg] was used for in the adolescents' age group.
- Similarly, giving half the adult fixed-dose of ledipasvir/ sofosbuvir, 45 mg/200 mg, to children ages 6–11 resulted in comparable plasma exposure of ledipasvir, sofosbuvir, as in adults, without any severe adverse events or laboratory abnormalities and FDA approval of this dose for this age group of children is expected in the near future.

Non-Alcoholic Fatty Liver Disease (NAFLD)

Definition and spectrum:

- Paralleling the epidemic of childhood obesity, pediatric NAFLD has emerged as a growing global health problem worldwide and is considered the most common cause of CLD in pediatrics nowadays.
- It can range from fatty liver alone (steatosis) to a triad of fatty infiltration, inflammation, and fibrosis that is called nonalcoholic steatohepatitis (NASH) that resembles alcoholic liver disease but occurs with no exposure to alcohol.
- The pathogenesis of NAFLD is multifactorial; it is strongly associated with obesity/overweight and insulin resistance. Also, in addition to environmental factors, there is strong genetic predisposition to NAFLD & NASH.



Prevalence:

Liver histology from autopsy data suggest that 10% of children and 38% of obese children aged 2-18 yrs. might have NAFLD.

Risk factors:

include children with overweight or central obesity, insulin resistance, type 2 diabetes mellitus, male gender, hypertriglyceridemia. The risk is higher in white or Hispanic ethnicity, but lower in African American children.

Clinical picture and course:

Many patients are asymptomatic. Enlarged liver can be present in a minority of cases. Hepatic steatosis alone may be benign, but up to a quarter of patients with NASH can develop progressive fibrosis with resultant cirrhosis and portal hypertension with its sequelae.

Diagnosis:

- All other causes of CLD and steatosis must be excluded firstly.
- Elevated serum aminotransferase levels are not sensitive or specific markers for NAFLD. A normal serum ALT level is present in 21-23% of pediatric patients with NAFLD.
- Imaging procedures: Although ultrasonography, MRI and MRS can detect most NAFLD cases, no current imaging modalities can distinguish between steatosis and NASH.
- Liver stiffness measurement by elastography (FibroScan) can be used to predict liver fibrosis stages in cases with NASH.
- A liver biopsy may be required for definitive diagnosis especially for those with persistently elevated liver enzymes.

Treatment:

- Lifestyle modification (low calorie diet and exercise) is the main line of therapy.
- Some antioxidants like vitamin E and vitamin C may provide additional benefit to the efficacy of this line in improving liver histology and biochemical abnormalities.
- Metformin has produced mixed results in the treatment of NAFLD.

Cholestasis in infants and children

Definition:

Reduction in bile flow with retention of substances normally excreted in the bile (e.g. bilirubin, bile acids & cholesterol) with histopathologic features reflecting nature & degree of disturbances.

Mechanisms of cholestasis:

A. **Hepatocellular cholestasis:** Where an impairment of bile formation occurs.

B. **Obstructive cholestasis:** Where impedance to bile flow occurs after it is formed.

Causes:

I. Extrahepatic biliary obstruction:

1. Extrahepatic biliary atresia (EHBA).
2. Choledochal cyst.
3. Spontaneous rupture of the bile duct.
4. Extrinsic compression.

II. Intrahepatic biliary hypoplasia or paucity of interlobar bile ducts (PIBD):

1. Alagille's syndrome.
2. Non syndromic ductal paucity.

III. Hepatocellular disease:

1. Neonatal hepatitis.
2. α 1antitrypsin deficiency, Cystic fibrosis.
3. Inborn errors of bile acid synthesis.
4. Drug induced cholestasis.
5. Total parenteral nutrition.
6. Progressive familial intraheptic cholestasis (PFIC).
7. Infections: TORSCH, Sepsis.

Approximately 75% of all cases of neonatal cholestasis are due to EHBA or neonatal hepatitis.

Clinical manifestations and consequences of cholestasis:

A- Early cholestasis:

I. Retention / Regurgitation of the different components of the bile:

- Conjugated Bilirubin → Jaundice with changes in color of urine and or stool.
- Bile acid → Pruritus, Bradycardia.
- Cholesterol → Xanthomatosis.

II. Decreased bile salts in intestine:

- -Malabsorption of long-chain triglycerides → Growth retardation, diarrhea / steatorrhea
- -Vit.A malabsorption → Thick skin, Night blindness.
- -Vit.D malabsorption → Metabolic bone disease (Osteoporosis, rickets).
- -Vit.E malabsorption → Hemolytic anemia, Neuromuscular degeneration.
- -Deficiencies of Vit.K-dependent coagulation factors → bleeding tendency.

B-Late or complicated cholestasis:

1. Biliary liver cirrhosis.
2. Portal hypertension with development of gastroesophageal varices.
3. Liver cell failure.

Diagnosis of Cholestasis

- The initial step in identification of cholestasis is the finding that the conjugated (direct) bilirubin is more than 20% of the significantly elevated level of total bilirubin (conjugated hyperbilirubinemia).
- The next step: Is the early recognition of the treatable medical or surgical causes of cholestasis.

- A. Medical causes** (sepsis, endocrinopathy e.g. hypothyroidism or panhypopituitarism, or galactosemia).
- B. Surgical causes (e.g.** extrahepatic biliary atresia as early surgical correction of the lesion within the first 2 months after birth will save the liver cells from early cirrhosis.

Investigations include:

- I. Laboratory procedures:** Serum bilirubin fractionation, Hepatic synthetic function (albumin, coagulation profile), Liver enzymes (ALT, AST, ALP, GGT), Exam of aspirated duodenal fluid for presence of bile, TORSCH screening, Sepsis work-up, Hepatitis markers, Urine/serum bile acids measurement, Urine/serum amino acids measurement and urine reducing substances, α 1-antitrypsin phenotype, Thyroxine and TSH, Sweat chloride/mutation analysis,.
- II. Imaging procedures:** -Abd Ultrasonography -MRI of liver & biliary ducts (MRCP).
- III. Hepatobiliary scintigraphy (HIDA scan).**
- IV. Liver biopsy.**
- V. Intraoperative cholangiography (IOC) for suspected cases of EHBO only.**

Management of infantile cholestasis:

A. Surgical Correction for EHBO:

- a. **Correctable lesions** (i.e. distal atresia with patent proximal portion of the extra hepatic duct): Direct drainage of the biliary system into the intestine (hepatico-jejunostomy).
- b. **Non-correctable lesions** (i.e. No patent extra hepatic bile duct): Hepatic portoenterostomy (Kasai procedure) is performed before the age of 2 months before development of liver cirrhosis.

B. Medical Treatment of Cholestasis:

- a. Adequate calories for maintenance of good nutrition.
- b. Malnutrition due to malabsorption of dietary long-chain triglyceride:
Replace with dietary formula or supplements containing readily absorbed medium-chain triglycerides.
- c. Large doses of fat-soluble vitamins (A, D, E and K) to correct malabsorption of these vitamins.
- d. Retention of biliary constituents such as bile acids and cholesterol (itch/xanthomata): Administer choleretics such as ursodeoxycholic acid (5-10 mg/kg/day) or phenobarbital or bile acid binders (cholestyramine 8-16 g/day).

C. Liver transplantation: if end-stage liver failure occurs.

Liver Cirrhosis

Definition:

It implies chronic irreversible liver damage defined histologically as a diffuse hepatic process characterized by necrosis of hepatocytes and fibrosis of whatever etiology with the conversion of normal liver architecture into malfunctioning regenerating nodules. The progression of liver injury to cirrhosis may occur over weeks to years. It results in disturbances of the normal lobular and vascular pattern of the liver. It may be compensated or de compensated. Also, It may be active or in active.

Causes of cirrhosis in childhood:

A. Post-necrotic cirrhosis:

1- Post-hepatic:

- Viral hepatitis (B, C, D).
- Idiopathic neonatal hepatitis.

2- Venous congestion:

- Tricuspid regurgitation/right heart failure (cardiac cirrhosis)
- Budd-Chiari syndrome
- Hepatic veno-occlusive disease

3- Toxins:

- Drug induced hepatitis: actinomycin D, methotrexate amiodarone.
- Alfatoxin.
- Chronic alcoholism.

B. Biliary cirrhosis:

- Extrahepatic biliary atresia, Intrahepatic biliary hypoplasia, Cystic fibrosis, Biliary stenosis, Familial intrahepatic cholestasis, Primary sclerosing cholangitis, Choledochal cyst.

C. Genetic or metabolic causes:

- Non-alcoholic steatohepatitis, α 1-Antitrypsin deficiency, Wilson disease, Galactosemia, some glycogen storage diseases, hemochromatosis, Gaucher disease, Niemann-Pick disease, Sickle cell anemia, Thalassemia, etc.

D. Cryptogenic cirrhosis

Pathology:

Regardless of etiology, in all cirrhotic patients, the triad of liver cell necrosis, regenerating nodules and fibrosis is present.

Pathophysiologic consequences of cirrhosis:

A. Alteration of hepatic blood flow: leading to portal hypertension.

B. Reduction in functional liver cell mass:

- a. **Decreased synthesis:** Albumin, coagulation proteins, other proteins.
- b. **Decreased detoxification and conjugation of:** bilirubin, ammonia, methyl mercaptan, drugs and hormones.

Investigations of cirrhosis:

- 1) **Laboratory Investigations:** Liver function tests that may be entirely normal in a patient with cirrhosis (inactive). CBC, Urea and creatinine.
- 2) **Imaging Investigations:** ultrasound with Doppler, FibroScan, CT, MRI.
- 3) **Upper GIT endoscopy** to diagnose varices.
- 4) **Liver biopsy.**
- 5) **Etiological investigations:**
 - Serological tests for viral hepatitis.
 - Serum immunological tests for autoimmune chronic active hepatitis.
 - Special tests for metabolic disorders: Wilson's disease, Alpha 1 antitrypsin deficiency, hemochromatosis, etc.

Treatment of cirrhosis

A. Supportive therapy:

- Provide sufficient calories, proteins, essential fatty acids, minerals, trace elements and vitamins for growth and normal activities.
- Proteins: High biological value protein. The protein is not restricted except with clinical and biochemical evidence of hepato-cellular failure.
- Vitamin supplements: Daily requirements of both water-soluble and fat-soluble vitamins should be taken.

B. Management of complications:

- Hepatic encephalopathy, Ascites, Bleeding varices, Hypersplenism.

Portal Hypertension (PH)

Definition:

PH exists when pressure in portal venous system rises above 10-12 mmHg.

Pathology:

- Increased vascular resistance caused by obstruction of portal blood flow leads to hemodynamic changes.
- Increased COP with decreased splanchnic arteriolar vasodilatation leads to increased portal inflow resulting in increased portal pressure (PH).
- Increased portal blood flow and resistance lead to formation of porto-systemic collaterals that divert portal blood flow to the systemic circulation, bypassing the liver.

Etiological classification:

Causes of PH are classified according to the anatomic location of the disease:

A. Pre-hepatic obstruction:

1) Portal vein occlusion:

- Thrombosis (umbilical sepsis, umbilical venous catheterization in the neonate).
- Extrinsic compression.

2) Splenic vein thrombosis: This might be a congenital anomaly or acquired.

B. Hepatic obstruction:

- Cirrhosis: post-necrotic, biliary, cardiac, autoimmune, drug-induced, cryptogenic.
- Schistosomiasis.
- Congenital hepatic fibrosis.

- Veno-occlusive disease.

C. Post-hepatic obstruction:

- Budd-chiari syndrome.
- Right ventricular failure.
- Constrictive pericarditis.

Clinical picture:

- 1) Features of the underlying hepatic disease.
- 2) GIT bleeding: hematemesis or melena.
- 3) Splenomegaly with features of hypersplenism (low Hb concentration, low total white count and thrombocytopenia).
- 4) Liver size is normal in pre-hepatic obstruction whereas in hepatic and post-hepatic obstruction the liver may be enlarged, normal-sized or shrunken depending on the stage of the underlying disease.
- 5) Dilated cutaneous collateral vessels.
- 6) Ascites.
- 7) Failure to thrive due to malabsorption and porto-systemic shunts.
- 8) Hepatic encephalopathy due to porto-systemic shunts.

Diagnosis:

A. Non-Invasive Investigations of PH (routinely done):

1. **Initial Lab Investigations:** full blood count, liver and renal function tests.
2. **Ultrasonography with Doppler:** to assess liver size, echogenicity, intrahepatic bile ducts, Patency and diameter of portal vein, velocity and direction of blood flow, Extent of collaterals, splenomegaly and ascites.
3. Liver stiffness measurement by ultrasound-based elastography (**FibroScan**) or by **MRI- based elastography** to predict liver fibrosis stages and the presence of varices.

4. **Endoscopy of upper GIT:** to detect esophageal varices, gastric varices, peptic ulcers, PH gastropathy.

B. Invasive Measurements of PH (not-routinely done).

- Operative portal vein measurement.
- Percutaneous transhepatic measurement.
- Transjugular measurement.
- Hepatic vein catheterization.
- Intrasplenic measurement.

Treatment:

1. **Gastrointestinal bleeding:** it requires emergency treatment (Resuscitation of the patient followed by urgent endoscopic variceal sclerotherapy or endoscopic variceal band ligation).
2. **Hepatic encephalopathy:** Nasogastric administration of neomycin or lactulose, I.V vitamin K, Restriction of protein intake and control of any triggering factors.
3. **Surgical procedures in portal hypertension:**
 - Porto-systemic shunts (selective or non-selective).
 - Transjugular intrahepatic portosystemic shunting (TIPS).
 - Liver transplantation: if ESLF occurs.

Ascites

Definition:

Ascites is accumulation of fluid in the peritoneal cavity.

Etiology:

Transudate	Heart failure, Nephrotic syndrome, Liver cirrhosis, Constrictive pericarditis.
Exudate	Peritonitis, Tuberculosis, Malignancy e.g. neuroblastoma, Polyserositis.
Haemorrhagic	Trauma, Bleeding tendency, Malignancy.
Biliary	Spontaneous perforation of common bile duct, Post-operative, Congenital obstruction.
Chylous	Trauma, Malignant infiltration, Thoracic duct obstruction.

Pathogenesis of ascites in hepatic cirrhosis:

Two main factors in liver disease favor the development of ascites:

- a. **Hypoalbuminemia:** reduced albumin synthesis lowers plasma osmotic pressure, allowing the transfer of fluid into the tissue spaces and hence into the peritoneal cavity.
- b. **Intra-hepatic vascular obstruction** leads to increased portal venous pressure.

The above mechanisms lead to

- 1) **Accumulation of fluid in peritoneal cavity (ascites)**, this may lead to reduced plasma volume and so reduced glomerular filtration.
- 2) **This results in increased aldosterone** and retention of sodium and water leads more ascites.
- 3) **Increased hepatic lymph formation** due to the increase in intra-sinusoidal pressure and this adds to the ascites.

Clinical picture:

Ascites may appear insidiously or may develop suddenly when hepatocellular function is reduced e.g. by hemorrhage, shock and infection.

The symptoms of ascites include: Abdominal distension, abdominal pain and discomfort.

Clinically ascites can be detected by the following methods:

- a) Abdominal percussion in knee- chest position can detect minimal ascites, but abdominal ultrasound is easy and accurate than this uncomfortable test.
- b) Shifting dullness which can detect moderate ascites.
- c) Transmitted thrill in cases of massive ascites.

Differential diagnosis:

Ascites should be differentiated from:

- Gases.
- Obesity.
- Abdominal cysts.
- Full urinary bladder.

Ascites of liver cirrhosis should be differentiated from other causes of ascites:

A - Tuberculous ascites

B - Malignant ascites:

- There may be symptoms and localizing signs due to primary tumor.
- The ascetic fluid is exudates, may be sanguineous and may contain malignant cells.

C - Constrictive pericarditis:

- Diagnostic points include the very high jugular venous pressure and the paradoxical pulse.

- The radiological demonstration of a calcified pericardium and characteristic ECG and echocardiographic changes.

Diagnosis:

- **Abdominal ultrasonography** to detect the degree of ascites.
- **Ascetic fluid tabbing** for chemical & cytological examination.
- **Liver function tests:** Usually show impaired levels of transaminases, Low plasma albumin.

Treatment:

- 1) Sodium restriction.
- 2) Diuretics: used cautiously because they may lead to hypovolemia. Start with spironolactone, but furosemide can be used in combination with spironolactone in severe cases.
- 3) IV Albumin infusion + IV Furosemide $\pm$ therapeutic paracentesis for refractory symptomatic severe cases with ascites.

Causes of Hepatomegaly in Children

I. Inflammation/Infections:

a) Infections:

- Viral (hepatitis A, B, C, D, E, Cytomegalovirus, Epstein-Barr virus, etc.)
- Bacterial (sepsis, pyogenic liver abscess, miliary TB, Brucellosis, typhoid fever)
- Parasitic (Schistosomiasis, malaria, hepatic amebiasis, hydatid cyst, visceral larva migrans, Fasciola hepatica, etc.)

b) Toxins

c) Drugs

d) Idiopathic neonatal hepatitis

e) Autoimmune liver disease

f) Kupffer cell hyperplasia

II. Inappropriate Storage

a) Glycogen: Glycogen storage disease, diabetes mellitus, parenteral nutrition.

b) Lipids: Niemann-Pick disease, Gaucher disease, Wolman disease

c) Fat: Fatty acid oxidation defect, obesity, diabetes mellitus, parenteral nutrition, mucopolysaccharidoses

d) Metals:

- Copper: Wilson disease
- Iron: hemochromatosis

e) Abnormal proteins: Alpha-1-antitrypsin deficiency

III. Infiltration

a) Primary neoplastic tumors: Hepatoblastoma/Hepatocellular carcinoma

- b) *Primary non-neoplastic tumors:*** Hemangioma, hemangioendothelioma, teratoma, focal nodular hyperplasia
- c) *Metastatic or disseminated tumors:*** Leukemia, lymphoma, neuroblastoma, histiocytosis
- d) *Cysts:*** Parasitic cyst, choledochal cyst, polycystic liver disease
- e) *Hemophagocytic syndromes***
- f) *Extramedullary hematopoiesis***

IV. Vascular Congestion

- a) *Suprahepatic***
 - Congestive heart failure, Restrictive pericardial disease, Suprahepatic web
 - Hepatic vein thrombosis (Budd-Chiari syndrome)
- b) *Intrahepatic***
 - Veno-occlusive disease

V. Biliary Obstruction

- a) *Cholelithiasis***
- b) *Choledochal cyst***
- c) *Biliary atresia***
- d) *Tumors (Hepatic, Biliary, Pancreatic, Duodenal)***

Practice Questions

(Choose one correct answer)

- 1- Regarding hepatitis A, which of the following is true ?
 - a) it is complicated by liver cirrhosis in few cases.
 - b) chronicity is a common complication.
 - c) acute fulminant hepatitis is rare.
 - d) it is usually more severe in children than in adults.

- 2- Neonates of HBs-Ag positive mother should receive :
 - a) hepatitis B vaccine.
 - b) hepatitis B immunoglobulin.
 - c) both of them.
 - d) none of them.

- 3- The following are modes of transmission of hepatitis C EXCEPT :
 - a) intravenous drug use.
 - b) contaminated food and water.
 - c) occupational and sexual exposure.
 - d) blood transfusion.

- 4- Which statement is false in biliary atresia :
 - a) onset of jaundice is usually noticed in the 2nd week of life.
 - b) decreased serum albumin and elevated serum conjugated bilirubin.
 - c) increased alkaline phosphatase and prolonged prothrombin time.
 - d) dark stool and dark urine.

- 5- Which of the following is not a common cause of ascites ?
 - a) congestive heart failure.
 - b) kwashiorkor.
 - c) nephrotic syndrome.
 - d) veno-occlusive disease.



Chapter 12 Respiratory Disorders

Objectives:

1. Describe the clinical features of common upper and lower respiratory problems in pediatrics.
2. Understand the underlying etiological factors in each condition.
3. Correlates between the clinical presentations and the pathogenesis of each disorder
4. Enumerate findings in common investigations in different diseases
5. Formulate a management plan for respiratory disorders.

Contents:

1. Tonsillo – pharyngitis
2. Laryngeal obstruction
3. Acute bronchiolitis
4. Bronchial asthma
5. Pneumonias
6. Pleurisy
7. Pleural effusion
8. Pneumothorax
9. Primary pulmonary tuberculosis

Tonsillo – Pharyngitis

It is the acute inflammation of the pharynx and the tonsils.

Etiology:

Acute pharyngitis is not common during the first year of life, and peaks by 4-7 years.

1. Viral in $\geq 80\%$ e.g., adenoviruses, rhinoviruses and enteroviruses.
2. Bacterial: most common is group A β -hemolytic streptococcus. Rarely other bacteria e.g., pneumococci, Staphylococci, H. influenza. Diphtheria should not be forgotten.

Clinical picture:

1. Fever, sore throat, malaise, anorexia, cough, pharyngeal congestion and exudates and cervical lymphadenopathy are features common in both viral and streptococcal pharyngitis.
2. In viral cases conjunctivitis, rhinitis, and hoarseness are common. The course is 1-5 days.
3. In streptococcal cases pharyngeal and tonsillar congestion and exudate are more marked, and tonsils are enlarged with yellow beads of pus may be seen. A pseudo-membrane may cover the tonsils. Breath smells offensive. The course is 1-2 weeks.

Investigations:

1. In both viral and bacterial cases there is polymorph leukocytosis.
2. Streptococcal infection can be diagnosed by:
 - a. Rapid antigen detection test of throat swabs (needs only 2 hours).
 - b. Bacterial culture of throat swab, this needs two days.

Complications:

1. Bacterial otitis media or sinusitis as well as mesenteric adenitis may follow viral or streptococcal pharyngitis.
2. Streptococcal pharyngitis may be complicated by abscess of the cervical lymph nodes or by peritonsillar abscess.
3. Sequelae of streptococcal pharyngitis:
 - a. Rheumatic fever.
 - b. Acute glomerulonephritis

Differential diagnosis:



- A. The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens.
- B. This intense erythema, seen in association with acute tonsillar enlargement and palatal petechiae, is highly suggestive of group A β -streptococcal infection, though other pathogens can produce these findings.
- C. This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection.
- D. When a membrane is formed on the tonsils, diphtheria should be confirmed or excluded. If doubt exists, the case should be treated as diphtheria.

Treatment:

Symptomatic:

1. Rest.
2. Antipyretics and analgesics. Paracetamol 50 mg/kg. / day or ibuprofen 20 mg/kg/day.
3. Diet: milk pudding, fruit juice and warm fluids. Then give small amounts of other foods as appetite improves.

Antibiotics:

If streptococcal etiology is confirmed or highly probable give a ten days course of penicillin or erythromycin.

- Penicillin:

- 1) Oral penicillin for the first 4 hours to test for penicillin allergy. Start with 5 mg, double the dose every ½ hour, and give 7 doses. If no allergic reaction was observed start I.M penicillin.
- 2) I.M. penicillin: There are several methods for giving i.m penicillin. Any method can be applied.

A practical method is as follows:

- i. Start with three days course of benzyl penicillin - procaine penicillin mixture. Dose = 50-100 thousand units / kg /day, divided.
- ii. Then give a single I.M injection of benzathine penicillin 300,000 units for ages 2-5 years, 600,000 units for ages 5-8 years, 1,200,000 units if older than 8years.

- **Other antibiotics:**

- 1) Amoxicillin once-daily dosing (750 mg fixed dose or 50 mg/kg, maximum 1 g) given orally for 10 days OR amoxicillin plus clavulanic acid for 10 days
- 2) Erythromycin: If the child is allergic to penicillin, give erythromycin in a dose of 50 mg/kg per day for 10 days. The addition of sulphonamide potentiates the action of erythromycin.
- 3) Azithromycin: 12 mg/kg/day as single dose for at least 5 days.
- 4) Cephalosporin (cephalexin or cefadroxil) for 10 days.

NB. Cefotaxime should not be prescribed for patients with acute tonsillopharyngitis, because it is ineffective, is costly, and predispose to bacterial resistance to cefotaxime.

Prevention:

- 1) Avoid overcrowded places and school class.
- 2) Avoid contact with patients.
- 3) In patients with rheumatic fever, benzathine penicillin injection is given to prevent strept. pharyngitis and rheumatic recurrences. The above doses of benzathine penicillin are given every two weeks till the age of 20 ys or older.
- 4) Removal of the tonsils does not reduce the frequency or complications of pharyngitis.

Indications of tonsillectomy:

1. Severe obstruction of airways
2. Tonsillitis more than six times in the last year.
3. Chronic tonsillitis e.g. chronic enlargement of tonsillar lymph nodes or chronic hyperemia of anterior pillars.
4. Peritonsillar abscess.

Laryngeal Obstruction

Manifestations:

A- Stridor: This is a harsh, crowing, inspiratory noise.

1. ***In mild obstruction***, stridor is absent during sleep or rest and appears only after disturbing the infant, crying or on effort.
2. ***Moderate and severe degrees of obstruction*** are dangerous and are characterized by:
 - a) Stridor is loud, heard during rest, and may be heard also during expiration.
 - b) Inspiratory retractions; suprasternal, supraclavicular, intercostal and subcostal.
 - c) Restricted expansion of the chest during inspiration.
 - d) Increasing respiratory and heart rates.
 - e) Restlessness, passing to lethargy (CNS hypoxia).
 - f) Cyanosis is an alarming sign.
 - g) Reduced arterial O₂ and increased arterial CO₂ tensions.
3. If laryngeal ***obstruction is nearly complete***, stridor may not be heard.

B- Other manifestations of laryngeal disease: These may be present in addition to stridor.

1. Voice changes e.g., hoarseness, aphonia.
2. Croupy cough which has a brassy or barking quality.

C. Fever: in cases caused by viral or bacterial infection.

Etiology:

A- Congenital:

- a- Congenital laryngeal obstruction (laryngomalacia).
- b- Other causes, as vascular ring.

B- Acquired:

- a- Infections: viral, and bacterial (this is called croup).
- b- Foreign body aspiration.
- c- Spasm: Acute spasmodic laryngitis (midnight croup), and tetany (laryngismus stridulosa).
- d- Trauma: natal, postnatal, surgical
- e- Laryngeal tumors: polyps, others.

Laryngeal obstruction is more common in infants and young children due to small size of larynx, soft cartilage, loose submucosa and rich nerve supply.

Congenital Laryngeal Stridor (Laryngomalacia)

- The onset is after the first few days of life and more common in males.
- It is caused by abnormal flaccidity of the laryngeal cartilages of the epiglottis.
- Most cases are mild, the stridor may not be heard while the infant is asleep or at rest and appears when the infant lies on back or is disturbed.
- More severe cases may result in feeding difficulties e.g., frequent choking and mild aspiration.
- Spontaneous cure within the first one or two years of life. Some children continue to have stridor with respiratory infections.

Differential Diagnosis:

- Congenital web or polyp, birth trauma to larynx, aspiration of debris, during birth, neonatal tetany, macroglossia, hypoplasia of the mandible, and congenital goiter.

Treatment:

Prone position, slow feeding, 0.3% of affected infants need tracheostomy.

Laryngeal Foreign Body

- Age: common between 2-4years.
- History of foreign body aspiration is usually present.
- This is associated with choking, hoarseness, croup and croupy cough.
- The foreign body may be vegetable or non-vegetable. It may be radio-opaque or translucent.
- Bronchoscopy is needed for diagnosis and removal of the foreign body.

Acute Viral Laryngitis

Age: 3 months – 5 years,

More common in males, and in cold seasons.

Etiology:

About $\frac{3}{4}$ of cases are caused by parainfluenza viruses, and the remaining $\frac{1}{4}$ by adenoviruses, respiratory syncytial virus, influenza measles, herpetic, ...etc. Positive family history in 15% of cases. It tends to recur in the same child.

Clinical picture:

- Gradual onset and course.
- 1-2 days of mild nasopharyngitis followed by hoarseness and croupy cough.
- Laryngeal obstruction is mild except in young infants in whom it may be severe.
- Mild to moderate fever may be present.
- The throat is inflamed and red (viral pharyngitis).

Viral laryngotracheobronchitis

A common disease.

Etiology:

As viral laryngitis, the infection involves, in addition, the trachea, bronchi, and bronchioles.

Clinical Picture:

1. The patient has moderate to high fever.
2. Signs of laryngitis and laryngeal obstruction.
3. Signs of bronchial obstruction e.g. wheezy respiration.
4. Dyspnea is marked (inspiratory and expiratory).
5. Chest examination reveals rhonchi and crepitations.
6. Course is prolonged for 1-2 weeks.
7. Secondary bacterial infection may occur.
8. Recurrence occurs in young children.



Radiograph of an airway of a patient with croup, showing typical subglottic narrowing (steeple sign).

Acute Bacterial Laryngitis

- This occurs as a complication of streptococcal pharyngitis tonsillitis or scarlet fever.
- It combines the clinical picture of the original streptococcal infection together with the signs of laryngitis and mild croup.

Acute Epiglottitis

Age: 2-7 years.

More common in males.

Etiology:

Bacterial, almost always *Hemophilus influenzae* bacillus type b (Hib). Rarely other bacteria e.g., streptococci, pneumococci, or staphylococci.

Clinical picture:

- Sudden onset and rapidly progressive signs of severe laryngeal obstruction.
- Temperature is high and Toxemia is marked.
- Posture of the patient is useful in diagnosis. The young child held by his mother, sits or lies with extended neck. The older child sits tripod, leaning forward with open drooling mouth and slightly protruded tongue. Respiratory distress and dyspnea increase in the supine position.
- Dysphagia is present.
- Severe cases are fatal.
- An ENT specialist should be called urgently if epiglottitis is suspected.
- Pharyngeal examination is dangerous because patients may get fatal laryngeal obstruction and cardiac arrest as a reflex following pharyngeal exam or even head titling. It shows copious mucus and saliva, and large swollen red epiglottis.
- Lateral neck X-ray shows the swollen epiglottis.
- Blood picture shows PMN leukocytosis.

A physician skilled in airway management and use of intubation equipment should always accompany patients with suspected epiglottitis.



Lateral roentgenogram of the upper airway reveals the swollen epiglottis (Thumb sign).

Diphtheritic Laryngitis

- Most cases are secondary to faucial diphtheria with the characteristic membrane.
- Moderate fever. Moderate toxemia with gray face
- Progressive laryngeal obstruction
- Tonsillar lymph nodes markedly enlarged.
- Almost always there is a history of defective vaccination against diphtheria.

Treatment of infective croup:

- Mild viral or bacterial laryngitis can be treated at home
- Other cases should be hospitalized because of possible need for intubation or tracheotomy.
 1. Hydration: plentiful fluids e.g oral warm sweetened fluids or I.V. infusions.
 2. Analgesic, anti-inflammatory, and antipyretic e.g ibuprofen 20 mg/kg/day.

3. Sedatives should be avoided.
4. Inhalation of hot steam medicated with Tr. Benzoin Co or inhalation of nebulized warm water for 5-15 minutes.
5. This is followed by continued use of warm or cool humidification near the child's head for 2-3 days.
6. Inhalation of 3/1000 solution of epinephrine is useful of laryngotracheobronchitis.
7. Subcutaneous adrenaline, 0.1mg/10kg.
8. Careful observation for need of:
 - a) Oxygen, and
 - b) Digitalis for heart failure.
9. ENT consultation for hospitalized cases.
10. **Tracheostomy or intubation** is needed in all cases of acute epiglottitis and may be in other cases with severe obstruction.

11. Antibiotics:

- a) Erythromycin orally 50-100 mg/kg/day to treat strept. laryngitis and to prevent bacterial superinfection in cases of laryngotracheobronchitis.
 - b) Ampicillin + chloramphenicol or cefotaxime, for ten days to treat acute epiglottitis.
 - c) In cases of laryngeal diphtheria, we give antidiphtheritic serum and penicillin. Antidiphtheretic serum is given in a dose of 50 to 100 thousand units.
12. **Dexamethasone:** Orally or IM may be useful in allergic cases or cases with severe obstruction with a dose of 0.3mg/kg, once.

Acute Spasmodic Laryngitis (Mid-night croup)

- Age: 1-3 years.
- Child goes to bed with mild nasopharyngitis with or without hoarse voice. About midnight he awakens with severe loud croup and struggles for breath.
- The attack subsides spontaneously after a few hours.
- By daytime, he is well except for some hoarseness.
- The next night he may develop a similar but less severe attack.
- The patient is afebrile.
- The condition tends to recur in the same child.
- It reflects the response of the nervous or allergic child to a mild viral laryngitis.

Treatment:

If seen during the attack, inhalation of medicated water vapor from a vaporizer or nebulizer, SC adrenaline and IM dexamethasone.

To prevent the attack on the second or third night:

1. Treat viral nasopharyngitis.
2. The patient is given Promethazine HCl (Phenergan) 0.5 mg/ kg. Before bedtime.

Hypocalcaemic Laryngeal Spasm (Laryngismus stridulosa)

- This occurs as a manifestation of hypocalcemic tetany in Vit. D deficiency rickets.
- The infant usually has manifestations of rickets and there may be carpopedal spasm or tetany.
- Croup occurs by night or early morning.

- It can be precipitated by disturbing the infant or irritation of the larynx.
- Treatment: 5 ml of 10% calcium gluconate solution slowly IV relieves the laryngeal and carpopedal spasm. The usual treatment of rickets is then given.

Acute Tracheobronchitis

Definition:

Acute catarrhal inflammation of the trachea and bronchi.

Etiology:

- i. Most cases occur in association with viral nasopharyngitis and are caused by rhinoviruses and other viruses. Viral tracheobronchitis is also caused by such specific viral infections as influenza, measles and German measles.
- ii. Bacterial cases may be caused by:
 - Pneumococci, and streptococci, on top of viral tracheobronchitis.
 - Primary bacterial infection e.g., scarlet fever, pertussis, diphtheria and typhoid.

Bacterial tracheitis due to staph. aureus presents with severe stridor, high fever, high, toxicity and severe dyspnea with copious, purulent secretions seen below the glottic opening and included in differential diagnosis of acute epiglottitis.

Predisposing Factors:

These include malnutrition, rickets, exposure to cold, allergy, chronic upper respiratory diseases (adenoids, tonsils, and sinuses) passive smoking and heart disease (congestive heart failure)

Clinical Picture:

1. Cough, dry at first, then becomes loose later on. Infants swallow their sputum. Cough may be paroxysmal and distressing.
2. Fever mild to moderate up to 39°C. Significant malaise may be present.
3. Low substernal pain and chest discomfort may be complained of.
4. Dyspnea with or without wheezing occasionally present in infants.
5. Vomiting may occur and may contain swallowed sputum.

Chest Signs:

1. Breath sounds may become harsh.
2. Rhonchi may be heard especially in infants with or without few scattered crepitations.
3. X-ray chest: Free or shows prominent bronchovascular shadows.

Course And Prognosis:

1. The condition gradually subsides within 7-15 days.
2. Complications occur in malnourished or rachitic patients e.g., otitis media, sinusitis, or bronchopneumonia.
3. Recurrent acute bronchitis occurs if predisposing factor is not treated.

Treatment:

1. Bed rest with frequent change of position in infants to facilitate drainage of mucus.
2. Warmth.
3. Adequate fluid intake especially warm fluids.
4. Antipyretic e.g., Paracetamol 50 mg/kg/day, or Ibuprofen 20 mg/kg/day.

5. If cough is distressing and interfering with sleep or feeding a cough suppressant may be prescribed.
6. If bacterial super infection is present an antibiotic is given.
7. Mucolytic e.g., Carbocysteine or Ambroxol syrup (one ml /10 kg) 4 times daily.
8. Expectorant e.g., Syrup Ipecac (1 ml /10kg) 4 times daily.

Acute Bronchiolitis

Definition:

Acute viral infection of the bronchioles during the first two years of life, causing their obstruction.

Etiology:

- Respiratory syncytial virus (RSV) causes more than 50% cases. Other causative viruses include parainfluenza, adenoviruses, human metapneumovirus, other viruses and mycoplasma.
- The source of infection is usually an older family member with mild viral resp. illness.

Season: Winter and early spring

Age: Highest incidence by age 2-10 months, rare below 2months and during the 2nd year of life.

Predisposing factors:

- Subject: male, preterm, narrow airways,
- Environment (preventable): Exposure in day – care or crowded rooms, tobacco passive smoking, non –breast feeding, low socioeconomic state.

Pathology:

1. Diffuse partial bronchiolar obstruction due to bronchial wall infiltration, mucosal edema and luminal debris and mucus.
2. Generalized obstructive emphysema.
3. Scattered areas of collapse and consolidation.

Clinical Picture:

1. Common cold like manifestations of several days, followed by progressive development of mild to severe wheezing dyspnea and cough.
2. There is mild to marked tachypnea, working alae nasi, chest retractions, irritability and feeding becomes difficult.
3. Dehydration, cyanosis and exhaustion may occur in severe cases.
4. Chest exam. shows generalized obstructive emphysema i.e. signs of bronchial obstruction plus signs of emphysema.

Course:

- In mild cases the disease subsides in 1-3 days.
- In severe cases peak of suffering is by the 2nd or 3rd day, then the condition gradually subsides in 3-10 days.
- Recurrence is rare but may occur for another single infection.

Complications:

1. Hypoxia early in the course, proportionate to the degree of tachypnea.
2. Respiratory acidosis also occurs in patients with respiratory rates more than 60/minute.
3. Apneic spells in infants less than 6 months age.

4. Bacterial super infection causes bronchopneumonia.
5. Congestive heart failure in patients with congenital heart disease.
6. Death in 1% of cases from respiratory failure, C.H.F., dehydration or pneumonia.
7. Bronchial hyperreactivity and bronchial asthma may occur during the following 5-10years.

Investigations:

1. Chest X – ray shows marked translucency with or without scattered areas of increased density.
2. Blood picture shows normal leukocyte profile.
3. Reduced arterial oxygen saturation and Oxygen tension (PaO₂) and/or increased arterial carbon dioxide tension (PaCO₂) in severe cases.
4. The causative virus may be detected in nasopharyngeal secretions.

Differential diagnosis:

1. Bronchial asthma (recurrence, allergic history, eosinophilia, response to bronchodilators).
2. Bronchopneumonia (fever, primary cause, crepitations, PMN leukocytosis).
3. **From other causes of wheezing in infancy**
 - a. Congenital lung diseases
 - b. Chronic lung diseases (bronchopulmonary dysplasia
interstitial lung disease,
 - c. Mucociliary disorders
 - d. Immunodeficiency states
 - e. Aspiration syndromes

f. Others: heart failure, anaphylaxis, foreign body

Treatment:

- Outpatient treatment for mild cases.
- Hospitalization for severe cases. ((hypoxia, inability to take oral feedings, extreme tachypnea).
- Risk factors for severe disease include age <12 wk, preterm birth, or underlying comorbidity such as cardiovascular, pulmonary, or immunologic disease
 1. Hydration, oral, IV in severe cases.
 2. Humidified oxygen is the most important line of treatment.
 3. Racemic adrenaline inhalation
 4. Nebulised hypertonic (3%) saline
 5. Antibiotics for secondary bacterial infection.
 6. Aspiration of secretions and assisted ventilation may be needed.
 7. Digitalis for heart failure.
 8. Bronchodilators and corticosteroids (as for asthmatic paroxysm) use are controversy
 9. Ribavirin aerosol is useful for severe cases, but costly. *Indicated for:* cases with ARF, co-existing disease e.g. congenital heart disease and cases with low immunity.

Prevention:

- Reduction in the severity and incidence is possible through the administration of RSV intravenous immunoglobulin considered for infants with chronic lung disease, and congenital heart diseases.

Bronchial Asthma

Definition:

Asthma is a chronic inflammatory disease of the airways in susceptible individuals. It is characterized by airway hyper-responsiveness to a variety of stimuli, reversible airflow obstruction, and bronchospasm, variable and recurring symptoms include episodes of wheezing, coughing, chest tightness, and shortness of breath.

Epidemiology:

- **Prevalence:** 5-10 % of children.
- **Sex:** incidence before puberty, boys to girls = 2: 1 and later on it becomes gradually equal.
- **Family history of allergic disease** (respiratory, skin, ENT, eyes) is positive in 50% of asthmatic children.
- **Age of onset:**
 - 30% < 1 year,
 - 50% < 2 years, and
 - 80 – 90% < 5 years of age.

Etiology And Pathogenesis:

A: Genetic predisposition:

Asthma is caused by the interaction of many genetic loci in chromosomes 5, 6, 11, 14 and other chromosomes.

B: Anatomic characteristics of early childhood:

1. Relatively narrow bronchial lumen.
2. Increased number and activity of mucus secreting glands.

3. Weak collapsible bronchial walls.

C: Abnormal characteristics of allergic child:

1. Excessive production of Ig E in response to antigen exposure (i.e., Atopy). There is an increased amount of Ig E molecules on the surface of mast cells and basophils present in bronchial mucosa.
2. Irritability or hyperreactivity of bronchi (BHR) to various stimuli (physical or chemical).
3. Autonomic imbalance in the form of increased cholinergic and decreased adrenergic function at the level the bronchi.

D: Exposure of the child to non-antigenic and/or antigenic stimuli:

a) **Non antigenic stimuli:** are common causes of asthma in the 1st five years of life.

- i. Viral infections: RSV, parainfluenza, rhinovirus, and influenza virus.
- ii. Physical irritants: smoke, fumes, dust, strong odors, and cold air, and drinks.
- iii. Chemical irritants: kerosene, insecticides, and sulfur dioxide.
- iv. Strenuous exercise especially running.
- v. Emotional stress.

b) **Antigenic stimuli:** are common causes of asthma in older children.

- i. Inhalants (aeroallergens): the most common allergens are: house dust mite, animal dander (cats, dogs, birds, cattle, sheep), pollens, fungi, insect parts and house dust.
- ii. Food: Milk, fish, eggs...etc.
- iii. Drugs: penicillin, aspirin and some non-steroidal anti-inflammatory drugs.

E: The result of this:

1. Non antigenic stimuli irritate and damage bronchial epithelium causing the release of neuropeptides and cytokines which cause inflammation of bronchial tissues.
2. Allergens binds to the numerous Ig E molecules present on the surface of mast cells and basophils resulting in the release of mediators → allergic bronchitis. Some of the important mediators are leukotrienes, histamine, prostaglandins F, eosinophil chemotactic factor, neutrophil chemotactic factor, nitric oxide and eosinophil cationic protein.

F: Bronchitis will cause:

1. An increase of the already present BHR → perpetuation of disease on exposure to stimuli.
2. Partial bronchial obstruction through:
 - Bronchospasm,
 - Mucosal edema,
 - Increased secretion and desquamated epithelial debris in bronchial lumen,
 - Bronchial wall thickening by inflammatory cells and by collagen deposition under mucus basement membrane (remodeling).

G: Bronchial obstruction

Bronchial obstruction results in air trapping → generalized obstructive hyperinflation, scattered areas of atelectasis → labored breathing.

H: Hyperinflation

Hyperinflation being non uniform + Atelectasis areas → ventilation/perfusion mismatch → Decreased Pa O₂ and increased P a CO₂ + respiratory and/or metabolic acidosis.

Pathology:

1. *Bronchi:*

Diffuse partial obstruction of small ($< 2\text{mm}$ lumen) and large bronchi caused by bronchospasm, edema of the mucosa, increased mucus secretion and cellular debris, and thickened walls (due to infiltration by inflammatory cells and deposition of collagen under the basement membrane i.e., remodeling).

2. *Alveoli:*

- i. Generalized hyperinflation due to air trapping.
- ii. Scattered small areas of collapse may be present.

3. *Complications may be found:*

- i. Bronchopneumonia
- ii. Pneumothorax
- iii. Massive collapse of one lobe or the whole lung.

Clinical picture:

The asthmatic paroxysm:

1. It is characterized by gradual or sudden onset of mild to severe chest wheeze and cough.
2. The majority of attacks are mild to moderate.
3. Gradual development of asthmatic paroxysm over a few days is triggered by exposure to irritants or allergens
4. The paroxysms are more frequent and are more severe at night and early morning hours.
5. Cough may be mild or severe, and in some case, it may be present without evidence of bronchial obstruction i.e., cough variant of asthma.

In mild attacks, the condition is represented by:

- Complaint of intermittent chest wheeze or rattle.
- Slight increase in respiratory rate (RR)
- End expiratory rhonchi.
- PEF and O₂ saturation are still normal.

As the paroxysm gets more severe (moderate attack), there will be:

- Progressive increase in RR.
- Difficulty in feeding, chest wheezes, and rhonchi become louder and prolonged with the accessory muscles of respiration working.
- There will be retraction and hyperinflation.
- Both PEF and O₂ saturation start to fall.

In severe paroxysm, there will be:

- Dehydration,
- Fatigue,
- Refusal of feed,
- Cyanosis,
- Impaired consciousness, and
- O₂ saturation is low.

Chest signs during asthmatic paroxysm :

- Inspection:** Increased antero-posterior diameter of chest, rapid shallow breathing with intercostal and subcostal retraction, apex of the heart may become invisible
- Palpation:** diminished chest expansion bilateral, central trachea, diminished TVF, palpable rhonchi all over the chest
- Percussion:** hyperresonance all over the chest

D. **Auscultation**: vesicular breathing with prolonged expiration, sibilant ($\pm$ sonorous) rhonchi is present mainly expiratory $\pm$ non consunating crepitation, decreased vocal resonance

The asthmatic paroxysm usually subsides in 1-2 hours or days, rapidly or gradually, spontaneously or after treatment. Some degree of bronchial obstruction usually persists for several days especially in cases associated with respiratory infection.

Status asthmaticus:

- Sometimes the child suffers from a severe prolonged paroxysm that is not rapidly responsive to bronchodilator therapy, a condition called status asthmaticus or life-threatening asthma.
- In this case, excessive amounts of thick bronchial secretions share in the obstruction of the bronchi.
- The child is cyanotic, dehydrated, fatigued, and not alert.
- Prominent hypoxia and hypercarbia are present, and the mortality rate is about 1%.

Severity of Asthma Paroxysm

Six criteria or more of the following are needed to classify asthma paroxysm:

Criteria	Mild	Moderate	Severe
1- RR (% of normal)	$\uparrow$ up to 30%	$\uparrow$ 30-50%	$\uparrow$ $>$ 50%
2- Alertness	normal	agitated	$\downarrow$ consciousness
3- Feeding	normal	difficult	refused
4- Speech (fatigue)	normal	phrases	words
5- Accessory Ms use.	no	sternomastoid	alae nasi also
6- Retraction	no	+	++
7- Wheeze/rhonchi	end expiratory	throughout	Expir./ inspir.
8- Dyspnea	no	on exertion	At rest
9- Cyanosis	no	no	+/-
10- Hyperinflation	no	no	+++
11- Dehydration	no	+	++
12- O ₂ saturation (%)	$>$ 95 normal	95-91	$<$ 91
13- PEF/FEV ₁ (%)	$>$ 80 normal	80-50	$<$ 50

RR = Respiratory rate.

Course And Prognosis:

1- Recurrence:

- It is a characteristic feature of the disease.
- Its rate varies from one attack per day to once per a few months.
- Adequate prevention of exposure to triggering stimuli reduces the rate of recurrence and the severity of individual paroxysms.

2- Ultimate remission:

- It occurs as the child grows.
- 50 – 60% of infants and preschool children who were well treated during their active illness cease to wheeze by the age of 4-6 years of age. They are sometimes called transient wheezers.
- School children with asthma tend to have less frequent and less severe paroxysms as they grow older, and by puberty one third of patients become completely free, another third of children markedly improve and the remaining third will still suffer.

3- Risk of having status asthmaticus:

An increased risk occurs in the following:

- Inadequate response to one-hour bronchodilator therapy.
- Severe asthmatic paroxysm at present time.
- Past history of severe attacks or status.
- Chest X- ray showing pneumothorax or pneumomediastinum.
- Delayed use of steroids to treat an attack.
- Poor compliance with therapy (child and/ or family)
- Patients with steroid dependent asthma

Complications:

- 4- During the attack: Bacterial super infection, pneumothorax, and collapse of part or all of the lung and respiratory failure.
- 5- Chronic asthma results in: growth failure, chronic bronchitis, bronchiectasis, cor-pulmonale, emphysema, chest wall deformity
- 6- Badly controlled asthma can have an adverse effect on your quality of life. The condition can result in:
 - a. fatigue
 - b. underperformance or absence from school or work
 - c. psychological problems including stress, anxiety and depression.

Associated diseases may cause difficulty in asthma control:

- i. Allergic rhinitis and sinusitis ± infection.
- ii. Gastroesophageal reflux (GER)

Investigations:

- 1- Chest x-ray: Hyperinflation ± complications e.g., pneumothorax, collapse ..etc.
- 2- Pulmonary function tests (PFTs): PEFr, and FEV1 = < 80% of predicted values indicating bronchial obstruction
- 3- Blood gases: O₂ saturation ≤ 95%, ↓PaO₂, and ↑ PaCO₂.
- 4- Bronchial challenge tests: By exercise or inhalation of metacholine to detect mild or suspicious cases.
- 5- Sputum eosinophilia.
- 6- Blood eosinophilia: Of 5-10% (To be differentiated from parasitic infection).
- 7- Skin tests are positive for causative allergens in older children, (they are negative in most children below 5 years)
- 8- Serum Ig E: It is high in most of asthmatic infants and children.

9- Increased nitric oxide in exhaled air and sputum.

Diagnosis:

It depends on:

- 1- Characteristic symptoms and signs and recurrence $\pm$ associated upper resp. allergy or skin allergy $\pm$ positive family history of allergy.
- 2- Laboratory investigations are confirmatory and measure severity.
- 3- In difficult cases, PFTs (FEV1 or PEFr) will be reduced by more than 15%, after five-minute exercise and if they are reversed to normal value after beta agonist administration, the case is definitively asthma.

Differential Diagnosis:

- 1- Causes of stridor (laryngeal or extra thoracic trachea obstruction).
- 2- Other causes of wheezy chest, e.g., bronchiolitis or FB aspiration.
- 3- Pneumonia and TB.
- 4- Psychogenic cough or frequent sighing (disappear during sleep).

Treatment of Asthma Paroxysm

This includes:

1. Hospital admission if indicated.
2. Treatment of moderate – severe paroxysms.
3. Treatment of mild paroxysms.

1-Hospital Admission: is indicated for:

- 1- Moderate – severe attacks.
- 2- Status asthmaticus.
- 3- Child liable to get status asthmaticus.

4- Acute complication (bronchopneumonia, pneumothorax, massive collapse...).

2-Treatment of moderate – severe paroxysm:

A. General supportive:

- 1) *Oxygen inhalation*: 40 % humidified, to keep arterial oxygen saturation > 95 %.
- 2) *Hydration*:
 - a. Oral warm sweetened fluids, milk fruit juice
 - b. Intravenous for: 1- Status asthmaticus, and 2-Inadequate oral hydration, 40 – 50 ml / kg during first 12 hours (2 parts 5% glucose + one part saline)
- 3) *Antibiotics* for:
 - a. Febrile cases (>38.5).
 - b. Bronchopneumonia.
 - c. Status asthmaticus. (N.B. Avoid penicillin)
- 4) *Sodium bicarbonate infusion*: For cases of status asthmaticus if arterial PH < 7.30 (dose 1-2 mEq. /Kg.)

B. Specific treatment using quick-reliever medications:

1) β_2 - adrenergic agonists:

a) Aerosolized β_2 adrenergic agonists:

- One dose /20 minutes (2-3 doses are usually adequate).
- For cases of status asthmaticus or if response to 3 doses is inadequate repeated doses are given (max. = 6 doses) till the attack is controlled, then give one dose every 1-6 hour.
- β_2 agonists can be given either by :

1. Nebulizer + mask: for any age (Salbutamol 0.15 mg / kg in 2 ml saline / dose (max 5mg/ dose).
2. Metered dose inhaler (MDI) with a spacer (+/- a mask) is useful for school children. Salbutamol 4 puffs / dose, increase up to 8 puffs /dose if response is inadequate.



Jet Nebulizer



Ultrasonic Nebulizer



Nebuhaler



Aerochamber



Use of MDI with spacer

b) Subcutaneous β_2 agonists:

- They are indicated if aerosolized β_2 agonists are not available or if response to them is inadequate or if child is not cooperative with aerosol.
- **Drugs:** Terbutaline, salbutamol or adrenaline.
- **Dose:** 1/1000 salbutamol, 0.1 ml / 10 Kg (max 0.4 ml) repeat every 20 minutes, [max. 3doses] if needed. Terbutaline and salbutamol can be given IM or SC.

c) IV terbutaline:

- May be given with caution in ICU, for cases of status asthmaticus.

2) Corticosteroid therapy:

- For moderate paroxysm: Give oral Prednisone $\frac{1}{2}$ -2 mg / Kg / day (max 60 mg / day) divided in 3 doses, for 4 days. If needed give for another 3 days as a single dose after breakfast. You can stop without tapering.
- For severe paroxysm or status asthmaticus give parenteral drugs: e.g. IV or IM dexamethasone: 0.1 mg/Kg / dose, repeat / 6-12 hours or methyl prednisolone 1mg/kg q 6 hours if needed till dyspnea is relieved or up to 48h then give oral prednisone.
- In steroid dependent patients or those with chronic asthma, steroid therapy is continued in the least effective dose to control chest rhonchi. Steroid aerosol by MDI with spacer (+/- mask) e.g., fluticasone propionate, 2-4 puffs (50ug per puff) 6-12 hours. If this fails, oral steroids are given e.g., prednisone 0.1 – 0.5 mg / kg as a single dose after breakfast every day or every other day (EOD).

3) Anticholinergic aerosols:

- They are given if response to 3 doses of β 2 agonist is inadequate.
- Drug: ipratropium bromide
- By nebulizer, 250 ug / ml every 20 minutes for 3 doses, then every 2-4 h.
- By MDI, 4-8 puffs / dose, every 20 minutes as needed.

4) Aminophylline:

- IV infusion: Given for cases of status asthmaticus, or if combined β 2 agonist (3 doses) and corticosteroids failed to control asthmatic attack.

- IV aminophylline diluted in 30 ml saline, rarely indicated 4 mg / kg / dose may be repeated after 6 hours (to be given by infusion pump).
- The presence of fever or viral infection necessitates reduction of the dose by 50 %.

5) Mechanical Ventilation:

Indicated if any of the following occurs:

1. Failure of maximal pharmacological therapy including I.V beta agonist.
2. Exhausted child.
3. Impending respiratory failure (RF).
4. Respiratory or cardiac arrest.

Treatment of Mild Paroxysm

1. Beta-adrenergic agonist.
 - For 1 weeks.
 - Aerosol 2-4 puffs / 6 hours or by nebulizer
2. Oral aminophylline may be added 2-4 mg / kg / 6h.
3. Oral prednisone:

May be added if:

 - Otherwise not controlled
 - For patient with history of previous severe paroxysms.
4. Antibiotic for febrile cases.
5. Hydration by oral warm fluids.

Classification of asthma severity

Intermittent asthma

A child is defined as having intermittent asthma if he or she has asthma with minimal symptoms and infrequent asthma flares. Specifically, children with intermittent asthma have the following characteristics:

- Symptoms of asthma occur two or fewer times per week
- Awakenings during the night due to asthma symptoms occur two or fewer times per month
- Asthma flares require oral steroids no more than once per year
- Asthma does not interfere with daily activities

Persistent asthma

Children with persistent asthma have symptoms regularly. There may be days when activities are limited due to asthma symptoms, and the child may be awakened from sleep. Lung function is usually normal between episodes but becomes abnormal during an asthma attack. Persistent asthma can be mild, moderate, or severe.

The criteria that are used to determine a child's asthma severity include the number of days per week that a child has one or more of the following:

- Symptoms, such as cough, wheeze, or shortness of breath
- Awakenings during the night due to cough or wheeze
- Use of a bronchodilator (reliever medication)
- Symptoms that affect the child's ability to participate in normal activities
- The number of asthma flares per year that require treatment with oral steroids

Control of bronchial asthma

- Children with persistent asthma need to take medication on a daily basis to keep their asthma under control, even if there are no symptoms of active asthma on a given day. Medications taken daily for asthma are called "long-term controller" medicines and function to decrease inflammation and to control chronic symptoms and to prevent asthma attacks.
- Long-term controller" medicines include Inhaled corticosteroids, leukotriene modifiers (montelukast), long-acting beta-agonists and theophylline and a monoclonal anti-IgE antibody (Omalizumab) in some patients

Prevention of bronchial asthma

Asthma is a preventable disease which could be controlled.

- i. Adequate treatment of asthma paroxysms by beta agonists and corticosteroids prevents early recurrence.
- ii. Reduction of exposure to various antigenic and non – antigenic stimuli is both very useful and difficult. It reduces the rate of recurrence and severity of asthma paroxysms.
- iii. Treat associated upper resp. allergy (URA) by antihistamines.
- iv. Treat Gastroesophageal reflux (GER) if present.
- v. Control of persistent asthma.
- vi. Prevention of exercise induced asthma (EIA):
 - Beta agonist (aerosol) or
 - Fluticasone by MDL

A single dose of any of them 15-30 minutes before exercise is adequate.

- vii. Annual vaccination against influenza virus may be useful in preventing asthmatic paroxysms precipitated by influenza virus infection.
- viii. Allergen Immunotherapy (Hypo-sensitization): this is the administration of gradually increasing doses of one or two of causative allergens to the asthmatic atopic child. This may reduce the severity of atopic asthma when the child exposed later to the administered allergens. It is indicated to control chronic asthma when all other measures failed. Allergens can be administered by injection, inhalation or sublingually.

Patient and family education:

The child and his parents should be educated about:

1. Nature of the disease, its course and prognosis.
2. The goal of management is to get normally active child who sleeps well.
3. Role of various antigenic and non-antigenic stimuli.
4. Role of allergic rhinitis, sinusitis, and gastroesophageal reflux.
5. Side effects of asthma medications.

Pneumonias

Definition:

Pneumonia is an inflammation of lung parenchyma.

Classification:

A- Etiologic :

1. Infectious pneumonia due to infectious agents: viruses, mycoplasma, bacteria, fungi or protozoa .
2. Non – infectious pneumonia is designated as pneumonitis.
Pneumonitis may be due to chemical agents, hypersensitivity, and irradiation or may be idiopathic.

B- Anatomic:

- Up till now, diagnosis of the etiology of pneumonia is very difficult and costly. The methods to obtain infective material from lung tissue is still hazardous and not widely available.
- Therefore, a more practical and easier method for classifying and treating pneumonia is identifying its anatomy clinically and by chest X-ray. Considering the prevalence of certain microorganisms at various ages will then make possible managing children with pneumonia.
- Two main types are identified: lobar pneumonia and bronchopneumonia.

(I) Lobar Pneumonia

Definition:

Acute pulmonary infection affecting all alveoli in one or more lung segments or in one or more lung lobes sparing other parts of the lungs.

Etiology:

A- Predisposing factors:

1. Viral upper respiratory tract infection (common cold).
2. Malnutrition.
3. Cigarette smoking.
4. Chilling.

All these factors lower pulmonary defenses e.g., ciliary activity, and alveolar macrophages.

B- Causative microorganisms and age:

1. Most cases are caused by the Gram positive strept. pneumoniae (pneumococcus). **Age:** *at any age after the first month.*
2. Some cases are caused by Gram negative Hemophilus influenza type b. **Age:** *below 5 y.*
3. Some by Gram positive Staph. aureus. **Age:** *70% below 1 y, and 30% 1-3 y.*
4. Viral infections. **Age:** *at any age.*

C- Source of infection:

A. Pneumococcus and H. influenza bacillus:

- a. From patient with upper respiratory tract infection, rarely from patient with pneumonia.
- b. From contact carrier with the microorganism in his throat.
- B. Staph.aureus from skin pyoderma of infant, or contact carrier of the organisms in his nose, or from maternal breast abscess.

D- Season: More in winter and spring.

Pathology:

A. Lungs: Affected areas pass by 4 stages: congestion, red hepatization and grey hepatization and resolution. Staph. pneumonia cases are characterized by the formation of lung abscesses and pneumatoceles (right side in 2/3 cases, bilateral ¼ cases, very rarely in the left side alone).

B. Pleura: Dry fibrinous pleurisy overlying affected lung. This may pass to sero-fibrinous pleurisy or empyema. Staph. aureus → empyema in > 70 %, pyopneumothorax in 25 % of cases.

Clinical Picture:

An upper respiratory infection (nasopharyngitis) of a few days is followed by symptoms and signs of pneumonia.

A- Symptoms:

- 1) Sudden rise of temp. to 38.5 or more, with shivering in older children. Febrile convulsions may occur in susceptible patients.
- 2) Dyspnea and grunting.
- 3) Chest pain of pleuritic nature (local over the affected side or radiated to the other sites of the chest or to the abdomen).
- 4) Cough is an infrequent complaint at the onset.

B- General signs of pneumonia:

1] Characteristic triad of:

- a) Dyspnea with expiratory grunt.
- b) Inverted breathing rhythm.
- c) Inspiratory flaring of the nostrils (working alae nasi).

2] Fever 38.5 C or more.

3] Restlessness, anxiety, apprehension, may be drowsiness (toxic facies).

4] Toxic shock may be seen in staph. pneumonia.

*In mild cases, only tachypnea may be present.

Chest signs of lobar pneumonia:

1. During the first or second day of disease, one may detect diminished air entry over affected area; however, chest X- ray may show infiltrates.
2. Later on, the signs of consolidation become evident.

Chest sings of consolidation

- i. **Inspection:** normal shaped chest, central mediastinum
 - ii. **Palpation:** diminished chest expansion on affected side, central trachea, increased TVF over the affected lobe, no palpable rhonchii
 - iii. **Percussion:** dullness over the affected lobe
 - iv. **Auscultation:** bronchial breathing over the affected lobe with increased vocal resonance (bronchophony). Pleural rub may be heard
3. When resolution starts, crepitations become prominent while other signs gradually fade.

Course and Prognosis:

- 1) In pneumococcal cases recovery may start towards the end of the first week. The initial occasional cough becomes more frequent, productive and may be blood tinged.
- 2) In untreated cases the mortality rate is 5-50 %.
- 3) H.influenza pneumonia has insidious onset and prolonged course of a few weeks.
- 4) Staph.pneumonia has a stormy course with delayed resolution after several weeks.
- 5) Antibiotic treatment hastens resolution and markedly lowers mortality. Despite treatment, the mortality rate is still around 30 % in Staph. pneumonia.

(II) Bronchopneumonia

Definition:

Acute bronchopulmonary infection of the bronchial tree, alveoli and interstitial tissue of the lung, affecting all segments in one or both lungs, and occurring as a complication of pre-existing bronchitis in a predisposed child.

Etiology:

A. Predisposing factors:

- a. Factors lowering pulmonary defenses and resistance to infection e.g. P.E.M., rickets, gastroenteritis, tobacco smoke.
- b. Certain viral and bacterial infections: measles, influenza, pertussis, and scarlet fever.
- c. Bronchial asthma.

- d. Aspiration of food or vomitus in cases of: cleft palate, gastroesophageal reflux, impaired consciousness, severe debility and swallowing dysfunction.
- e. Congenital heart diseases with left to right shunt.
- f. In neonatal pneumonia: prolonged rupture of membranes and prolonged labor.

B. Causative microorganisms:

- I. Exclusively viral:** RSV, influenza, parainfluenza, adenovirus and measles.
- II. Exclusively bacterial:** The most common organism differs according to the age of child:
 - (a) In neonates, Strept. Group B and E. Coli.
 - (b) Age 1-3 months, Strept. B and Chlamydia.
 - (c) Pneumococcus is the most common after the age of 3 months.
 - (d) Staph. aureus in preschool age.
 - (e) Streptococcus-A and Mycoplasma, by school age.
 - (f) Oral anaerobes at any age in cases of aspiration pneumonia.
- III. Mixed viral and bacterial superinfection.**

C. Source of infection:

- 1. From patients or carriers (as before).
- 2. From oral flora in aspiration pneumonia.
- 3. Neonatal pneumonia from carriers, patients or vaginal flora.

Pathology:

1] Lungs show a mixture of lesions diffusely scattered in one or both lungs:

- i. Bronchitis and bronchiolitis with variable degrees of obstruction and secretions.
- ii. Alveoli: in some lobules they are consolidated, in others collapsed, and in others emphysematous.
- iii. Inflammatory infiltrate of interstitial tissue.
- iv. Lung abscess may be present.

2] Pleura: pleural effusion and empyema are frequent in 25 % of cases.

Clinical Picture:

A- An infant or child with bronchitis who is suffering from one of the predisposing factors.

B- Onset of bronchopneumonia is shown by development of:

1. Symptoms and general signs of pneumonia.
2. Variable degrees of wheezing, more marked in cases complicating asthma.
3. Cough is early and prominent and may be productive.
4. In neonatal pneumonia, manifestations of neonatal sepsis may be present.

C- Chest examination:

1. Marked dyspnea: increased RR, working accessory muscles of resp., & retractions.
2. Breath sounds: Harsh vesicular breath sounds all over, but if large areas of consolidation are present near lung surface, they cause tubular breath sounds here and there.
3. Added sounds:

i- Rhonchi: sibilant and sonorous, diffuse and most marked in asthmatic cases.

ii- Crepitations: numerous medium sized crepitations throughout the whole lung.

Course and Prognosis:

1. The disease is more severe, the course is more prolonged, complications more frequent and mortality rate higher than in lobar pneumonia.
2. Neonatal pneumonia has the highest mortality rate.
3. Recurrence of pneumonia indicates the continued existence of the predisposing factors.

Complications of pneumonia:

1. Distressing tympanitis (abdominal distension with gas).
2. Otitis media is frequently seen at the onset of pneumonia in H. influenza pneumonia.
3. Pneumatocoles, empyema, pyopneumothorax and lung abscess.
4. Disseminated infection: Meningitis, pericarditis, peritonitis and arthritis.
5. Slow resolution over several weeks (H. influenza).
6. Heart failure.
7. Respiratory failure.
8. Pulmonary sequelae may complicate bronchopneumonia e.g., flaring of dormant pulmonary T.B., pulmonary fibrosis, and bronchiectasis.

Complications are more common in infants, in H. influenza and Staph. pneumonias and in bronchopneumonia.

Investigations for pneumonia:

A- Chest X-Ray postero-anterior and lateral.

This should be done in every case and repeated a few days later and if the case deteriorates.

1. Lobar pneumonia shows opacity of one segment, lobe or even one lung. Rapid progression with development of empyema, pyopneumothorax or lung abscess occurs in staph. pneumonia. In H. influenza pneumonia, unilateral opacity remains rather stable.
2. Bronchopneumonia shows patchy areas of opacity scattered in one or both lungs. The radio-opacities of pneumonia appear very early at its onset and may persist for 3-6 weeks following clinical recovery.

X- ray chest cannot differentiate between viral and bacterial pneumonia.

B- Blood Picture:

1. CBC shows leukocytosis.
2. Neutrophilia more common in bacterial cases.
3. Lymphocytosis in viral cases.
4. Eosinophilia in Chlamydia pneumonia.

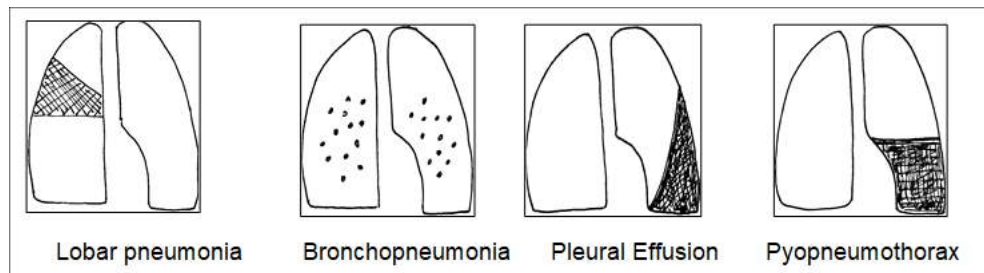
C- Etiologic Diagnosis: This is difficult and costly:

Combined viral and bacterial infections coexist in 40 % of cases.

1. Demonstrating microorganisms in bronchial secretions, lung aspirate, pleural fluid and blood by Gram stain or culture. Bacteremia is present in 10 – 20 % of untreated cases. One or more days are needed.
2. Rapid bacterial antigen detection in bronchial secretions, pleural fluid or in urine, only few hours are needed.

3. High A.S.O. titer in strept. pneumonia.
4. Viral diagnostic studies if available: antigen detection, PCR, serologic tests and culture.
5. Tuberculin test (if antibiotic resistant or delayed resolution).

D- **Blood Gases:** O₂ saturation, Pa O₂, Pa CO₂, and pH.



Chest X – ray (postero-anterior) in lobar pneumonia, bronchopneumonia, pleural effusion and pyopneumothorax

Diagnosis of Pneumonia:

1. WHO recommends that pneumonia is diagnosed if : Temp. > 38.5 C. + respiratory rate > 50 per minute in an infant+ retractions.
2. Symptoms, chest signs and X-ray.
3. Causative microorganisms: From clinical situation and investigations.

Differential Diagnosis

- 1- Acute tracheobronchitis.
- 2- Acute bronchiolitis.
- 3- Status asthmaticus.
- 4- Tuberculous bronchopneumonia.
- 5- Meningitis (versus upper lobe pneumonia).
- 6- Acute abdomen (versus basal pneumonia).

Treatment of Pneumonia

Hospital care for:

- 1- Infants (first year of life).
- 2- Severe distress: (Respiratory rate increased by $> 50\%$, marked retractions, patients not alert and/or cyanosis).
- 3- Empyema or significant effusion.
- 4- Possible Staph. etiology.
- 5- Inadequate home care.

General supportive measures:

- 1- Bed rest, with frequent change of the position in bed for infants and young children.
- 2- Antipyretic and analgesic for pleural pain.
- 3- Aspirate oral secretions and clear nasal obstruction.
- 4- Adequate fluid intake, soft easily digested diet to avoid tympanitis.
Intravenous fluids may be needed in infants.
- 5- If abdominal distension is present, give prostigmine 1/2- 1 ml I.M. or S.C.
- 6- Oxygen, if there is severe dyspnea, even in absence of cyanosis, or if O_2 sat. $< 90\%$.
- 7- Deep tracheal suction for patients with ineffective cough.
- 8- Bronchodilators for asthmatic bronchopneumonia.
- 9- Mechanical ventilation for respiratory failure. Digoxin for heart failure.

Drainage of Pleural Fluid:

- 1- Small amount of effusion will absorb spontaneously.
- 2- Significant amounts should be aspirated as they collect.
- 3- Tube drainage is needed for rapidly collecting effusion and for empyema.
- 4- Consult a thoracic surgeon for cases with chronic empyema.

5- Pleural fluid pH < 7.2 or glucose < 50 mg/dl or lactic dehydrogenase > 1000 μ / L.

Antibiotic therapy for pneumonias:

- This is indicated if viral etiology cannot be proved.
- Parenteral antibiotics are obligatory for at least one week in uncomplicated pneumonia.
- For cases complicated with empyema at least 3 weeks of parenteral antibiotics are needed.
- Type of antibiotic depends on the age of patient, the most commonly causative bacterium in this age and the type of pneumonia (lobar or bronchopneumonia), chest X-ray and the results of rapid antigen test or culture.

A- If clinical manifestations, X-ray or rapid antigen test suggest a specific microorganism, start treatment with antibiotic effective against it e.g.

- Penicillin or ampicillin or amoxicillin or first-generation cephalosporin for pneumococcus, streptococcus A or B.
- Oxacillin or first-generation cephalosporin for Staph. aureus.
- Ceftriaxone, cefotaxime or cefuroxime sodium for H.influenza.
- Gentamicin or amikacin for E. coli.
- Amoxicillin + Azithromycin for Mycoplasma pneumonia.

B- If this is not possible, start empiric antibiotic therapy:

- Infants less than 2 months: 3rd generation cephalosporins ± amoxicillin.
- Infants aged 2 months – one year:
 - Give amoxicillin + gentamicin, or 3rd generation cephalosporins for any type of pneumonia, for 2 – 3 weeks.

- Patients aged 1 – 5 years:
 - Give amoxicillin for 4 days. Then,

C- If the response is good, it is most probably pneumococcal pneumonia.

- Continue with ampicillin for 10 days.

D- If the disease rapidly progresses:

- repeat chest X-ray, Staph pneumonia is most probable, therefore continue with ampicillin + gentamicin for 3 weeks.

E- If response is slow and slight, this is probably H. influenza pneumonia,

- Ceftriaxone, cefotaxime or cefuroxime sodium should be used.
- When results of bacterial culture and susceptibility of bacterium to antibiotics are sent from the laboratory change to the type of antibiotic suggested by the lab. If response to empiric therapy is not satisfactory.

Antibiotic dosage for pneumonia:

- Ampicillin: 150 – 200 mg / kg / day, q 6 hours.
- Penicillin-G sodium: 150 – 200 thousand units / kg / day q 6 hours.
- Oxacillin: 100 – 200 mg / kg / day, q 6 hours.
- Amikacin: 15-22 mg/Kg/day,q 8 hours.
- Cefuroxime sodium (2nd gener Cephalosporin):100-150 mg/kg/day q 6 hours.
- Cefotaxime (3rd gener. Cephalosporin): 100 – 150 mg / kg / day, q 6 hours.
- Ceftriaxone (3rd gener. Cephalosporin): 50 – 75 mg / kg / day, q 12 hours.
- Gentamicin (aminoglycoside): 6 mg / kg / day, q 8 hours.

Pleurisy

Definition:

Inflammation of the pleura.

Types:

- 1- Dry or plastic pleurisy.
- 2- Serofibrinous pleurisy.
- 3- Purulent pleurisy (empyema).

Dry Or Plastic Pleurisy

Etiology:

- 1- Bacterial pulmonary infection: Pneumonias, lung abscess, and pulmonary TB.
- 2- Acute upper respiratory tract infection.
- 3- Connective tissue disease e.g., rheumatic fever, SLE.

Pathology:

- Inflammation of the pleura with fibrin deposition and small amount of yellow serous fluid.
- Adhesions between the two pleural surfaces and variable degrees of thickening of the pleural layers.
- In TB, the adhesions develop rapidly, and the pleura is often thickened.

Clinical picture

- 1) Symptoms and signs of the etiologic disease.
- 2) Pleural pain: Stabbing, or dull ache, over the chest and may be radiated to upper abdomen, shoulder, and the back, exaggerated by deep breath, coughing or straining, and relieved by lying on the affected side.
- 3) Pleural friction rub heard over the affected area, usually disappears after a few hours to days.

X ray chest:

Diffuse haziness of the pleura.

Differential Diagnosis:

From other causes of chest pain, and dry cough.

Treatment:

- a) Treat underlying disease.
- b) Analgesic antipyretics.

Pleural Effusion

Definition: This is the collection of fluid in the pleural space.

Types and Etiology:

The following table illustrates the most common types of pleural effusion and their etiology.

Type	Characteristics	Etiology
Serofibrinous	- Exudate - Clear or cloud - Sp. Gravity > 1016 - Proteins > 3g/dl - WBC > 1000/cmm - LDH > 200U/L (>60% of serum level) - Glucose less than serum - PH < 7.2	- Para pneumonic - Pulm. TB - Collagen disease - Infections in the mediastinum or abdomen - Malignancy.
Purulent	- Cloudy or pus - PMNs > 5000 /cmm - Glucose < 50mg /dl - Microorganism on smear.	- Purulent pleurisy (Empyema) - Para pneumonic lung abscess - Lung abscess - Chest trauma
Hydrothorax	- Clear transudate (i.e. not exudate) - Few mesothelial cells - Glucose same as serum - LDH (<60% of serum)	- Nephrotic syndrome - Glomerulonephritis, and CHF - Venous obstruction.
Hemothorax	- Uniformly bloody - Does not clot - Its hematocrit > ½ blood Ht. - Hemosiderin-laden macrophages.	- Chest trauma - Hemorrhagic diseases - Pulm.embolism - Malignancy
Chylothorax	- Milky - Triglycerides > 50mg/dl - Lymphocytes > 5000 /cmm - Becomes clear when shaken with ether	- Lymphatic obstruction (tumor) - Thoracic duct injury (trauma) - Chest surgery.

Serofibrinous Pleurisy

Etiology:

1. The most common causes are pneumonia or pulmonary TB. In pneumonia amount of fluid is usually small, while in TB it is large.
2. Other causes:
 - a) Inflammatory conditions in the mediastinum.
 - b) Inflammatory conditions in the abdomen.
 - c) Connective tissue disorders.
 - d) Primary or metastatic neoplasms of the lung, pleura or mediastinum.

Clinical Picture:

A- Symptoms and signs of underlying disease

B- Symptoms of pleural disease:

- a) Pleural pain early in disease and disappears when fluid accumulates.
- b) Large amounts can cause cough, dyspnea, cyanosis, retractions, tachypnea or orthopnea.

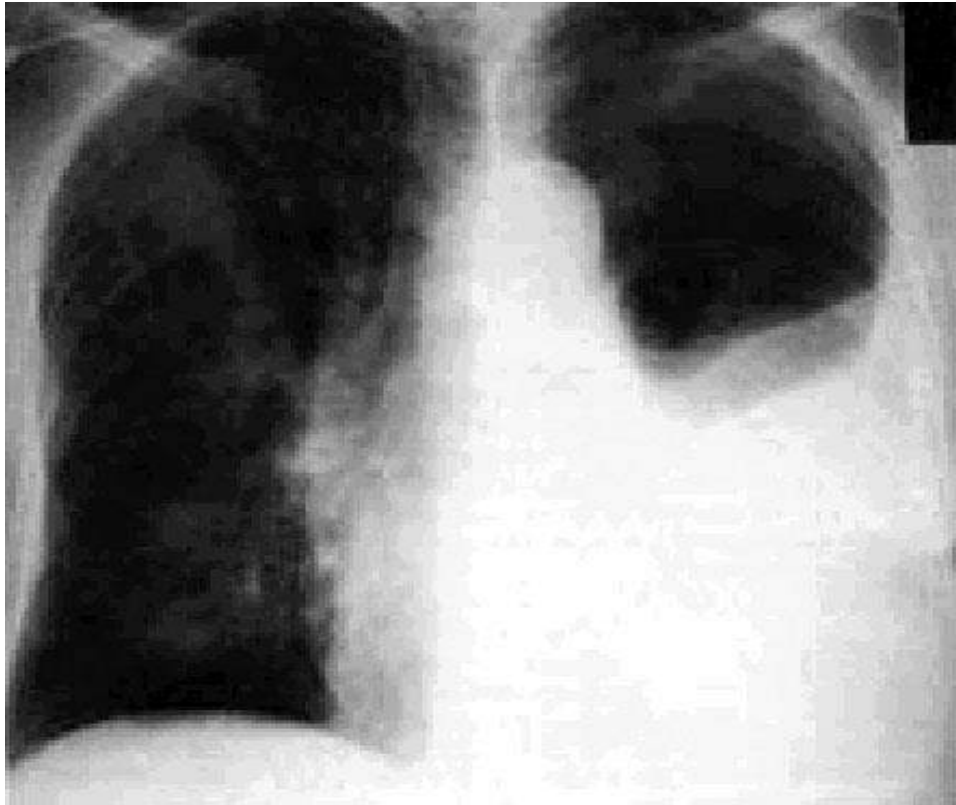
C- Signs of pleural effusion:

- 1- Small amounts may be detected only by X-ray.
- 2- Large amounts give chest signs of pleural fluid
- 3- In infants bronchial breathy may be heard all over the affected side.

Chest X-Ray:

- a) Small amounts are detected as obliteration of the costophrenic and cardiophrenic angles or widening of the interlobar septa.

- b) Large collections show homogenous opacity obliterating the angles and ascending in the axilla with shift of the trachea and mediastinum to the other side and lung collapse upward & medially



X ray chest show left pleural effusion

Thoracocentesis:

Shows the characteristics of the effusion.

Differential Diagnosis:

- 1- Other causes of pleural effusion
- 2- Lobar pneumonia
- 3- Massive collapse
- 4- Pneumothorax.

Course And Prognosis:

1. With cases of pneumonia the fluid usually is absorbed rapidly. However, it may become purulent i.e. empyema.
2. Tuberculous cases absorb in a few weeks. Pleural adhesions and thickening may result but usually resolve after a variable time leaving no functional impairment.

Treatment:

1. That of underlying disease. In tuberculous cases Prednisone is useful in addition to anti-TB drugs.
2. In case of large effusions aspirate slowly as much as possible up to one liter when the patient is first seen. If significant amount re-accumulate repeated aspiration or tube drainage is indicated.
3. Management as empyema if it is purulent.

Purulent Pleurisy (Empyema)

Definition:

Accumulation of pus in the pleural space.

Etiology:

1. Most cases are secondary to staphylococcal pneumonia, and some cases complicate pneumonia caused by Pneumococci and H. influenza bacillus. Patients are usually infants and preschool children.
2. Other causes include rupture of lung abscess, chest trauma, or extension of subphrenic abscess.

Pathology:

1. Pus frequently is located allover large area of the pleural cavity.
2. The parietal pleura is thickened.
3. If undrained, the pus may penetrate the pleura and dissect into the lung parenchyma producing bronchopleural fistula and pyopneumothorax.
4. Pockets of loculated pus may develop into thick-walled abscess.
5. In neglected chronic cases the exudate will organize into a thick inelastic envelope (peel) and the lung may collapse

Clinical Picture:

1. An infant or preschool child with pneumonia, which is treated with inappropriate, or inadequate antibiotic.
2. Sudden onset of fever and dyspnea may occur while on treatment or after apparent cure. Preschool children appear more ill than infants.
3. Signs of pleural effusion on chest exam.

Investigations:

1- Thoracocentesis:

- Purulent exudate, PMNs > 5000/cmm, and glucose < 50mg/dl.
- Causative organism determined by Gram-stained smears, latex agglutination and culture. Antibigram is done.

2- Chest X-ray:

1. Like serofibrinous pleurisy
2. When loculated no shift of fluid is observed when the child's position is changed.

Complications:

1. With staphylococcal cases, bronchopleural fistula and pyopneumothorax are common.
2. Purulent pericarditis, and lung abscess.
3. In H. influenza and pneumococcus cases, septicemia with osteomyelitis, arthritis and meningitis may occur.
4. Chronic empyema causes pulmonary atelectasis.

Diagnosis and DD: As for serofibrinous pleurisy.

Treatment:

1. Drainage: the maximum amount of pus should be aspirated. This is followed by continuous closed drainage under water seal through a wide catheter in the pleural cavity for 1-2 wks. More than 1 tube is needed to drain loculated areas.
2. Systemic antibiotics IV or IM:
 - Duration: 3-4 weeks for staph. cases, and 2 weeks for other cases.
 - Types: according to sensitivity of isolated microorganism to antibiotics.
 - a) Staph. aureus → give oxacillin or cephazolin
 - b) Pneumococci → give cefuroxime, cefotaxime or ceftriaxone
 - c) H. Influenza → give cefotaxime or ceftriaxone
3. Oral antibiotics for 2-3 weeks after IV antibiotics.
4. Symptomatic treatment: Oxygen, analgesic antipyretic, and light diet during febrile period.
5. For chronic empyema decortication of the lung and pulmonary exercises are needed to regain lung function.

Pneumothorax

Definition:

It is the presence of air in the pleural space.

Types And Etiology:

A. Spontaneous

- a. **Primary:** Rare without apparent cause usually in tall and thin males with subpleural blebs in the apex of upper lobe.
- b. **Secondary: to underlying lesions** Pneumonia, bronchial asthma, Pulm. Abscess, Cyst, FB and Cystic fibrosis

B. Traumatic:

- a. **Accidental:** by external blunt or penetrating injury of the chest.
- b. **Iatrogenic:** during thoracocentesis, ventilation, neonatal resuscitation, bronchoscopy, or lung biopsy.

Pathogenesis

- Transforms the potential space into a real one
- Air in the pleural space → lung collapse → Hypoxemia (ventilation-perfusion mismatch).
- In **simple pneumothorax**, intrapleural pressure is atmospheric, and the lung collapses up to 30%.
- In **tension pneumothorax**, continuing leak causes increasing positive pressure in the pleural space, which exceeds atmospheric pressure, and the lung totally collapses with shift of the mediastinum towards the opposite side.

Clinical Picture:

- A. Symptoms and signs of underlying etiology.
- B. Small amount of air may be discovered on chest X-ray.
- C. Larger amounts give varying degrees of:
 - 1- Chest pain.
 - 2- Dyspnea with or without cyanosis
 - 3- Signs of pleural air or signs of pleural air and fluid.

Tension pneumothorax:

- It is the presence of a large amount of air under tension in the pleural space.
- It results in:
 - 1- Symptoms and signs of pleural air are severe.
 - 2- The expansion of the contra lateral lung is diminished.
 - 3- Interference with venous return results in cardiovascular collapse (shock).

Investigations:

- i. Chest X-ray: Homogeneous translucency on affected side with no lung reticulation markings. There is shift of the trachea and mediastinum to the other side. A small amount of barium is needed to differentiate pneumothorax from diaphragmatic hernia.
- ii. Thoracocentesis: Air is aspirated. A hiss may be heard in cases of tension pneumothorax.

Differential Diagnosis:

- 1- Pleural fluid
- 2- Pneumonia

- 3- Severe asthma
- 4- Diaphragmatic hernia

Treatment:

(I)General:

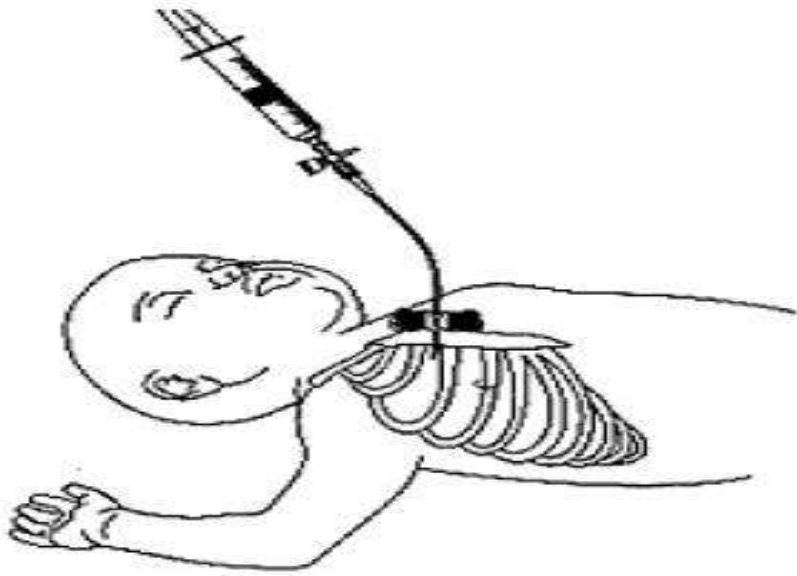
- O₂ therapy if there is tachypnea or dyspnea
- Analgesics for pleural pain

(II)Drainage:

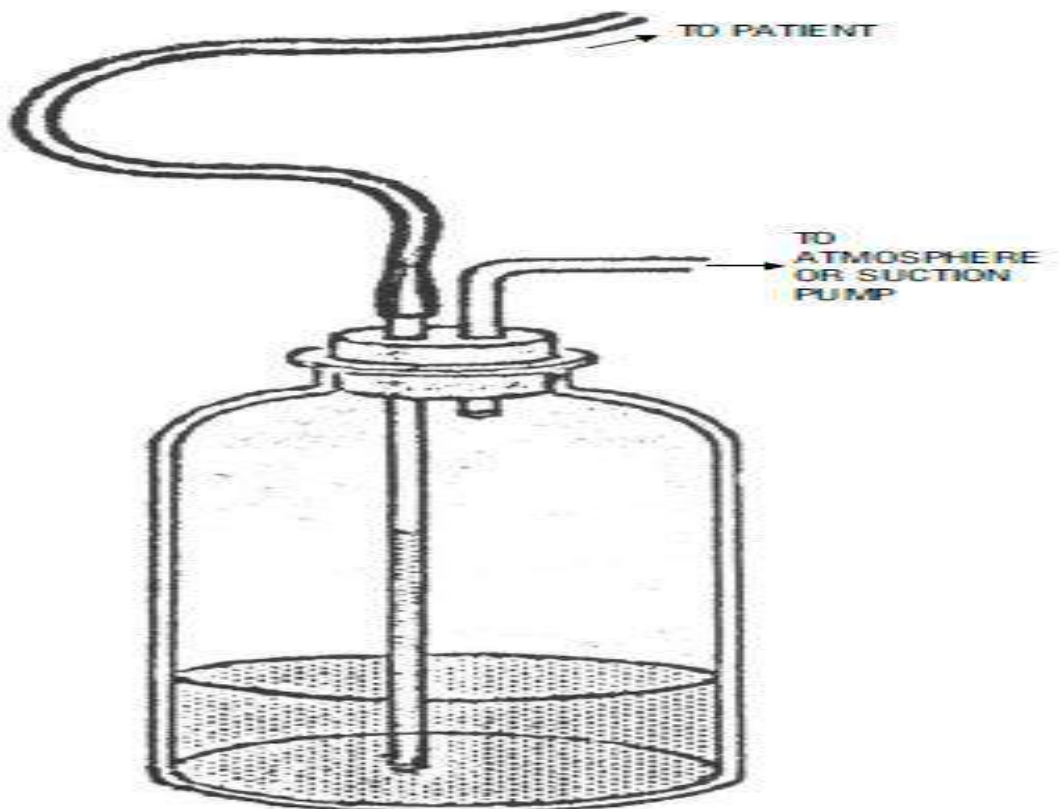
- 1- Mild cases with less than 5% collapse need no treatment, they will absorb spontaneously in about one week.
- 2- Drainage is needed for cases with more than 5% collapse and for tension pneumothorax closed drainage of air under water seal is adequate to relax the collapsed lung in most cases.

(III)Treat the underlying condition.

(IV)For recurring cases thoracic surgery is needed.



Needle aspiration of pneumothorax



Closed drainage of pneumothorax

Primary Pulmonary Tuberculosis

Etiology:

- **Causative organism** is Mycobacterium tuberculosis, an acid-fast, weak gram positive, 2- 4 μm bacillus.
- **Source of infection** is an adolescent or adult patient with productive cough or pulmonary tuberculous cavity more commonly at home or school.
- Infection is person to person by droplets of sputum, rarely patient fomites. Adequate treatment with anti-TB drugs for a few weeks reduces the infectivity of patients.

Predisposing Factors:

A- Environmental:

1. Poorly ventilated rooms
2. Over crowding

B- Lowered cell-mediated immunity:

1. Malnutrition
2. Bronchopneumonia
3. Measles
4. Pertussis
5. Diabetes mellitus
6. Corticosteroid therapy.

Age factor: the age range 5-14 yr has the lowest incidence of TB

Sex factor: adolescent girls are more liable to get TB than adolescent boys.

Genetic factors: Predisposition to TB was observed.

Race factor: Negroes are more liable to infection with TB.

Pathology:

- When an infant or child's lung is infected with the TB bacillus for the first time, he develops what is called initial or primary pulmonary TB.
- This consists of two components: a pulmonary focus and infected tuberculous mediastinal lymph nodes, which form what is called the primary complex.
- The pulmonary TB focus is about 1 cm in diameter, and single subpleural and in any lung segment the mediastinal nodes are slightly enlarged, matted and adherent to surrounding structures.
- Left side focus causes bilateral adenopathy, while right side focus causes Rt. side adenopathy.

Fate of primary complex:

I. Healing in 60-95% of cases:

- More common in the older child.
- Healing by calcification of both the pulmonary and the mediastinal lesions.
- Radiologic detection of calcified nodes required >6 months from infection.
- Many of these lesions resorb and disappear completely in a few years.
- Viable mycobacteria may persist in calcified lesions for years.

II- Progression:

- This is more common in infants and young children.
 - i. If the patient's lung resistance is low (or is lowered by PEM, diabetes, pulmonary infections, and steroid therapy).
 - ii. If bacilli are numerous or virulent.
- In these patients the primary lesion may remain (or become) active and results in what is called progressive primary pulmonary TB.

- Progression occurs by several mechanisms:
 - i. Direct spread into surrounding tissues: The pulmonary focus will progress to give a larger area of consolidation (Pneumonic TB).
 - ii. The mediastinal nodes enlarge, invade, compress and completely obstruct the nearby bronchus producing consolidation – collapse that is the most common lesion in infants and young children.
 - iii. The pulmonic or mediastinal lesions may erode a bronchial wall or lumen. Tuberculous granuloma and / or bronchogenic dissemination of bacilli to other parts of one or both lungs may result in tuberculous bronchopneumonia.
 - iv. Lymphatic spread causes small pleural effusion. Significant effusion may occur in children >6yr never associated with pulmonary TB consolidation.
 - v. The primary lesion may erode into blood vessel causing hematogenous dissemination to form:
 - 1. Widely spread milliary lesions all over the body.
 - 2. Isolated foci (tuberculomas) in lungs, bones, kidneys, liver or CNS. Tubercle bacilli may remain dormant in hematogenous pulmonary foci for years till adolescence or adulthood when they may multiply and produce the characteristic lesion of reactivation or adult type pulmonary TB.

Tuberculin Test:

- Two to ten weeks after infection with tubercle bacilli, the child becomes sensitive to the tuberculous protein.
- This sensitivity can be detected by the tuberculin test. In this test, 5 i.u. of purified protein derivative (P.P.D) of tubercle bacillus is injected intradermally in the dorsal surface of the forearm.
- The site of injection is inspected 48 hours later, and the length of any elevated firm (indurated) area is measured.

(1) An induration of 10 mm or more is a positive test and indicates TB disease.

(2) An induration of 5-9 mm:

a- It may be due to B.C.G. vaccination 3-10 years ago.

b- It may be evidence of TB disease:

- If the child is contact of TB patient,
- If the child has a disease or chest X-ray suggestive of TB,
- If the child is debilitated,
- If the child is under steroid therapy,
- If has associated measles, mumps, varicella, and influenza, or
- If he is recently vaccinated with live viral vaccines.

(3) An induration less than 5 mm is a negative test:

- It occurs when the child is not tuberculous.
- Bad technique or misreading gives false negative test.
- 10% of children with TB and up to 50% of children with milliary TB have false negative test, which becomes positive after treatment with anti-TB drugs.

Clinical Picture:

A- In a large proportion (>60%) of infected children, primary pulmonary TB is represented only by a tuberculin test more than 5 mm while chest X-ray is free.

B- Intrathoracic pulmonary lesions occur in < 40% of infected children 3-24 months after infection. The younger the child the greater the risk of developing intrathoracic pulmonary lesions.

I- Enlarged non-calcified or calcified mediastinal nodes detected 3 months or more after infection.

- These nodes are usually discovered on routine X-ray chest. Respiratory symptoms and chest signs are usually minimal or absent.
- Low-grade fever, erythema nodosum or phlyctenular conjunctivitis may be present.

II- Progressive primary pulmonary TB:

- **General:** Fever 38-39°C, night sweats, pallor, anorexia, and failure to gain weight or marasmus.
- **Respiratory:** as dry or productive cough, dyspnea, and grunting, wheezing or pleural pain.
- **Chest signs:** Progressive pulmonary TB may give chest signs, which can simulate any acute or chronic lung disease.
 1. Signs of consolidation i.e., pneumonic TB.
 2. Signs of consolidation – collapse, the most common presentation especially during infancy and early childhood.
 3. Signs of partial bronchial obstruction caused by enlarged lymph nodes and positive D'Espine sign due to enlarged mediastinal nodes.
 4. Signs of bronchopneumonia with tubercle bacilli in the sputum.

5. Signs of pleural effusion in a child of six years or more in age are highly suggestive of TB as a cause (5-7% of cases). TB effusion is never associated with pulmonary consolidation.
6. In milliary TB and in addition to the diffuse minute pulmonary infiltrations, there may be pleurisy, peritonitis, meningitis, splenomegaly, and choroidal tubercles in the eyes.

III- Reactivation (Adult type) pulmonary TB:

- Clinical manifestations occur by adolescent age.
- This is more common in those who acquired primary TB after the age of 7 years.
- The primary lesion heals but when the resistance of adolescent is lowered, dormant bacilli in the original primary TB focus or the hematogenous tuberculomas multiply and produce a caseous pulmonary lesion.
- The site is more commonly in the lung apex but may be anywhere.
- The clinical picture includes productive cough, hemoptysis, weight loss, night sweats, fever, signs of pulmonary consolidation or cavitations are present.
- The mediastinal nodes are not enlarged. The adolescent is considered a source of infection to his contacts.

Diagnosis Of Pulmonary TB:

1. Suspect TB as the cause of any broncho-pulmonary disease.
2. Family history of contact with adolescent or adult patient with open pulmonary T.B.
3. Chest X-ray examination.
4. Tuberculin test.
5. Acid-fast TB bacilli in sputum obtained by gastric lavage.
6. Recent methods:

- a. Polymerase chain reaction (PCR) for sputum. Results are obtained after 1 hr.
- b. BACTEC radiometric system for sputum culture. Only 1 – 3 weeks are needed to report culture and susceptibility to anti-tuberculous drugs.

Set of diagnostic criteria of pulmonary TB in children when culture is not available

- A. Positive acid-fast stain of sputum or gastric aspirate or
- B. Two or more of the followings:
 - History of contact with a tuberculous adult
 - Cough lasting longer than 2 weeks
 - A reactive tuberculin test:
 - 1) ≥ 10 mm in children without prior BCG vaccination.
 - 2) ≥ 15 mm in children with prior BCG vaccination.
 - Radiologic findings comparable with TB
 - Response to anti-TB therapy (increased body weight by 10% after 2 months, decrease in symptoms)

Differential Diagnosis:

I-Bronchopulmonary diseases:

- 1- Chronic bronchitis in a malnourished infant or child.
- 2- Unresolved lobar pneumonia
- 3- Bacterial bronchopneumonia.
- 4- Non-tuberculous pleural effusion.
- 5- Bronchial asthma.

II-Fever of undetermined cause:

- 1- Collagen disease.
- 2- Enteric fever, bilharziasis, brucellosis, and urinary tract infection.
- 3- Malignancy as lymphoma or leukemia.

Prognosis:

- Most children recover especially if treated early.
- Anti-TB drugs result in striking decrease in the incidence of hematogenous extra thoracic lesions e.g., TB meningitis.
- The fatality rate is highest in the first two years of life and in adolescents.

Treatment:

A- General:

- 1- Diet adequate in quality and quantity.
- 2- Rest during the early period of treatment.
- 3- Symptomatic for cough, fever, pain etc.

B- Anti-tuberculous drugs:

I-The infant or child with only a tuberculin test more than 5 mm:

- A. Isoniazid (INH) 15 mg /kg /day (max 300mg) divided into 2 doses for one year plus vitamin B₆ 25-50 mg/day to prevent neuropathy.
- B. Chest X-ray every 3 months during therapy in order to diagnose early intrathoracic lesions.

II- Infant or child with intrathoracic lesions:

Three anti-TB drugs combination is given in order to prevent and treat infection with drug-resistant strains of TB bacilli e.g., Pyrazinamide + INH + Rifampicin.

Doses:

- Pyrazinamide: 20-40 mg /kg /day, orally in one or two doses (Max 2 gm/day)
- INH: 10 mg /kg /day (Max 300 mg), oral divided into 2 doses.
- Rifampicin: 15 mg /kg /day (Max 600mg) divided into 2 doses, on empty stomach. + Vit. B6: 25-50mg/day.

Duration:

- Pyrazinamide is given for first 2-3 months for all cases.
- INH + Rifampicin for 6-9 months for all patients with intrathoracic TB.
- Streptomycin is added as a fourth drug for 2-3 months if resistance to INH is suspected.

C- Corticosteroids:

Prednisone in a dose of 1-2 mg /kg /day for 1-2 months is added to the anti-tuberculous drugs in the following cases:

- Marked enlargement of mediastinal nodes causing collapse, obstructive emphysema or dyspnea.
- Tuberculous bronchopneumonia.
- Millitary pulmonary T.B.
- Tuberculous pleural effusion.

Prevention of TB:

- A. Early detection and treatment of pulmonary TB in adolescents and adults e.g., by mass screening.
- B. Keep the child away from any adolescent patient even if under treatment.

C. Isoniazid prophylaxis: If child gets in contact with an adolescent or adult with open pulmonary tuberculosis, he or she should be given I.N.H. in a dose of 10-20 mg/kg/day for one year.

D. Vaccination with BCG:

- Routine vaccination with BCG is given during the first 2 months of life, at school entry and by the age of 10-12 years.
- Booster vaccination is given if the child is a contact of patient.
- The dose is 0.1 ml intradermally in left deltoid region.
- BCG cannot prevent infection, but it prevents TB dissemination.
- About 50% of vaccinated infants demonstrate tuberculin never become tuberculin positive, these 50% lose their positive test in 3 years.
- Vaccinated older children frequently become tuberculin positive and lose their positive reaction in 10years.
- A tuberculous abscess may result from subcutaneous administration of BCG or from a virulent strain and is treated by anti-TB drugs.

E. Social measures:

Adequate diet, good hygiene, good housing, and avoidance of overcrowding.

Practice Questions

(Choose one correct answer)

- 1- Stridor is characteristic feature of the following diseases EXCEPT:
 - a) laryngeal diphtheria.
 - b) angioneurotic edema.
 - c) adenoid hypertrophy.
 - d) bilateral abductor vocal cord paralysis.

- 2- The most appropriate treatment option of a 10 yr old child with intermittent symptoms of mild asthma is:
 - a) environmental control and patient education only; no medication is indicated.
 - b) oral theophylline.
 - c) inhaled β 2 –agonist as needed for symptoms.
 - d) daily inhaled corticosteroid.

- 3- Causes of bronchiolitis include all of the following EXCEPT :
 - a) Respiratory syncytial virus(RSV).
 - b) Parainfluenza virus.
 - c) Adenovirus.
 - d) Chlamydia pneumoniae.

- 4- Characteristic physical signs of pneumothorax include :
 - a) rhonchi are heard on the affected side.
 - b) percussion over the affected side reveals dullness.
 - c) end-rspiratory crepitations are detected.
 - d) the mediastinum is shifted towards the opposite side.

- 5- The following are causes of serofibrinous pleurisy EXCEPT :
 - a) para-pneumonic pneumonia.
 - b) thoracic duct injury.
 - c) collagen diseases.
 - d) pulmonary TB.



Chapter 13 Cardiology

Objectives:

1. Describe the clinical features of congenital and acquired cardiovascular disorders in pediatrics.
2. Understand the underlying etiological factors in each condition.
3. Correlates between the clinical presentations and the pathogenesis of each disorder
4. Enumerate findings in common investigations in different diseases
5. Formulate a management plan for cardiovascular disorders.

Contents:

1. Congenital heart diseases

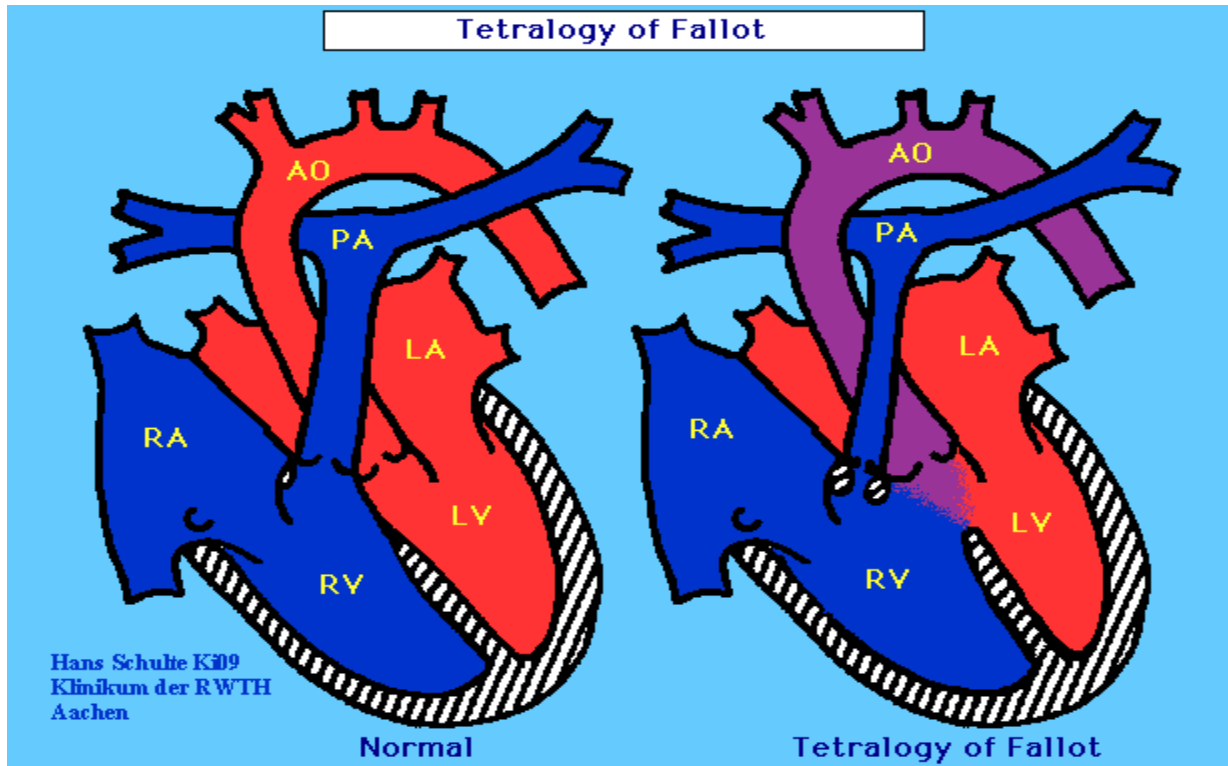
- Tetralogy of Fallot
- Ventricular septal defects
- Patent ductus arteriosus
- Pulmonary valve stenosis

2. Acquired heart diseases

- Rheumatic fever & Rheumatic heart disease
- Congestive heart failure
- Infective endocarditis
- Cardiac arrhythmias
- Diseases of the pericardium
- Systemic Hypertension

Congenital Heart Diseases

1. Tetralogy of Fallot (TOF)



Definition:

TOF describes the spectrum of conditions consisting of Ventricular Septal Defect (VSD), aortic overriding, right ventricular outflow obstruction, and right ventricular hypertrophy.

Embryology:

It is due to failure of the sub-pulmonary conus to expand normally.

Classification

A. The classic form includes:

1. Overriding aorta (Ao),
2. Right ventricular hypertrophy (RVH),
3. Right ventricular outflow tract obstruction (RVOTO); pulmonary infundibular hypoplasia and obstruction or PS.
4. Ventricular septal defect (VSD), which is large nonrestrictive.

B. The extreme form:

- Consists of pulmonary atresia in which cyanosis may appear since birth.

C. The pink form:

- Consists of mild RVOT obstruction; therefore, the patient may not be visibly cyanotic.

Pathophysiology

- I. The VSD is usually large, resulting in equal peak systolic pressures in the two ventricles.
- II. Severe obstruction to RVO leading to:
 1. Decreased pulmonary blood flow and pulmonary hypoperfusion
 2. Shunting of large amount of unsaturated blood to overriding aorta and systemic circulation and persistent cyanosis.
- III. Persistent systemic unsaturation leading to secondary polycythemia and increased hematocrit and blood viscosity which have serious consequences.

Clinical Manifestations

I- Symptomatology:

1-Cyanosis:

- Cyanosis usually appears during first month with closure of the ductus arteriosus.
- Cyanosis at birth is not common unless there is pulmonary atresia.

2-Dyspnea:

- Dyspnea occurs on exertion. Infants and children will play actively for a short time and then sit or lie down.
- Exercise produces decreased systemic resistance and decreased pulmonary blood flow.

3-Blue Spells (TET spell):

- These paroxysms are characterized by increasing rate and depth of respiration, with increasing cyanosis progressing to limpness, syncope and, occasionally, ending in convulsions and death.
- Crying, intramuscular injection, and feeding are the most frequent precipitating events.

4-Squatting:

- It is a characteristic posture of children with TOF when resting after exertion.
- Child sitting on the heels with the chin on the knees.
- The mechanism is that compression of femoral arteries increasing systemic vascular resistance, leading to increase pulmonary blood flow and decrease right to left shunt.

II-General Examination:

1-Central Cyanosis:

Cyanosis occurs, most prominently on the mucous membranes of the lips and mouth and in the fingernails and toenails.

2-Blue Clubbing:

Clubbing of the fingers and toes, recognizable in older infants and children, is a manifestation of chronic desaturation.

3-Growth Retardation:

Growth is limited in severely cyanotic, unoperated patients.

III-Heart Examination:

1-Inspection:

The left anterior hemithorax may bulge anteriorly (RVH).

2-Palpation:

Substernal right ventricular impulse in 50% of cases, a systolic thrill is felt along the left parasternal area (RVOTO).

3-Percussion:

The heart is usually normal in size.

4-Auscultation:

- The 2nd heart sound is single and produced by closure of the Ao valve.
- The systolic murmur is frequently loud, ejection, harsh, and heard at pulmonary area. It is due to turbulence over the RVO tract.

- VSD murmur is usually not heard due to equalization of systolic pressure in both ventricles.

Complications

1-Infective endocarditis:

It usually occurs in infundibulum. Routine prevention is helpful.

2-Cerebral Thrombosis:

- The long-standing polycythemia leads to high blood viscosity, also microcytic RBCs secondary to iron deficiency anemia are responsible for cerebral thromboses.
- These complications are usually precipitated by dehydration.
- They usually occur in cerebral veins. Recurrent phlebotomies and/or partial blood exchange, with continuous iron therapy prevent thrombotic formation.

3-Cerebral Ischemia

- The presence of anemia and persistent O₂ unsaturation may lead to hypoxic brain insult with depressed intelligence quotient (IQ).
- Therefore, early intervention in these cases is mandatory.

4-Brain Abscess

- Any patient with right-to-left shunting is at risk for brain abscess.
- Patients are usually over the age of 2 yr.
- With the appearance of any central nervous system symptoms or signs; ultrasonography, computed tomography, or magnetic resonance of the brain must be done to confirm the diagnosis.
- Massive antibiotics and surgical drainage are usually indicated.

5-Congestive Heart Failure (CHF):

It is rare in TOF, except in presence of severe anemia or atypical forms of TOF (absent pulmonary valve).

Investigations

I-Laboratory findings:

1. **RBCs status:** RBCs count, Hemoglobin concentration, Hematocrit value, and Blood indices.
2. **Iron status:** Serum iron, Serum ferritin, and Iron-binding-capacity.
3. **Hypoxic status:** O₂ saturation, pH, and HCO₃.

Determination and follow up of RBCs count, hematocrit, serum ferritin, and O₂ saturation is mandatory for prevention of complications and selection of optimum time for intervention.

II-Radiological Features: X-ray chest shows:

- Decreased pulmonary vascularity.
- Normal sized heart: narrow base (PA segment is deficient), cardiac apex is elevated and rounded (hypertrophy RV). The cardiac silhouette has been likened to that of wooden shoe (Coeur en sabot).



X-RAY: Tetralogy of Fallot

III-ECG: shows right-axis deviation and right ventricular hypertrophy.

IV-Echo-Doppler:

On echo-Doppler examination it is possible to demonstrate the tetrad of Fallot. The anatomy of branch pulmonary arteries and left coronary artery can be seen in echocardiography. Associated cardiovascular lesions can be also demonstrated in good echocardiography evaluation.

V-Cardiac Catheterization:

Angiography is usually done prior to surgical repair to clarify all anatomical abnormalities when an echocardiographic finding is not conclusive.

Management

I-Medical Treatment:

1-Ductal Dependent TOF:

Prostaglandin E1 (PGE1), starting at 0.1 µg/kg/min is given when the diagnosis is established in extreme TOF in neonates.

2-Blue Spells:

- Placement of infant in knee chest position.
- O₂ administration.
- Morphine, 0.2 mg/kg subcutaneously.
- Sodium bicarbonate, 3mEq/kg IV.
- Propranolol, 0.1-0.2 mg/kg intravenously, followed by 1mg/kg/day divided every 6hr orally.

II-Palliative Intervention:

It is indicated in young infants with recurrent blue spells and/or Hct >60% and O₂ saturation <75%, in whom repair cannot be done:

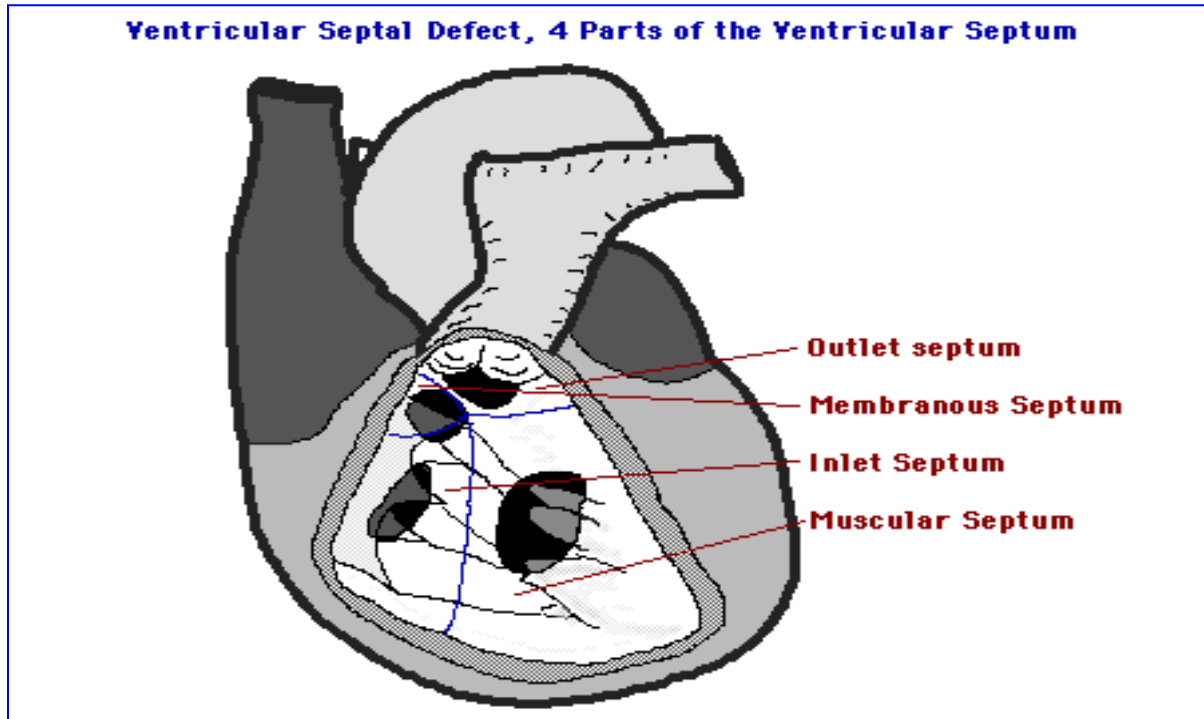
1. Systemic-pulmonary shunt (Blalock-Taussig shunt).
2. Balloon pulmonary dilatation.

III-Definitive Correction:

- Repair of TOF is usually done at age 6-12 months according to severity of lesions, body weight and facilities of center.
- It consists of closure of VSD, and relieving RVOT obstruction.

- Long-term follow up shows marked improvement in operated TOF.
- Some are left with rhythm problems, RV dysfunction, residual pulmonary stenosis, pulmonary or aortic regurgitation.

2. VENTRICULAR SEPTAL DEFECTS (VSD)



Definition: The term of VSD describes an opening in the ventricular septum

Embryology

A VSD results from a delay in closure of interventricular septum(IVS) beyond the first 7 weeks of intrauterine life; the reasons for this delay are unknown.

Anatomy

VSDs are classified by their location in the septum:

- Membranous.
- Muscular.
- Infundibular (outlet septum).

- AV canal type (inlet septum).

Classification

VSDs are classified according to their size into:

- Small (restrictive) VSD.
- Large (non-restrictive) VSD.

Large (Non-Restrictive) VSD

Pathophysiology

The flow across the defect is regulated by:

- A. The relation between systemic vascular resistance, SVR (16mmHg/L/min/M²) and pulmonary vascular resistance, PVR (2mmHg/L/min/M²).
- B. The pressure gradient (PG) between LV (100/8mmHg) and RV (25/3mmHg):
 - At birth, the increased PVR acts as a protective mechanism against massive shunting.
 - In the first few months of life, a gradual decline in PVR results in augmentation of shunting.
 - According to PG between LV & RV the shunting occurs from Lt-to-Rt, and the major flow occurs during ventricular systole and is ejected into the RVOT without any load on RV.
 - Massive flow of blood occurs through lungs (pulmonary plethora).
 - Increased venous return to left heart results in an enlarged LA & LV (volume overload), leading to increased LV mass, LV dilatation and ending in CHF.
 - Compensatory mechanisms occur that include increased sympathetic stimulation.

- Long-standing increased pulmonary blood flow (PBF), results in stretch of the pulmonary vessels and hypertrophy of the media ending by intimal sclerotic changes. All these pathological changes lead to increased PVR & pulmonary arterial pressure (pulmonary hypertension).
- Increased PVR & PH result in:
 1. RV afterload (RV hypertrophy, dilatation and CHF).
 2. Decreased PBF.
 3. Gradual decrease of volume load on LA & LV (decreased LA & LV size).
 4. Decreased Lt-to-Rt shunting and later on reversed shunting (Rt-to-Lt) and cyanosis (Eisenmenger syndrome).

Clinical Manifestations

I-Symptomatology:

- 1-Feeding problems:** The infant is unable to nurse normally, resting frequently and requiring more than 20 minutes to ingest appropriate feeding.
- 2-Fatigue:** Because feeding is the most strenuous activity in the early life, the infant progressively tires with feeding.
- 3-Increased sweating:** because of increased sympathetic tone.
- 4-Respiratory symptoms:** Dyspnea is usually due to pulmonary venous congestion and/or respiratory infection.

II-General Examination:

- 1. Poor growth:** it is a common problem, and due to poor caloric intake and increased oxygen consumption due to excessive work of the heart and lung.

- 2. Pallor:** It is due to vasoconstriction of blood vessels secondary to increased sympathetic tone.

III-Cardiac Examination:

1-Inspection:

1. Diffusely increased precordial activity, over RV (parasternal), and over LV (apical) areas.
2. Precordial bulge (large shunt for 4-6 months or longer).

2-Palpation:

1. LV impulse is displaced laterally
2. A palpable systolic thrill along the lower left sternal border.
3. A hyperdynamic apex (LV volume load).
4. RV lift usually felt over the anterior precordium.

3-Percussion:

Cardiomegaly, mainly LV enlargement.

4-Auscultation:

1. S1 is normal, S2 is increased pulmonary component, with narrow split (PH).
2. Gallop rhythm may be heard (CHF).
3. A holosystolic, mid-frequency murmur in left parasternal area.
4. A mid-diastolic flow rumble may be audible in the apical area (large VSD).

Complications

1. Pulmonary Vascular Obstructive Disease :
 - Marked elevation of PVR usually seen in children with unrepaired large VSD.
 - Patients are cyanotic at rest.

- Examination reveals very short or no systolic murmur of VSD; signs of PH. X-ray demonstrates RV dilatation with prominent PA and its branches, and decreased pulmonary vascular markings in outer third of the lung fields.
 - ECG reveals Rt. Atrial hypertrophy (RAH) and pure Rt. Ventricular hypertrophy (RVH).
 - Echo-Doppler estimates pulmonary arterial pressure (PAP) which is usually above systemic arterial pressure (SAP).
2. Repeated episodes of respiratory infections.
 3. Repeated episodes of CHF & pulmonary edema.
 4. Infective endocarditis.
 5. Infundibular pulmonary stenosis.
 6. Chronic LV & RV dysfunction.

Investigations

I-Laboratory findings:

1. **CBC.**
2. **Blood culture** (indicated only when infective endocarditis is suspected).

II-Radiological Features:

- Generalized cardiomegaly LV enlargement then LV & RV enlargement.
- Prominence of PA and increased pulmonary vascular markings.

III-ECG:

- LAH and LVH in early cases.

- Later on, combined ventricular hypertrophy may develop.

IV-Echo-Doppler:

- The diagnosis of VSD can be confirmed using echocardiography.
- Echo-Doppler examination is useful for determination of:

1. Size:

Size of the defect is often expressed in terms of the size of the aortic root.

VSD > aortic dimension is large.

2. Site:

Determination of the site of VSD has prognostic and therapeutic values, e.g. of all VSDs, muscular VSDs have the highest rate of spontaneous closure.

3. Severity of PAP:

Echo-Doppler examination can estimate pulmonary artery pressure.

Treatment

I-Medical Treatment:

1. Afterload reduction: Captopril in a dose of 0.2-2.0 mg/kg/d, q 12 h.
2. Prevention and treatment of complications: Diuretics and digoxin in CHF.

II-Palliative Intervention:

Pulmonary artery banding is only indicated in critically ill infant with large VSD and closure cannot be done.

III-Definitive Correction:

a-Transcatheter closure.

b-Surgical closure:

It is indicated in all patients with large VSD before age of 1 year with the following:

1. Growth failure.
2. Life-threatening pulmonary infections.
3. Recurrent uncontrollable CHF.
4. $PAP > 50\% \text{ SAP}$.

Prognosis

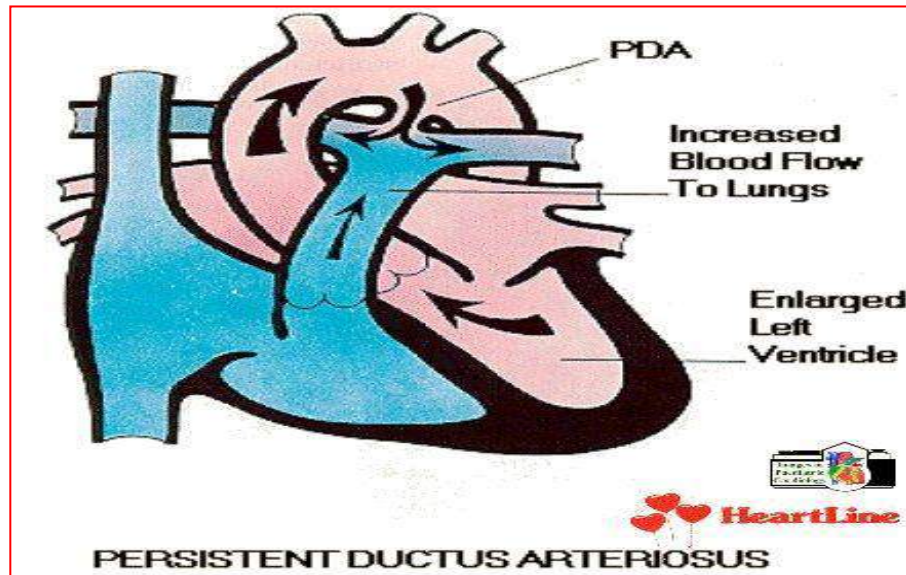
- Patients with closure of VSD in optimum time have good prognosis and need only endocarditis prophylaxis.
- Second operation to close residual or recurrent VSD is rare (5%).

Small VSD

- It is defined as defect less than the size of the aortic orifice, or defect less than 0.5 cm^2 which limits the left-to-right shunt (restrictive), or defect associated with pulmonary flow/ systemic flow ratio ($Q_p / Q_s < 1.5$).
- Patients with a small VSD are usually asymptomatic, discovered accidentally with routine examination when classic pansystolic, harsh murmur is heard at left parasternal area, associated with systolic thrill. X-ray and ECG are normal.
- Echo-Doppler examination confirms the diagnosis and PAP is normal.
- Complications are rare, just a small risk of infective endocarditis. It is associated with excellent prognosis because spontaneous closure within the first 2 years is high (80%).

- Therefore, surgical or transcatheter closure is not indicated.
- Only, endocarditis prophylaxis and follow up with echo-Doppler examination are recommended.

3-Patent Ductus Arteriosus (PDA)



Definition

Functional patency of the ductus arteriosus beyond a few hours after birth.

Embryology

- The ductus develops from the distal portion of the sixth aortic arch.
- It connects the main pulmonary trunk with descending Aorta.
- By 6 weeks of gestation, it carries RV output to aorta.
- Patency of the duct depends on placental prostaglandin (PGE₂) & low pO₂.

Anatomy

It begins at the descending aorta, 5-10 mm distal to the origin of the left subclavian artery and ends at the main pulmonary artery at the origin of left pulmonary artery.

Etiology

The exact cause of PDA is unknown, however, genetic factor, congenital rubella, and infant born at high altitudes may be predisposing factors.

Classification

- I. Small PDA.
- II. Large PDA.

I- Large PDA

Pathophysiology

As a result of the higher aortic pressure throughout the cardiac cycle (AOP =100/60mmHg, PAP=25/10mmHg); blood flow through the duct goes from aorta to PA during systole and diastole.

This leads to:

- Increased blood flow to PA, lungs, LA, and LV with sequelae similar to that of large VSD.
- Runoff of blood from aorta to PA during diastole, which leads to wide pulse pressure.

Clinical manifestations

1-Symptomatology:

Same as large VSD (dyspnea, fatigue, sweating).

2-General examination:

- Growth failure; only in large shunt with repeated CHF.
- Bounding peripheral arterial pulsations.
- Wide pulse pressure.

3-Cardiac examination:

Inspection: The precordium is bulging (cardiomegaly) and hyperactive (LVH)

Palpation:

- Hyperdynamic apex, which is shifted laterally & downward (LVD).
- A thrill, maximal in the 2nd left interspace. It is usually systolic but also may be palpated throughout the cardiac cycle.

Percussion: Cardiomegaly (LVD).

Auscultation:

- The P2 may be accentuated (PH).
- The classic murmur is:
 - Machinery, high frequency murmur associated with coarse sounds during systole.
 - Continuous, it begins soon after onset of S1, reaches maximal intensity at the end of systole, and wanes in late diastole.
 - Localized to the 2nd Left intercostal space or radiate to left sternal border or to left clavicle.
- Mid-diastolic rumbling murmur may be audible at the apex in case of large PDA shunt.

Complications

- Repeated CHF & chest infections.
- Infective endocarditis.
- Pulmonary or systemic emboli.

- Aneurysmal dilatation of the duct.
- PH & Eisenmenger syndrome.

Differential diagnosis

- Venous hum.
- AR+MR.
- AR+VSD.
- Any arteriovenous connection.

Investigations

1-Laboratory: For infective endocarditis.

2-X-ray: A prominent PA, increased pulmonary vascular markings, and enlarged heart, LA & LV.

3-ECG: LVH & LAH.

4-Echo-Doppler:

- The presence and size of a PDA must be confirmed using echocardiography.
- The presence and severity of PH are detected using Doppler study.

5-Cardiac Catheter: There is no longer use of catheter in diagnosis of PDA.

Treatment

1-Medical:

Treatment and prevention of complications.

2-Intervention:**➤ Indication:**

Irrespective of size, severity of shunt or age, patients with PDA require closure of the duct.

➤ Types of closure:

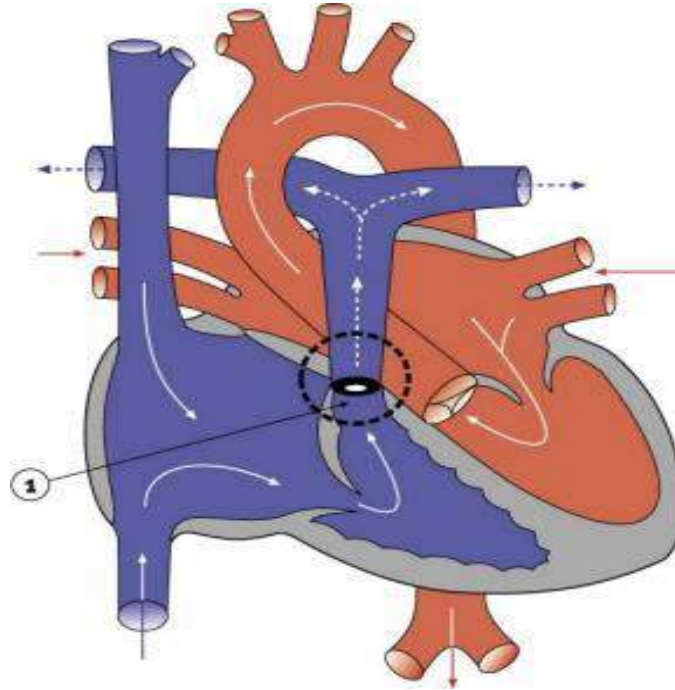
1-Transcatheter closure: In small and moderate-sized ducts, this technique has been shown to be effective and safe.

2-Surgical closure: In all PDA surgical division rather than simple ligation is performed.

II- SMALL PDA

- Usually, there are no significant hemodynamic changes.
- Patient is asymptomatic.
- By examination, only classic murmur is audible.
- ECG and x-ray are normal.
- Diagnosis is confirmed using echo-Doppler examination.
- Even small PDA should be closed because the risk for closure is less than the risk for endocarditis.

4-Pulmonary Valve Stenosis (PVS)



Definition

Obstruction to outflow from RV at Pulmonary valve.

Anatomy

It is characterized by fused commissures, the valve is mobile, dome-shaped structure with an orifice that may be tiny and sometimes eccentric.

Etiology

- Familial occurrence has been reported.
- The probability of recurrence in siblings has been estimated to be up to 3.0%.
- PVS is the most common cardiac anomaly in Noonan's Syndrome (autosomal dominant trait).

Classification

PVS is classified according to pressure gradient (PG) across the valve to:

- 1) Mild PS: PG=10-30 mmHg.
- 2) Moderate PS: PG=30-60 mmHg.
- 3) Severe PS: PG>60 mmHg.
- 4) Critical PS: PG>100 mmHg.

I- Moderate to Severe PVS

Pathophysiology

Right ventricular outflow tract obstruction (RVOTO) leads to:

- RV afterload which leads to increased RV pressure RVH and with long-standing disease subendocardial ischemia and impaired relaxation may occur (diastolic dysfunction with or without diastolic HF).
- Decreased RVOP which may lead in severe longstanding cases to impaired pulmonary function.

Clinical Manifestations

1-Symptomatology:

- Most patients with PS are asymptomatic.
- Dyspnea on exertion and exercise intolerance may occur in severe chronic cases.

2-General examination:

- Growth and development usually are normal.
- Cyanosis is common in severe PS (pulmonary hypoperfusion).

- Prominent venous pulsation" a wave" in the neck usually indicates severe PS.

3- Cardiac Examination:

Inspection:

- Diffuse apex left parasternal pulsation and precordial bulging may occur in severe longstanding cases.

Palpation:

- Left parasternal lift, tapping apex, RV epigastric pulsation.
- A systolic thrill at the 2nd and 3rd left space.

Percussion:

- Cardiomegaly in severe chronic cases.

Auscultation:

- S1 is normal, S2 is usually single with decreased P2.
- May be of a systolic ejection click (opening of pulmonary valve).
- The murmur is ejection systolic maximally audible over the pulmonary area. The duration of murmur is proportional to the degree of obstruction.

Complications

- Diastolic HF.
- IE.
- Arrhythmias.
- Syncope and sudden death.

Differential Diagnosis

1. Innocent murmur.
2. VSD.
3. ASD.
4. Pink Fallot.

Investigations

1-Laboratory: For infective endocarditis.

2-ECG: RVH, RAH.

3-X-Ray: Prominence of the main PA (post-stenotic dilatation), decreased pulmonary vascular markings (decreased pulmonary blood flow) and mild degree of cardiomegaly (RV).

4-Echo-Doppler: Confirmation of the presence of PVS, estimation of the severity (mild-moderate-severe) and evaluation of RV & LV diastolic and systolic functions.

5-Cardiac Catheter: Usually is not indicated in diagnosis of PVS.

Treatment

I-Medical: For prevention and treatment of complications.

II-Intervention:

1. Transcatheter Interventions: In patients with PG >50mmHg, balloon valvuloplasty is the treatment of choice.
2. Surgical correction: Only indicated in severely thickened cusps or severe annular hypoplasia or short PA.

Prognosis

Results of balloon valvuloplasty are excellent.

II-MILD PVS

- *It is defined as PVS with PG=10-30mmHg.*
- Usually, there are no significant hemodynamic changes.
- Patients are asymptomatic, X-ray and ECG are normal.
- Diagnosis is confirmed using echo-Doppler.
- Just, prevention of IE and follow up using Doppler examination are indicated.

III-Critical PVS

- In neonates with critical PS, the RV fills with the normal volume of blood, most of which must return to the RA via tricuspid regurgitation (TR) and then to persistent foramen ovale (PFO) to LA and LV and aorta, resulting in central cyanosis and severe distress.
- Pulmonary blood flow is ductal- dependent.
- 2-D echocardiography makes the diagnosis.
- The first step in treatment is PGE1 to make the ductus arteriosus open , then transcatheter repair.

II. Acquired Heart Diseases

1-Rheumatic Fever

- Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are considered the most important disease states that affect children in developing countries, including Egypt.

Etiology

Factors that have been considered in the development of rheumatic fever are the genetic susceptibility and streptococcal infection of the throat (group A β -hemolytic streptococcus= GAS).

1 - Susceptibility:

- This hereditary susceptibility is very important particularly in closed areas as in our villages where there is widespread marriage between relatives.
- This may be one of the factors leading to the high incidence of acute rheumatic fever and rheumatic heart disease in Egypt.
- The exact mode of inheritance is not really known. There may be association between some HLA markers and genetic susceptibility to RF.

2 - Streptococcal infection of the upper respiratory tract (i.e. tonsils, pharynx, middle ear, sinuses, and carious teeth)

- This is considered the second important factor in the etiology of the disease. In all the countries with controlled incidence of rheumatic fever and rheumatic heart disease their success is due to control of the streptococcal infection.

- Lack of measures to control streptococcal infection in Egypt is a very important factor in the failure to reduce the high incidence of acute rheumatic fever and rheumatic heart disease.
- It was noticed that streptococcal infection of the skin is not followed by acute rheumatic fever. This is because the skin contains lipids in a high concentration that have the ability to antagonize the streptococcal toxins and prevent them from reaching the reticuloendothelial system, thus no antistreptococcal antibodies could be formed.

Pathogenesis

The precise pathogenesis of acute rheumatic fever remains incompletely known. The various studies on the pathogenesis of acute rheumatic fever that were suggested by many workers over many years concluded the following theories or hypothesis:

1- Hypersensitivity Hypothesis:

- Allergy to infection by group A-beta hemolytic streptococcal strains
- It is suggested that the susceptible child reacts in a hypersensitive way to the streptococcal infection of the upper respiratory tract. It has been observed that the process of acute rheumatic fever development is characterized by the following phases:

a - Phase I: Streptococcal upper respiratory tract infection.

b - Phase II: Latent (silent) period, from 1-3 weeks.

c - Phase III: Acute rheumatic fever.

2 - Autoimmunity hypothesis:

- The basis of this hypothesis suggests that there is cross antigenicity between the streptococcal toxins and myocardial tissue, joints, or basal ganglia of the brain.

- Antistreptococcal antibodies, formed in the reticuloendothelial system, react with these tissues, and thus an antigen - antibody reaction occurs with development of rheumatic myocarditis, arthritis, or chorea.

3 - Circulating Immune - Complexes (CIC) Hypothesis:

- Streptococcal toxins secreted by the hemolytic streptococci induce the formation of antibodies in the reticuloendothelial system.
- The streptococcal toxins (being antigenic) react with the already formed antibodies, combining with the serum complement to form immune complexes that circulate in the blood.
- When the concentration of these complexes reaches a certain threshold, it reacts with the tissues of the susceptible children.

Epidemiology

Age:

- Acute rheumatic fever is rare under two years of age and uncommon under 5 years.
- Most cases occur between 5 and 15 years, with a peak incidence around 8 years of age.
- First attacks are uncommon after 25 years of age.

Sex:

- Rheumatic fever affects males and females equally. However, females are more susceptible to chorea.

Pathology

Two pathological lesions characterize acute rheumatic fever:

a - Exudative lesion: which occurs in cavities as pericardial sac (rheumatic pericarditis), and synovial cavity (rheumatic arthritis).

b - Proliferative lesion:

- It occurs in the heart (rheumatic carditis), basal ganglia (rheumatic chorea), and skin (skin manifestations).
- The characteristic lesion is the Aschoff bodies, which affect all the heart layers.
- The valve leaflets and chordae tendinae are swollen and edematous. Rheumatic vegetations are formed on the lines of valve closure.
- Manifestations of Acute Rheumatic Fever
- In about 50% of the cases, history of upper respiratory infection is obtained in the preceding two to three weeks.
- Following a latent period, manifestations of acute rheumatic fever appear.

Modified Jones Criteria for diagnosis of ARF (1992):

A - Major manifestations

- 1 – Carditis.
- 2 – Polyarthritis.
- 3 - Chorea.
- 4 - Erythema marginatum.
- 5 - Subcutaneous nodules.

B - Minor manifestations

1-Clinical:

- Fever.
- Arthralgia.

2- Laboratory:

- Increased ESR, and positive C-reactive protein.
- Prolonged P-R interval on electrocardiogram.

C- Supporting evidence of previous streptococcal infection

Positive throat culture or elevated ASOT.

The presence of two major or one major and two minor manifestations strongly favors the diagnosis of acute rheumatic fever, provided that evidences of recent streptococcal infection can be demonstrated.

Major manifestations**1- Carditis:**

- This is the most serious manifestation of ARF that may lead to significant mortality or morbidity.
- The cardiac affection may lead to pancarditis; with inflammation of endocardium, myocardium, and pericardium.

a) Endocarditis (Valvulitis)

It manifests by one or more cardiac murmurs

A- In children without previous RHD:

- Presence of apical pansystolic murmur (mitral regurgitation).
- With or without apical mid-diastolic murmur (Carey-Coombs murmur) with relative mitral stenosis due to edematous mitral valve.
- With or without basal early diastolic murmur (aortic regurgitation).
- Musical sound or murmur, due to rupture of chordae tendineae.

B- In children with previous RHD:

- Definite change in the character of any previous murmur.
- Or appearance of a new significant murmur.

b) Myocarditis

- The presence of persistent significant tachycardia out of proportion of fever (disproportionate tachycardia).
- Dyspnea.
- Gallop rhythm.
- Arrhythmias.
- Cardiomegaly.
- CHF may occur.

c) Pericarditis

- Rheumatic pericarditis is diagnosed by the auscultation of pericardial rub.
- Pericardial effusion may occur.

2 – Arthritis:

- Rheumatic arthritis has the following characteristics:
- The joints affected are hot, red, tender, swollen, with limitation of movements.
- It is migratory polyarthritis.
- The usual large joints affected are in that order of frequency, knees, ankles, wrists, elbows, hips, and shoulders.
- Small joints of the hands and feet may be affected.
- Joints of the spine (neck and back) may also be involved.
- There is dramatic response of rheumatic arthritis to therapeutic dose of salicylates.
- An affected joint frequently resolves within 5 days and, within 2 weeks, all joint symptoms usually subside completely.
- Rheumatic arthritis may involve only one joint (monoarthritis) and may not be fleeting.

3 – Chorea:

- Characteristically, the onset of (Sydenham chorea) is gradual or insidious, with irritability and apparent clumsiness. It is more common in girls.
- Grimacing, slurred speech, purposeless movements, muscular weakness (hypotonia) and emotional instability.
- Often, there is deterioration of handwriting and school performance.
- On raising the arms above the head, the patient turns them so as to oppose the backs of the hands.
- Also, stretching the arms in front of the body, there is hyperextension at the interphalangeal joints and flexion at the wrist joint producing the fork-like position.
- The condition is usually self-limited with complete recovery within three months.
- Purposeless involuntary movements affecting the muscles around the big joints.

- It may be mild or severe, unilateral (hemichorea), bilateral or one limb (monochorea) affection.
- The weakness and hypotonia may be so severe as to amount to paralysis (chorea mollis).
- Emotional instability may be mild or severe, with bouts of crying or laughing.

4 - Subcutaneous nodules:

- They usually appear only after several weeks of active rheumatic disease, and there is correlation between them and significant RHD.
- They are painless, firm, movable masses of variable size and are better seen than felt.
- The nodules are distributed over the extensor surfaces of certain joints particularly elbows, knees, wrists, the occipital region, knuckles, and over the spinous processes of the thoracic and lumbar regions.

5 - Erythema marginatum:

- Pink, slightly raised, small macules, annular or circinate rash.
- Occurring on the arms, trunk and legs (inner aspect of upper arms and thighs), but not on the face.
- It has an erythematous margin with sharply demarcated borders.
- There is no itching.

Diagnosis of Rheumatic Fever:

This includes the following items: clinical, laboratory, electrocardiographic, radiologic and echocardiographic diagnosis.

I. Clinical diagnosis

The presence of the clinical characteristics of any presentation of ARF, i.e., arthritis, carditis, chorea, skin manifestations, or any combinations.

II. Laboratory diagnosis

- **Determination of the acute phase reactants:** it is important in assessing the final diagnosis as well as the follow-up of the already diagnosed cases.
- **The laboratory tests include the following:**

a) Erythrocyte sedimentation rate (ESR):

- It is a non-specific test as it is raised in rheumatic as well as in non-rheumatic conditions. It is elevated in anemia, tuberculosis, liver cirrhosis and in renal disease. However, the sedimentation rate is within the normal levels in rheumatic congestive heart failure, simple rheumatic chorea and in cases presenting with erythema marginatum or subcutaneous nodules.
- The importance of the sedimentation rate is that it is a good negative test and in follow-up of rheumatic cases under treatment.
- The average normal values of the sedimentation rate are up to 20 mm and up to 40 mm in the first and second hours, respectively.

b) C-reactive protein:

- This is a protein produced by the liver, normal value up to 6mg/L.
- It is a non-specific test for rheumatic fever as it may be found in any pathological condition associated with tissue destruction or infection.
- Sometimes, it is normal in rheumatic chorea and erythema marginatum.
- On the other hand, unlike the ESR, the C-reactive protein is positive in rheumatic congestive heart failure.

c) Diagnosis of previous streptococcal infection:**I. Anti-Streptolysin -O– Antibodies Titer (ASOT):**

- The sera of all individuals contain anti-streptolysin - O – antibodies denoting previous streptococcal sore throat.
- The concentration of these antibodies has an inverse relationship to the time of occurrence of this infection.
- The antibodies start to rise in the second week of the attack.
- A rising titer is of more significant value than a non-rising one.
- The normal titer ranges from 160-400 Todd units in children.
- A titer higher than 400 is suggestive of the diagnosis of ARF, if correlated with the symptoms and signs together with the history.
- In 20% of children with acute rheumatic fever, ASOT may be within normal range, as in simple rheumatic chorea.

II. Throat culture:

- It may be negative due to the presence of a latent period between streptococcal infection and the appearance of ARF.

III. **ECG Diagnosis:**

Electrocardiographic changes that occur with acute rheumatic fever are characterized by:

a) Conduction abnormalities or arrhythmias:

- Prolongation of the P-R interval, which is a minor manifestation of ARF.
- Second or third-degree atrioventricular block may occur.
- Any arrhythmia may occur.

b) Changes related to myocarditis or pericarditis: ST-T wave changes.

IV. **Radiological Diagnosis:**

- Radiologic Features of the heart in ARF are non-diagnostic.
- Any of the following signs may appear in X-ray:
 - a) Cardiomegaly.
 - b) Pericardial effusion.
 - c) Signs of pulmonary venous congestion.

V. **Echo-Doppler Examination**

- It is very important in the diagnosis of active rheumatic carditis and chronic RHD.
- It can detect any valvular lesion, even without clinical manifestations (silent or subclinical rheumatic carditis).

Course and Prognosis

- The arthritis and chorea of ARF resolve completely without sequelae.
- The long-term sequelae are limited to carditis which leads to RHD with its complications.
- The prognosis depends on the clinical manifestations present at the time of the initial episode of ARF, its severity, and the presence of recurrences.
- Approximately 70% of patients with carditis during the initial episode (MR) recover with no clinical residual RHD.

Differential diagnosis

- Juvenile rheumatoid arthritis (Still's disease): the main differential features are high remittent fever, lack of organic heart disease, less salicylate response in Still's disease, and residual articular and periarticular swelling, with joint deformity.
- Infections in childhood, particularly acute osteomyelitis and septic arthritis.
- Systemic connective tissue disorders, especially polyarteritis nodosa and systemic lupus erythematosus.
- Acute leukemia: suspected when polyarthritis is associated with severe pallor and lymphadenopathy.
- Sickle cell disease.
- Rheumatic carditis must be differentiated from viral myocarditis or pericarditis, and infective endocarditis.
- Rheumatic chorea must be differentiated from cerebral palsy and tics.

Treatment of Acute Rheumatic Fever (ARF):

I. General treatment for all presentations:

1 - Bed Rest:

- Rest in bed is important especially in cases presenting with carditis to lessen the work and load on the heart.
- Rest in bed at hospital is obligatory in children presenting with congestive heart failure.
- Arthritis by itself limits movement of the child in bed.
- The duration of rest varies from one presentation to the other and usually varies from 1-3 months.
- Rest in bed is usually continued till disappearance of all the clinical signs of activity and return of the laboratory investigations to normal.

2 - For Streptococcal throat infection:

- Penicillin Procaine 600,000 I.U. per day for 10 days: this is to eradicate any streptococcal infection in the upper respiratory tract.
- Erythromycin: 30-50 mg/ kg/ day for 10 days in children allergic to penicillin.
- Culture and sensitivity of a throat swab to give the child the proper antibiotic.

3 - Supportive therapy:

- It is essential to give the diseased child with ARF a diet, which is easily digested and rich in vitamins.

II. Specific Treatment:

1 – Carditis:

- **Prednisone** 2 mg /kg / day, oral (tablet = 5 mg), in 4 divided doses after meals for 2-3 weeks.
- Dose of prednisone will be reduced gradually by 5mg/day every 2-3 days, over a period of 5 weeks.
- Rebound phenomenon can be minimized by the addition of aspirin therapy (overlap therapy), when starting the withdrawal of steroid treatment.

2 - Arthritis:

- **Salicylates (aspirin)** 75 mg/kg/day, oral, in 4 divided doses after meals to maintain a blood salicylate level of 25- 35 mg %.
- The salicylates should be given until the ESR levels are within the normal values.

3 - Simple Rheumatic chorea:

- Anti- inflammatory drugs are usually not indicated in treatment of rheumatic chorea.
- Sedatives are used:
 - a) **Phenobarbital (Luminal):** 3 mg/kg/day, oral.
 - b) **Haloperidol (Safenase):** 0.01 mg/kg/day, oral is an effective drug but long-term use may be complicated by drug-induced Parkinsonism.
 - c) **Recently, sodium valproate (Depakine);** an anti-epileptic drug, is used in a dose of 20-30 mg/kg/day, oral, with successful results.

4 - Skin manifestations:

Salicylates will be effective and sufficient in a dose of 60 mg/kg/day till the improvement of the clinical and laboratory manifestations.

Prevention of RF/RHD:

As rheumatic fever and rheumatic heart disease result from repeated attacks of Beta-hemolytic streptococcal infection of the upper respiratory passages in a hereditary susceptible individual, prevention of both initial (primary *prevention*) and recurrent (secondary *prevention*) episodes of ARF is very important to prevent RHD.

A. Primary prevention:

- I. General Measures:** good nutrition, proper housing, good ventilation, prevention of overcrowding and socio-economic development.
- II. Eradication of Streptococcal infection:**
 - Streptococcal infection is easily disseminated in over-crowded places with poor ventilation, which is commonly seen in classrooms and public places. Measures taken to control over-crowdedness and good ventilation are important.
 - Early diagnosis and proper treatment of streptococcal infection, using appropriate antibiotics for 10 days.

B. Secondary prevention:

- Continuous antibiotic prophylaxis (as long-acting penicillin) to prevent recurrences of RF.

- Continuous prophylaxis for all cases (secondary prevention of RF):

1. Benzathine Penicillin (Long-acting penicillin):

- IM injection, every 2 weeks.
- The dose according to body weight is:
 - Patients ≤ 27 kg $\rightarrow$ 600,000 IU.
 - Patients > 27 kg $\rightarrow$ 1,200,000 IU.

2. Sulfadiazine:

- Given orally if the child is sensitive to penicillin. The dose according to weight is:
 - Patients ≤ 27 kg $\rightarrow$ 0.5 gm once a day.
 - Patients > 27 kg $\rightarrow$ 1 gm once a day.

3. Penicillin V:

- given orally, in a dose of 250 mg twice/day.

Duration of secondary prophylaxis:

- If rheumatic fever occurs before or after the age of 12 years of life with valvular affection, the long-acting penicillin will be given for life.
- On the other hand; if rheumatic fever occurs before 12 years of age, without valvular lesion; it will be given till 25 years of age, and if it occurs after 12 years of age, prophylaxis will be given for 5 years from the last attack.

Chronic Rheumatic Heart Disease

Cases of chronic rheumatic valvular disease (RHD) that are inactive (quiescent) will be given only the prophylactic long-acting penicillin for life.

Types of valvular lesions:**a - Mitral Insufficiency:**

This clinical condition is characterized by:

- The first heart sound is muffled on the mitral area.
- Accentuated pulmonary component of the second sound, in cases complicated by pulmonary hypertension.
- The murmur is pansystolic, maximally heard on the mitral area and is transmitted to the axilla.

b - Mitral stenosis:

Valvular mitral stenosis varies from mild to severe degrees and this is characterized by:

- Usually takes 5-10 years, but the process may be accelerated in developing countries (2-3 years).
- Mitral stenosis may be isolated or together with mitral regurgitation.
- If the mitral stenosis is mild, the murmur will be mid-diastolic, and first sound may or may not be accentuated.
- If the mitral stenosis is severe (tight mitral stenosis), the mid-diastolic murmur will have a presystolic accentuation with a rumbling quality to end as an accentuated first sound.
- Also, an opening snap of mitral valve may be heard.
- The pulmonary component of the second heart sound will be accentuated together with signs of right ventricular hypertrophy.

c - Aortic Regurgitation:

- Rheumatic valvular affection of the aortic valve is less common than mitral valve disease.
- The murmur of aortic regurgitation is an early diastolic murmur, which is heard in the second aortic area.
- There are peripheral signs of high pulse pressure as water hammer pulse, pistol shot sign and nail-bed pulsations.

d - Aortic Stenosis:

- Isolated aortic stenosis is less common than aortic regurgitation.
- It is commonly associated with aortic regurgitation and the condition presents with double aortic lesion. There is an ejection systolic murmur at the first aortic area, which may be transmitted to the neck and apex.

Complications of chronic RHD:

1. Pulmonary hypertension.
2. Infective endocarditis.
3. Arrhythmias. e.g., AF.
4. Recurrent chest infections.
5. Growth retardation.
6. Embolic manifestations. e.g., Hemiplegia.

2-Congestive Heart Failure (CHF)

Definition

Inadequate oxygen delivery by the heart or circulatory system to meet the demands of the body.

Physiology

- Oxygen delivery is the product of the oxygen content of the blood and the cardiac output.
- Oxygen content is the oxygen saturation multiplied by the hemoglobin concentration.
- The cardiac output is the product of heart rate (chronotropic state) and stroke volume.
- Stroke volume is dependent on preload, afterload, and contractility (inotropic state).

Pathophysiology

Whatever the underlying cause of CHF, physiologic compensations and overcompensations may occur to combat the inadequate oxygen delivery (hypoperfusion).

1-Renal effect:

- Hypoperfusion stimulates the kidneys to release renin, which leads to:
- Release of angiotensin 1, which is converted to angiotensin 2 in the lung. This potent vasoconstrictor may improve tissue perfusion, although it increases afterload.

- Release of aldosterone which leads to salt and water retention and increase blood volume which improve tissue perfusion, although this may increase pre-load.

2-Cardiac effect:

- Increased pre-load may lead to increased myocardial contractility and increase stroke volume (Frank-Starling mechanism). Later on this may lead to ventricular hypertrophy and then dilatation and decreased systolic function.
- Increased after-load may increase myocardial oxygen demand and decrease ventricular compliance, which lead to decreased diastolic function.
- Increased pre and after load may increase intracardiac pressure which lead to release of atrial and ventricular natriuretic peptide (ANP & BNP), leading to vasodilatation and diuresis which compensate for loading effect.

3-Sympathetic effect:

Hypoperfusion causes increased circulating catecholamines → stimulation of β -receptors of the heart, → increasing heart rate and myocardial contractility → increase in COP + improve tissue perfusion → may alter chronotropic and inotropic states of the heart.

Pathology

Signs and symptoms of CHF may be due to:

- Pulmonary venous congestion (increased left-sided filling pressure).
- Systemic venous congestion (increased right-sided filling pressure).
- Decreased COP (decreased inotropic state).
- Loading effects (increased pre-and after-loading).
- Adaptive changes (increased neurohormonal responses), sympathetic stimulation and released atrial & ventricular peptides.

Classifications of CHF

A. Physiologic classification

1. Preload HF (VSD).
2. Afterload HF (AS).
3. Inotropic HF (myocarditis).
4. Chronotropic HF (arrhythmias).

B. Functional classification

1. Systolic HF (dilated cardiomyopathy).
2. Diastolic HF (hypertrophic cardiomyopathy).

C. Classification according to COP

1. Low COP (cardiomyopathy).
2. High COP (anemic HF).

D. Etiologic Classification:

1. CHD:
 - Acyanotic CHD with increased pulmonary blood flow (PBF): Large VSD, PDA, ASD, and common AV canal.
 - Cyanotic CHD with increased PBF: TGA, total anomalous pulmonary venous return (TAPVR), and truncus arteriosus.
 - Obstructive lesions: severe PS, AS, and coarctation of the aorta.
 - Coronary artery anomalies: origin of coronary artery from pulmonary artery.
 - Primary cardiomyopathies.

2. Acquired cardiac diseases:

- RHD (ARF).
- Anemic HF (hemolytic anemia).
- Hypertensive HF (PSAGN).
- Infectious disease: viral myocarditis.
- Dysrhythmias (SVT).
- Secondary cardiomyopathies: metabolic diseases.

Clinical Manifestations of CHF

I. Symptomatology:

A-Pulmonary Venous Congestion:

- a) **Tachypnea:** It represents the principle clinical manifestation of pulmonary edema.
- b) **Feeding difficulties:** These represent pulmonary venous congestion.
- c) **Dyspnea:** It signifies pulmonary congestion. Infants will require longer time to finish feeding, and this may be equivalent of dyspnea with exertion in older child.
- d) **Irritability:** It may be due to pulmonary congestion, feeding problems, and abdominal pain.
- e) **Cough:** It may be present in case of congestion of bronchial mucosa.

B-Systemic Venous Congestion:

- a) **Abdominal pain:** It is usually due to enlarged liver and stretching of the liver capsule.
- b) **Body swelling:** It represents edema of face or lower limbs.

- c) **Sweating:** It represents increase in sympathetic activity.
- d) **Palpitation:** Also, it is an indicator of increased sympathetic activity.

II. **General Examination:**

- a. Growth failure: Patients with HF are usually undernourished, this is due to impaired tissue perfusion, feeding problems, and hypermetabolism.
- b. Pulse: Pulse may be weak, rapid, and irregular (arrhythmias). Pulsus paradoxus or pulsus alternans may be present.
- c. Respiratory rate: Tachypnea secondary to pulmonary congestion and hyperpnea due to hypoxic stimulation of chemoreceptors may occur.
- d. Skin and mucus membranes: Pallor or cyanosis with or without mottling of the extremities is the manifestation of impaired arterial blood flow.
- e. Neck veins: Distended pulsating neck veins are seen in older children with HF. It is due to systemic venous congestion.
- f. Edema: Facial or peripheral edema usually signifies severe or longstanding HF.

III. **Systemic Examination:**

- a. Chest examination: wheezing may be a sign of LV failure, and rales are usually heard in case of pulmonary edema.
- b. Abdominal examination: Hepatomegaly is the most consistent sign of systemic venous congestion. The liver is usually soft, tender and may be pulsating due to tricuspid regurgitation.

IV. **Cardiac Examination:**

- Inspection & Palpation: Precordial activity may be decreased (impaired cardiac output) or increased (volume loading).

- Percussion: Cardiomegaly (ventricular dilatation to compensate impaired cardiac function).
- Auscultation: S3, S4 gallop {it may indicate rapid ventricle filling (volume loading) and/or decreased ventricle compliance (pressure loading)}. Murmur (usually AV valve regurgitation secondary to ventricular dilatation).

Complications of CHF

- Acute: Pulmonary edema, pulmonary infections, dysrhythmias, and Acute renal failure.
- Chronic: Cardiac asthma, Cardiac cirrhosis, and Cardiac cachexia.

Investigations

1-Laboratory:

- a. Blood gases and pH: Decrease PO₂ (ventilation-perfusion abnormality) and metabolic acidosis (impaired tissue perfusion).
- b. Serum electrolytes: hyponatremia (water retention), and hyperkalemia (tissue hypoxia) may occur.
- c. CBC: decreased Hb & RBC count and elevation of WBCs may be observed in CHF.
- d. Urinary findings: Albuminuria, microscopic hematuria, and low urinary output.

2-X-Ray Chest and Heart:

It is an excellent tool for assessing cardiac size and pulmonary congestion and pulmonary edema.

3-ECG:

Diagnosis of dysrhythmias as a cause or a complication and follow up of digitalis therapy and electrolyte changes.

4-Echo-Doppler:

- Diagnosis of underlying pathology. e.g. rheumatic carditis.
- Determination of systolic and diastolic functions of the heart:

✓ Systolic function is assessed by Ejection Fraction (EF):

$$EF = \frac{(\text{end-diastolic volume}) - (\text{end-systolic volume})}{(\text{End-diastolic volume})} \times 100$$

Normal value=45-65%.

✓ Diastolic function is assessed by E/A ratio:

E/A ratio=Early wave velocity of AV valve (E) / Atrial wave velocity of AV valve (A)

Normal value > 1.

Differential Diagnosis

- 1-D.D. from other causes of respiratory distress.
- 2-D.D. from other causes of generalized edema.
- 3-D.D. from other causes of systemic venous congestion.

Treatment of CHF

A. Medical:

1) General Measurements:

- **Hospitalization or intensive care unit:** Hospitalization is mandatory for patients with CHF, while ICU is indicated in acute severe and/or complicated cases.
- **Bed rest:** Bed rest with elevated head is recommended to ease respiration.
- **O₂ therapy:** Arterial O₂ tension is usually diminished in patients with CHF.
- **Diet:** Formulas are prescribed that provide adequate calories with low salt or completely restricted salt according to signs of systemic venous congestion.
- **Treatment Of Underlying Cause:** Prednisone in rheumatic carditis.

2) Specific Therapy:

- 1- **Preload reduction:** Diuretics (furosemide) 1-2 mg/kg/dose i.v., 1-4 mg/kg/day divided every 6-12 hours, PO.
- 2- **Afterload reduction:** ACE inhibitor (captopril) 0.2-2mg/kg/day, divided every 8-12 h, PO.
- 3- **Inotropic agents:** Digitalis (digoxin) which is indicated in Systolic Heart Failure.
 - Digitalizing dose=40-60 ug/kg, 1/2 of the dose initially followed by 1/4 every 6h, PO.

- Maintenance dose=25% of digitalizing dose, divided every 12h (IV dose is 75% of PO dose).

4- β -blockers: β -receptor blockade (propranolol). It is usually indicated in Diastolic Heart Failure and chronic HF.

Dose = 0.5-5 mg/kg/day divided every 6-12h, PO. β -blockers seem to up-regulate β -receptors or cause more receptors to become available on the cell surface, increasing contractility overall.

B. Interventional cardiac catheterization:

Balloon valvuloplasty in mitral stenosis or pulmonary stenosis.

C. Surgical treatment:

- **Palliative:** Pulmonary artery ligation in young infants with large VSD.
- **Corrective:** Closure of VSD or mitral valve repair.

Prognosis

The prognosis of CHF depends upon severity, duration of HF, and the availability of appropriate medical or surgical management of the underlying cause.

3-Infective Endocarditis (IE)

Definition

- It is the infection of the endocardial surface of the heart including the valves, or the intimal surface of certain arterial vessels.
- Infective endocarditis includes acute and subacute bacterial endocarditis as well as nonbacterial endocarditis caused by viruses, rickettsiae, and fungi.

Etiology

Predisposing factors:

Sources of bacteremia (in 30% of patients):

- Dental procedures with poor dental hygiene.
- Nonsterile surgical instrumentation of GIT, respiratory tract, or genitourinary tract (e.g., endoscopy or catheterization).
- Adenotonsillectomy.

High - risk groups:

- 1) Children with congenital heart disease (especially if associated with high velocity of blood) as Tetralogy of Fallot, VSD, Aortic stenosis, PDA, TGA, and palliative shunts.
- 2) Children with rheumatic heart disease (left -side valvular lesions) as mitral or aortic valve lesions.
- 3) Survivors of cardiac surgery, especially those with prosthetic material or valves.

- 4) Patients without pre-existing heart disease (rare) who have immune deficiency, taking immunosuppressant drugs, or with chronic intravascular catheters.

The organisms:

- Streptococcus viridans: (50% of cases). It was the most common organism.
- Staphylococcus aureus: (40% of cases). It is now more common even with no underlying heart disease.
- Others: (about 10% of cases). Enterococcus, Pseudomonas aeruginosa, viruses, and fungi (e.g. Candida).

Pathogenesis

- Normally, the body defense mechanisms can get rid of any bacteremia.
- If the endocardial surface has been damaged by any lesion like rheumatic or congenital heart disease, vegetations will be formed on this lesion and become large, friable, and containing viable organisms.
- Parts of vegetations may embolize to different parts of the body.

Epidemiology

- In developed countries: congenital heart disease is the main predisposing factor.
- In developing countries: rheumatic heart disease is the main predisposing factor.
- It is rare in infancy (usually follows open heart surgery in this age group).

Clinical Manifestations

I. History:

- Prior congenital or rheumatic heart disease.
- Preceding dental, intestinal, or urinary procedure.

II. Symptoms:

- Low - grade prolonged fever or high intermittent fever.
- Chills, fatigue, malaise, myalgia, arthralgia, night sweats, and headache.
- Chest and abdominal pain, nausea and vomiting, or weight loss and prostration.

III. Signs:

- Pallor, splenomegaly, petechiae, and may be pale clubbing.
- New or changing heart murmur, tachycardia, arrhythmias, or heart failure.
- Skin manifestations may develop late (Osler nodes in the pads of fingers, Janeway lesions on the palms and soles, and splinter nail bed hemorrhages).

IV. Manifestations of complications:

- Embolic phenomena (cerebral abscesses, mycotic aneurysms, CNS hemorrhage, or hematuria).
- Metastatic infections (arthritis, meningitis, pericarditis, or septic pulmonary emboli).

The identification of infective endocarditis is most often based on a high index of suspicion in the evaluation of infection in a child with an underlying contributory factor.

Laboratory Diagnosis

- Anemia, leukocytosis, elevated ESR and C-reactive protein, and hematuria.
- Blood culture: It is the most important for diagnosis and treatment, and it is positive in about 90% of cases within 48 hours.

Echocardiography:

It can detect the valvular vegetations (good +ve test).

Prognosis

- It was a fatal disease in the pre antibiotic era.
- Now, mortality rate is 20 - 25%.
- Morbidity occurs in 50 - 60% of diseased children due to heart failure, CNS complications, and systemic or pulmonary emboli.

Prevention (Endocarditis Prophylaxis)

- Proper oral hygiene and dental care.
- Antimicrobial prophylaxis must be given to susceptible children with heart disease prior to dental procedures, respiratory, GIT, or genitourinary surgery.
- For most children: Oral amoxicillin 50 mg / kg 1 hour before dental, oral, or respiratory tract procedures.
- For high - risk patients: IM Ampicillin 50 mg / kg + IM gentamicin 1.5 mg / kg 30 minutes before GIT or genitourinary surgery or instrumentation, and 6 hours later.

Treatment

I- Antibiotic treatment should be given:

- Immediately (based on clinical suspicion).
- By IV route.
- Combination antibiotics.
- For 4 - 6 weeks (hospitalization).

If a positive blood culture is obtained and the organism is identified, **specific therapy** should be instituted immediately. (Table)

II- Treatment of complications: e.g., heart failure.

III- Surgical treatment: Valve replacement is indicated in cases of:

- Unresponsiveness to medical treatment.
- Intractable heart failure due to severe valvular involvement.
- Infected prosthetic valve.
- Recurrent emboli.
- Myocardial abscess.
- Fungal endocarditis.

Organism	Drugs	Dose (IV)	Duration (Weeks)
1-Strept. viridans	Penicillin G	200,000 – 300,000 U/kg/day (every 4 hr)	4 - 6
	+ Gentamicin	5 mg / kg / day (every 8 hr)	2
2- Enterococcus	Ampicillin	300 mg / kg / day (every 4 hr)	4 - 6
	+ Gentamicin	5 mg / kg / day (every 8 hr)	4 – 6
3- Staph. aureus	Oxacillin	200 mg / kg / day (every 6 hr)	6 – 8
	Or Vancomycin	50 mg / kg / day (every 8 hr)	6 - 8

4-Cardiac Arrhythmias

Definition

- Disturbances of the rate and rhythm of the heart is called arrhythmia (dysrhythmia).
- Pediatric arrhythmias may be transient or permanent (according to the cause).
- **ECG** is the most important diagnostic method.

Etiology

1- Congenital: It may occur in normal or abnormal heart.

2- Acquired:

- Rheumatic fever.
- Myocarditis.
- Toxins (diphtheria).
- Drugs (theophylline, antiarrhythmic drugs).
- After cardiac surgery.

Classification

A. Tachyarrhythmias:

- Sinus tachycardia.
- Supraventricular tachycardia (SVT).
- Atrial flutter.
- Atrial fibrillation (AF).
- Ventricular tachycardia.
- Ventricular fibrillation.

B. Bradyarrhythmias:

- Sinus bradycardia.
- Sinus arrest & Sinoatrial block.
- Atrioventricular block (1 st , 2 nd , 3 rd degree heart block) .

C. Others:

- Extra systoles.
- Sick - Sinus Syndrome (tachycardia - bradycardia syndrome).

Supraventricular Tachycardia (SVT)

Paroxysmal atrial tachycardia or SVT is the most common tachyarrhythmia of childhood. It is caused by a re-entry circuit through the A - V node, which may be using an (accessory pathway).

Etiology

- Idiopathic (functional).
- Congenital heart disease. e.g. Ebstein anomaly , or atrial surgery .
- Rheumatic carditis.
- Cardiomyopathy.
- Adrenaline therapy.
- Acute systemic infection.
- Thyrotoxicosis.

Clinical Picture

- Abrupt onset and cessation.
- Attacks may last only few seconds or may persist for hours.
- The HR ranges from 180 - 300 / min.

1- Intrauterine SVT:

- Severe heart failure → hydrops fetalis.

2- SVT in neonates & infants:

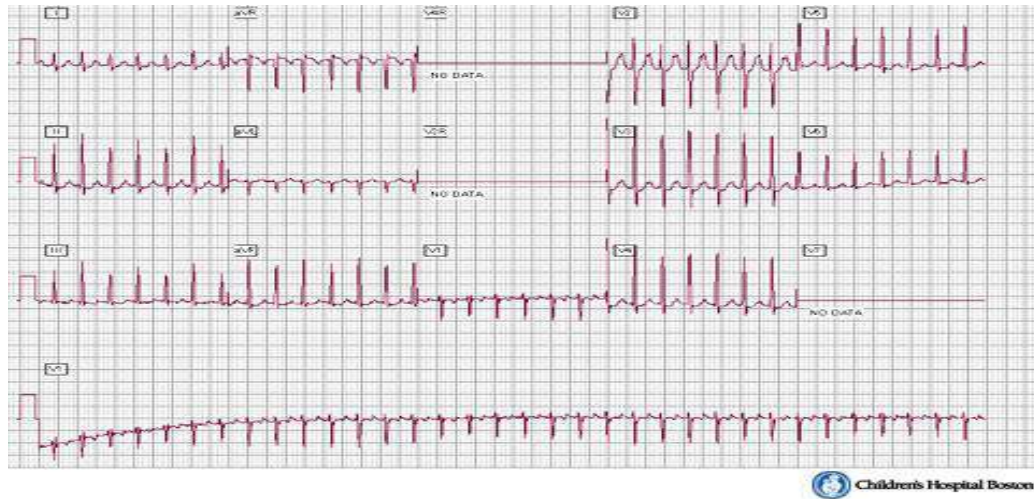
- Sudden pallor, tachypnea, refusal to feed, and vomiting.
- Baby looks ill, restless, irritable and mottled.
- Cardiomegaly and hepatomegaly.
- Tachycardia and congestive heart failure or death if prolonged SVT.

3- SVT in older children:

- Palpitation of sudden onset.
- Pulse is very rapid, regular and weak.
- Pallor and anxiety.
- Congestive HF may occur.

ECG: (the most important diagnostic method)

- Tachycardia (180 - 300 / min).
- Regular rhythm.
- P wave may or may not be present or may be inverted.
- Normal QRS.



Treatment

A- Initial therapy to convert the heart to sinus rhythm:

1- **Vagal stimulation:** (may abort the attack)

- For infants: an ice bag over the face.
- For children: carotid sinus massage, drinking ice water, straining, breath holding, or Valsalva maneuver.

2- **Electrical cardioversion:** Synchronized DC in urgent cases, as initial treatment when CHF occurs. The dose is 0.5-2 joules/kg.

3- **Adenosine:** It is the drug of choice, as it has negative chronotropic and inotropic actions and transient AV block, with a very short half-life. It is given by rapid IV push followed by saline flush in a dose of 100-150 µg/kg.

4- **Verapamil (isoptin):** It is a calcium channel blocker, given in older children in a dose of 0.1-0.2 mg/kg IV.

5- **Other drugs:** IV propranolol and digoxin may be used. Recently, **Amiodarone (cordaron)** IV infusion is effective.

B- Between the attacks:

- 1- **Digoxin or Propranolol or Amiodarone (oral):** as maintenance therapy.
- 2- **24-hour ECG (Holter) monitoring:** useful in diagnosis and treatment of some children.

Atrial Fibrillation (AF)

Etiology:

- Rheumatic mitral valve disease (MS).
- Intra-atrial surgery.
- Change from atrial flutter.
- ASD.
- Thyrotoxicosis.

Clinical Picture:

- Irregularly irregular pulse (120 - 180 / min.), with pulsus deficit.
- Palpitation (irregular).
- Absent (a) wave in neck vein pulsations.
- AF may precipitate heart failure or embolic complications.

ECG: (for diagnosis)

- Fibrillatory small waves before normal QRST waves.
- No P waves.
- QRST waves are irregular in timing.



Treatment:

- 1- **Electrical (DC) cardioversion:** It is the treatment of choice.
- 2- **Digoxin:** It restores the ventricular rate to normal. Then, sinus rhythm is restored with quinidine, procainamide, or DC cardioversion.
- 3- **Amiodarone:** IV infusion is effective.
- 4- **Anticoagulant therapy:** It is given to avoid thromboembolism. e.g. Warfarin.

Atrioventricular Block (Heart Block)

First - degree A-V block:

- Prolongation of the P-R interval.
- It is an ECG diagnosis.

Causes: ASD - rheumatic carditis - viral myocarditis - digoxin therapy.



Second - degree A-V block:

- Some sinus impulses are not conducted to the ventricles.

A. Mobitz type I (Wenckebach type): The P-R interval gradually lengthens until a QRS complex is skipped, and so on.



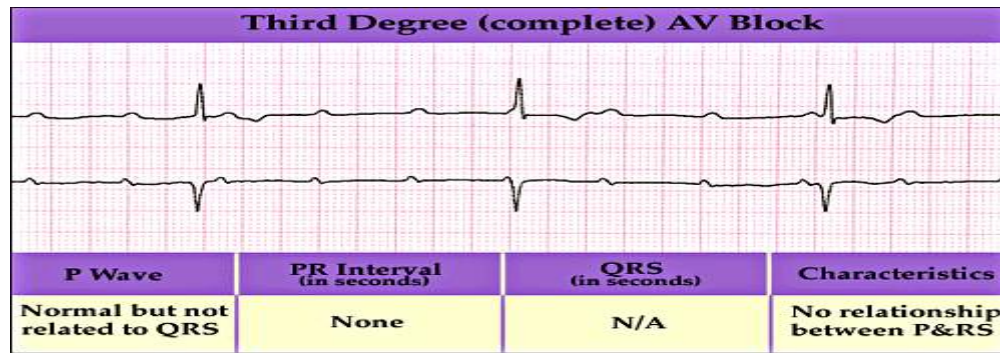
B. Mobitz type II: Occasional atrial contractions are not followed by QRS complexes (dropped beats).



- Second-degree heart block may occur in normal heart, with organic heart disease, or drug intoxication.

Third - degree A-V block: (Complete heart block)

- No impulses from the atria reach the ventricles (AV dissociation). So, they beat independently.
- ECG is diagnostic (P waves & QRS complexes have no constant relation).



Congenital complete A-V block:

Etiology: Maternal SLE - congenital heart disease as TGA and single ventricle.

Clinical picture: Hydrops fetalis - CHF - HR is less than 55 / min.

Acquired complete A-V block:

Etiology: Acute myocarditis - infective endocarditis - postsurgical repair of congenital heart disease - idiopathic.

Clinical picture:

- Commonly asymptomatic.
- Low COP symptoms: syncope, dizziness, and tiredness.
- Jugular venous pulse: cannon waves (A).
- HR is less than 55 / min.

Treatment:

- Drugs, which increase HR (Atropine, Isoproterenol, or Epinephrine).
- Cardiac pacing: Pacemaker implantation.

Pericarditis

Etiology of pericarditis

A. Infectious:

1. Viral: Coxsackie B - EB virus - influenza - others.
2. Bacterial (pyogenic, septic): Streptococcus - staphylococcus - pneumococcus - others.
3. TB: It may lead to constrictive pericarditis.
4. Fungal: Histoplasmosis - others.
5. Parasitic: Toxoplasmosis - others.

B. Connective Tissue Diseases:

1. Rheumatic fever.
2. Rheumatoid arthritis.
3. SLE.
4. Sarcoidosis.
5. Polyarteritis nodosa.

C. Metabolic - Endocrine:

1. Uremia.
2. Hypothyroidism.

D. Hematology - Oncology:

1. Bleeding diathesis.
2. Malignancy: primary, metastatic, leukemia.
3. Radiotherapy - induced.

E. Other Causes:

1. Trauma: Penetrating or blunt trauma.
2. Iatrogenic: Catheter - related.
3. Postpericardiotomy syndrome: After cardiac surgery. It may be autoimmune in origin.
4. Idiopathic: It may be viral or allergic.

Pathology & hemodynamics:

- Pericarditis may be fibrinous, purulent, or constrictive.
- Normal volume of pericardial fluid is 10 - 15 ml.
- Inflammation of pericardium → dry pericarditis → then accumulation of fluid (serous, fibrinous, purulent, or hemorrhagic) → pericardial effusion.
- Large amount of fluid → pericardial tamponade → decrease ventricular filling during diastole → elevated systemic and pulmonary venous pressures (if no treatment) → decrease COP, shock, and may be death.

Acute (Dry) Pericarditis**Clinical Manifestations****Symptoms:**

1. Chest pain (Pericardial pain): Sharp stabbing or stitching pain in the precordium, referred to the left shoulder. It may be epigastric. It is continuous not related to exertion, exaggerated on lying supine and relieved on leaning forwards.
2. Non-specific symptoms: Fever, malaise, vomiting, headache, dyspnea, cough, abdominal pain, and symptoms of the cause.

Signs:

- a. Pericardial friction rub: Superficial to-and-fro scratchy sound, unrelated to heart sounds, increased in intensity on increasing pressure on stethoscope over the chest wall, and best heard when the patient is leaning forward. It disappears with the development of pericardial effusion.
- b. other signs:
 - Signs of toxemia
 - Signs of the cause.

Pericardial Effusion

Clinical Manifestations

Symptoms :

1. Symptoms of low COP.
2. Symptoms of systemic congestion.
3. Symptoms of pulmonary congestion.
4. Dull aching pain over the precordium
5. Symptoms of the cause.

Signs:

Including Pericardial Tamponade & Constrictive Pericarditis

- Decubitus: Sitting and leaning forward (relieving posture).
- Signs of low COP: Pale cold skin, decrease systolic BP, pulsus paradoxus (paradoxical pulse) which is (exaggerated normal phenomenon of decrease systolic BP during inspiration with decrease pulse volume and return to normal during expiration).

- Signs of increased systemic venous pressure:
 - **Neck veins**: markedly congested with inspiratory filling (Kausmaul sign).
 - **Liver**: enlarged, tender and smooth surface.
 - **Ascites precox**: occurs before edema of lower limbs.
- Cardiac signs:
 - **Inspection & Palpation**: precordial bulge - apical impulse is weak or absent with quiet precordium.
 - **Percussion**: dullness outside the apex - dullness outside the right border of sternum - shifting dullness over the pulmonary area.
 - **Auscultation**: distant heart sounds.
- Signs of the cause.

Investigations:

- 1- **ECG**:
 - Early: ST- segment elevation above the isoelectric line.
 - After some days: ST- segment returns to the isoelectric line, with T-wave inversion.
 - Pericardial effusion: low voltage of the QRS complexes.
- 2- **Chest X- ray**: Cardiomegaly (increase C/T ratio), and Flask - shaped heart.
- 3- **Echocardiography**: It is a sensitive technique for detection of even mild effusion.

Differential Diagnosis:

- i. Other causes of chest pain: e.g., pleurisy, and spontaneous pneumothorax.
- ii. Differential diagnosis of the causes: by specific manifestations.



(Chest X-ray of pericardial effusion)

Constrictive pericarditis

- Thickening and fibrosis of the pericardium with calcification.
- Predisposing pericardial diseases: TB pericarditis, purulent pericarditis, malignancy, hemorrhages.
- Chest X- ray: small heart with calcification.
- Differential diagnosis: restrictive cardiomyopathy.
- Prognosis: good after treatment and surgery.

Treatment of Pericarditis

I. General lines:

- Symptomatic relief of pain.
- Treatment of the cause.
- Removal of fluid if there is danger of pericardial tamponade.

II. Specific lines:

- 1- Viral or Allergic pericarditis:
 - If mild: Aspirin (spontaneous recovery).
 - If severe: NSAID or corticosteroids.
- 2- Purulent (pyogenic) pericarditis:
 - IV antibiotics (according to culture & sensitivity).
 - Closed pericardial aspiration first (for diagnosis, culture & sensitivity, and decompression).
 - Open pericardial paracentesis (for treatment of pericardial tamponade).
- 3- TB pericarditis:
 - Anti-tuberculous drugs.
 - Corticosteroids.
- 4- Constrictive pericarditis:
 - Radical pericardiectomy (surgical removal of the thick pericardium)

6-Systemic Hypertension

In infancy and childhood

Definition

- Hypertension is diagnosed when the blood pressure (especially the diastolic value) is persistently above the 95th percentile for age.
- Because systemic BP gradually increases with age and correlates with weight and height throughout childhood and adolescence, reference standards of BP measurements are necessary for diagnosis.
- Repeated measurements of blood pressure are required for diagnosis.
- The prevalence of systemic hypertension in the pediatric age group is about 1-3 %.

Methods of accurate BP measurement

In infants:

- i. Auscultation method.
- ii. Palpation method.
- iii. Flush method.
- iv. Doppler & oscillometric devices.

In children:

- i. Auscultation method.
- ii. Doppler & oscillometric devices.

Etiology and Pathophysiology:

- Blood pressure (BP) = cardiac output x peripheral vascular resistance.
- An increase in cardiac output or peripheral vascular resistance results in hypertension.
- When the cause can be explained, it is called (secondary hypertension).
- Primary or essential hypertension implies that no known underlying disease is present.

Primary (Essential) Hypertension:

The cause is likely to be multifactorial; however, genetic alterations of calcium and sodium transport, the renin-angiotensin system, and insulin sensitivity have been implicated in this disorder.

The plasma renin activity level may be high, normal, or low.

The diagnosis of essential hypertension is suggested by:

1. The age of patient (usually adolescents, uncommon in children younger than 10 years of age).
2. Level of blood pressure elevation (usually mild, at or slightly above 95th percentile for age).
3. Weight (mild to moderate obesity).
4. Positive family history of essential hypertension.
5. No signs and symptoms of underlying disease.

Secondary Hypertension:

It is more common than essential hypertension.

The diagnosis of secondary hypertension is suggested by:

1. The age of patient (it may occur at any age even during the neonatal period as in renal artery stenosis).
2. Level of blood pressure elevation (mild to extreme).
3. Weight (normal or obesity or decreased).
4. Positive family history of renal disease or premature cardiovascular disease may be elicited.
5. The presence of signs and symptoms of underlying disease.

Secondary hypertension in infants and children may be transient (or intermittent) or chronic hypertension.

Causes

1- Renal: (represent about 75 – 80 % of the causes)

- Acute and chronic glomerulonephritis.
- Hemolytic-uremic syndrome.
- Chronic pyelonephritis.
- Acute tubular necrosis.
- Hydronephrosis.
- Acute pyelonephritis.
- Multi-cystic kidney.
- Renal trauma.
- Renal tumors.
- Hypervolemia.
- Ureteral obstruction.

Renal pathology → renal ischemia → hyperreninemia → angiotensinogen → angiotensin I → angiotensin II → vasoconstriction (Increased peripheral resistance) and aldosterone secretion (sodium and water retention).

2- Vascular:

- Coarctation of aorta.
- Renal artery stenosis or thrombosis.
- Renal vein thrombosis.
- Umbilical artery catheterization with thrombosis.
- Vasculitis.

3- Endocrinopathies:

- Hyperthyroidism.
- Hyperparathyroidism.
- Congenital adrenal hyperplasia.
- Cushing syndrome.
- Primary hyperaldosteronism.
- Pheochromocytoma (catecholamine-secreting tumors).
- Neuroblastoma.

4- Central and autonomic nervous system:

- Increased intracranial pressure (mass, tumor, hemorrhage).
- Guillain - Barre syndrome.
- Poliomyelitis.
- Encephalitis.

5- Drugs and poisons:

- Cocaine.
- Sympathomimetic agents.
- Amphetamines.
- Corticosteroids and cyclosporine.
- Lead & mercury poisoning.

- Vitamin D intoxication.

6- Miscellaneous:

- Hypercalcemia.
- Chronic upper airway obstruction (e.g., adenoids).

Clinical Manifestations

I. Asymptomatic hypertension: It is detected accidentally during routine examination.

II. Symptoms:

- Headache, dizziness, and blurring of vision.
- Hypertensive encephalopathy (vomiting, hyperthermia, stupor, seizures, and coma).
- Hypertensive heart failure and deterioration of renal function.

III. Clinical features of the cause:

- Measurement of height and weight.
- Measurement of blood pressure in all 4 limbs.
- Flank masses should be detected.
- Specific clinical signs of the cause.

Diagnosis

- 1- Repeated measurement of BP.
- 2- Screening tests:
 - Complete blood count.
 - Urinalysis & culture.
 - Serum electrolytes, BUN, creatinine and uric acid.
 - Renal imaging (IVP, ultrasound, radionuclide scan, Doppler ultrasound or renal angiography).

3- Plasma renin activity:

- Elevated: renal or renovascular involvement.
- Suppressed: mineralocorticoid excess.

4- ECG and Echocardiography: For cardiac assessment.

5- Other investigations: According to the cause.

Course and Prognosis

1- Primary hypertension: Most children continue to have hypertension as adults.

2- Transient 2ry hypertension: It usually disappears after treatment.

3- Chronic 2ry hypertension:

- Treatable causes: good prognosis.
- Untreatable causes: gradual deterioration of cardiac and renal function.

Death may occur due to heart failure, hypertensive encephalopathy, or intracranial hemorrhage.

Prevention

Avoid risk factors: obesity, elevated serum cholesterol, high dietary sodium intake, sedentary lifestyle, and smoking.

Treatment

- I. **Mild essential hypertension:** Weight reduction, decrease sodium and cholesterol intake, and increase physical activity.
- II. **Hypertensive crisis or emergencies (encephalopathy or HF):** Rapid reduction in blood pressure by the use of intravenous labetalol, hydralazine, diazoxide, or sodium nitroprusside. Sublingual nifedipine plus IV furosemide may be used.

III. Renal artery stenosis: Percutaneous transluminal balloon dilatation.

IV. Nephrectomy: It may be indicated in uncontrolled hypertension due to renal or renovascular disorders.

Antihypertensive Drugs:

Drugs	Dose	Route	Duration
1- Vasodilators: - Hydralazine - Diazoxide - Nitroprusside	0.1-0.5 mg /kg/ dose 1 - 5 mg / kg / dose 0.5- 8 ug / kg / min	IV IV push IV	2 - 4 hr 6 - 24 hr Infusion
2- Adrenergic Blockers: - Propranolol - Labetalol	0.25 - 1 mg / kg/ dose 0.2 - 2 mg / kg / hr	PO I V	6 - 8 hr Infusion
3- Sympatholytic Agents: - Clonidine	3 - 5 ug / kg / dose	PO	6 - 8 hr
4- Angiotensin Converting enzyme (ACE) Inhibitors: - Captopril	0.1 - 4 mg / kg / dose	PO	8 hr
5- Calcium Channel Blockers: - Nifedipine	0.2 - 0.5 mg / kg / dose	PO sublingual	4 - 6 hr
6- Diuretics: - Furosemide	1 - 2 mg / kg / dose	IV, PO	4 - 6 hr

Practice Questions

(Choose one correct answer)

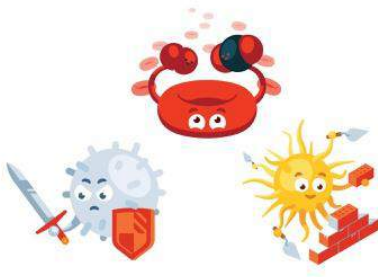
- 1- The commonest VSD location type is :
 - a) muscular.
 - b) membranous.
 - c) infundibular.
 - d) endocardial cushion defect.

- 2- In large PDA shunt, the following murmur may be heard at the apex :
 - a) continuous machinery.
 - b) pansystolic.
 - c) mid-diastolic.
 - d) ejection systolic.

- 3- The treatment of choice of valvular PS is :
 - a) medical treatment.
 - b) transcatheter balloon valvuloplasty.
 - c) surgical correction.
 - d) none of the above.

- 4- The drug used for afterload reduction in treatment of CHF in children is :
 - a) captopril.
 - b) propranolol.
 - c) digoxin.
 - d) furosemide.

- 5- Signs of low cardiac output in pericardial tamponade include the following EXCEPT :
 - a) pulsus paradoxus.
 - b) decrease systolic BP.
 - c) pale cold skin.
 - d) Kausmaul sign.



Chapter 14

Hematologic and Oncologic Disorders

Objectives:

1. Understand the process of hematopoiesis under normal conditions.
2. Classify different types of anemias, coagulation and bleeding disorders and common childhood malignancies.
3. Correlates between the clinical presentations and the special nature of each hematological disorder
4. Enumerate findings in hematological investigations in different diseases
5. Formulate a management plan for hematological disorders.
6. Understand the basics of transfusion medicine and the uses and side effects of different blood products.
7. Describe the basic steps of bone marrow transplantation, and its main indication

Contents:

1. Introduction

- Blood components
- Normal values
- Hematopoiesis

2. The anemias

- Physiologic anemia of infancy
- Iron Deficiency Anemia
- Hemolytic Anemias
 - o Thalassemia
 - o Sickle cell anemia
- Aplastic anemia

3. Hemorrhagic Diseases

- Normal hemostasis
- Coagulation disorders
- Purpura
- Idiopathic thrombocytopenic purpura
- Henoch-Schoenlein purpura

4. Childhood hematologic malignancies

- Childhood leukemia
- Childhood lymphomas

5. Blood Transfusion

6. Pediatric Bone marrow transplantation

Introduction to Pediatric Hematology

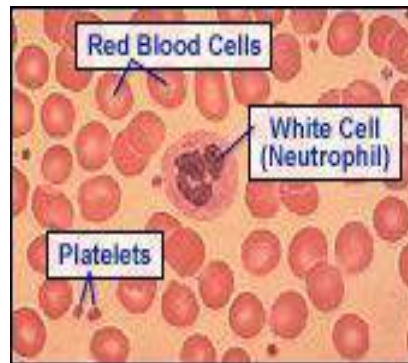
Definition

Hematology is the study of the blood forming tissues and circulating blood components.

Composition of The Blood

A. Cellular elements:

- 1) Red blood cells
- 2) Platelets
- 3) White blood cells which include:
 - a) **Granulocytes:** with granules in cytoplasm including:
 - i. Neutrophils: Act as phagocytes on infection.
 - ii. Basophils: Contains histamine, which increases blood flow to injured tissues and heparin, which inhibits clotting.
 - iii. Eosinophils: Kills parasites and helps in control of inflammation and allergic reactions.
 - b) **Agranulocytes:** with no granules in cytoplasm including:
 - i. Monocytes: which are important in protecting the body against bacteria.
 - ii. Lymphocytes (T& B lymphocytes): has role in immunity; produces antibodies that attack specific foreign substances.



B. Fluid elements:

Plasma is the fluid portion of the blood in which the cellular elements are suspended and circulate through the body, its function is to transfer RBCs, WBCs, platelets, and nutrients to every part of the body.

It is composed of:

- **Water**: 70% of the body, most of it contained in and around cells.
- **Electrolytes**: Na, K, Cl, Mg, hydrogen ions, and calcium.
- **Proteins**: which are classified into:
 - Coagulant proteins that form clots.
 - Anticoagulant proteins that break down excessive coagulation.
 - Antibodies including immunoglobulins & complement system.
 - Transport proteins:
 - ***Albumin***: which maintains the osmotic pressure & prevents extracellular leakage of blood fluids.
 - ***Transferrin***: binds and transports the iron to the bone marrow for RBCs production.
 - ***Transcobalamin***: transporter for vit B12.
 - ***Haptoglobin***: carrier of hemoglobin released from destroyed RBCs.
 - ***Lipoproteins***: for cholesterol, lipids & triglycerides.

Normal Blood Values

A. **Blood volume**:

- In premature neonates: 08 ml/kg
- In full term neonates: 85 ml/kg
- After the age of 2 months: 75-80 ml/kg

B. **Hematocrit value**: Packed Cell Volume (PCV)

C. **Red cell life span**: About 120 days

D. **Reticulocytes**:

4-6% at birth drops rapidly in the 1st week of life to reach 0.5 - 1.5%.

E. **Normoblasts**:

In full term 3-10% of white blood cells

In premature 10-20%.

Then disappear during the 1st week.

F. Red cell values at various ages: Mean and lower limit of normal:

Age	HB (g/dL)		PCV (%)		RBCs (million/mm ³)	
	Mean	-2SD	Mean	-2SD	Mean	-2SD
At birth	16.5	13.5	51	42	4.7	3.9
2 months	11.5	9	35	28	3.8	2.7
0.5 – 2 yrs.	12	10.5	36	33	4.5	3.7
2 – 6 yrs.	12.5	11.5	37	34	4.6	3.9
6 – 12 yrs.	13.5	11.5	40	35	4.6	4
12 -18 yrs.						
F	14	12	41	36	4.6	4.1
M	14.5	13	43	37	4.9	4.5

G. HEMOGLOBIN (Hb):

- Red blood cells are filled with a special red colored molecule called hemoglobin. It picks up oxygen in areas where oxygen is abundant and releases oxygen in tissues where the oxygen concentration is lowest.
- Hb is a complex protein consisting of iron containing heme groups and globin.
- The Hb molecule is a tetramer made up of two pairs of polypeptide chains, each chain having a heme group attached.
- The polypeptide chains of various Hb are of chemically different types.
- Within the cells of the embryo, fetus, child, and adult 3 different Hb may normally be detected.

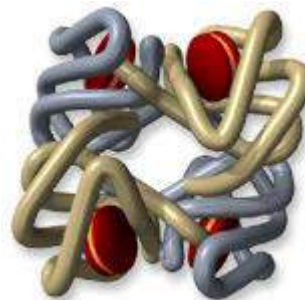


Fig.3:Proportions of the various human hemoglobin polypeptide chains through early life

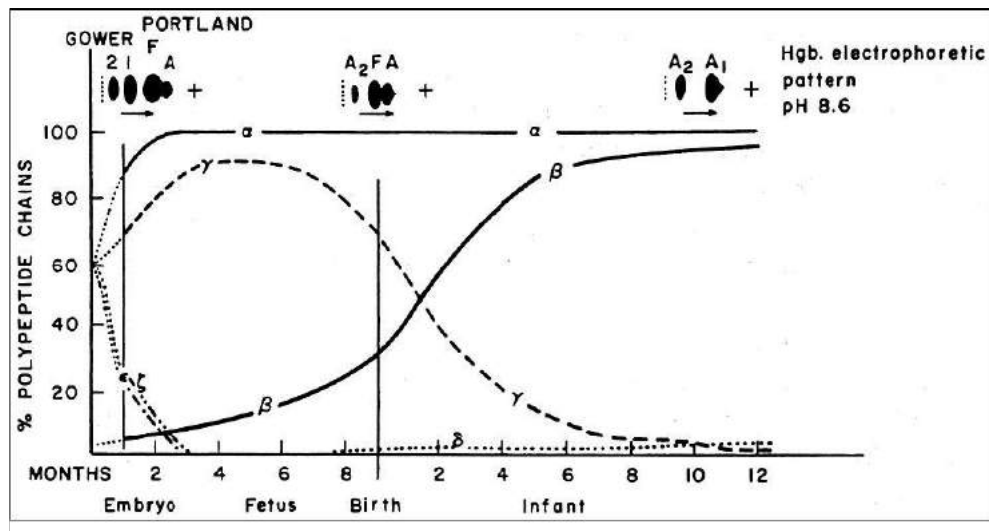


Table 1: Different Hemoglobin Types

Hb type	% At birth	% After 2 years
Embryonic type	Embryonic Hb may be present at birth in small percentage.	Major embryonic Hb is not present after 3rd month of gestation.
Fetal type($\alpha_2\gamma_2$)	45-90%	3%
Adult type		
A1 ($\alpha_2\beta_2$)	10-55%	95%
A2 ($\alpha_2\delta_2$)	0-1.5%	1.5-3.5%

H. RED BLOOD CELL INDICES:

➤ Mean corpuscular volume (M.C.V.)

- It is the average size of individual red cell.
- The lower limit for MCV is approximately 70 fL + age in years.
- The upper limit for MCV after 6 months of age is approximately 85 + 0.6 fL per year until the upper limit of 96 fL in adults is reached.

$$\text{Hematocrit \%} \times 10$$

$$\text{➤ } \underline{\text{M.C.V (fL)}} = \frac{\text{Hematocrit \%} \times 10}{\text{Red cell count (million/m}^3\text{)}}$$

➤ **Mean corpuscular hemoglobin (M. C. H):**

It is the average quantity of Hb in individual red cell (27 - 32 Picogram.)

$$\text{Hb. (gram \%)} \times 10$$

➤ **M. C. H.(pg) =**
$$\frac{\text{Hb. (gram \%)} \times 10}{\text{R.B.Cs (millions/ m}^3\text{)}}$$

➤ **Mean corpuscular hemoglobin concentration (M. C. H. C):**

Average concentration of Hb in individual RBC (32 - 38 %)

$$\text{Hb (g/ 100 ml)} \times 100$$

M.C.H.C. (%) =
$$\frac{\text{Hb (g/ 100 ml)} \times 100}{\text{Hematocrit \%}}$$

I. WHITE BLOOD CELLS

- At birth: 20000/c.mm. Then drops
- In the first week of life: 12000/c.mm.
- At the end of the 1st year: 4000 to 11000/c.mm.

J. PLATELET COUNT:

- Normal count is 150,000 - 450,000/c.mm

Hematopoiesis

Hematopoiesis is the formation of the blood cellular components. All the cells of the hematopoietic system originate from hematopoietic stem cells (HSCs) which originate from pluripotent stem cell, which originate from the totipotent stem cell.

Hematopoietic stem cells have the intrinsic capacity for self-renewal and differentiation into the common lymphoid progenitor (CLP) which develops into T and B cells (T and B lymphocytes), and common myeloid progenitor (CMP) gives rise to erythrocytes, megakaryocytes, monocytes, and granulocytes.

Erythropoiesis:

Is a process of formation of mature red blood cells from HSCs under the control of erythropoietin hormone.

- Erythrocytes progress from blast precursors in the marrow over a period of five days.
- Then they are released into the blood as reticulocytes.
- The reticulocyte changes to an erythrocyte in one day and circulates for 120 days before being destroyed in the reticuloendothelial system.

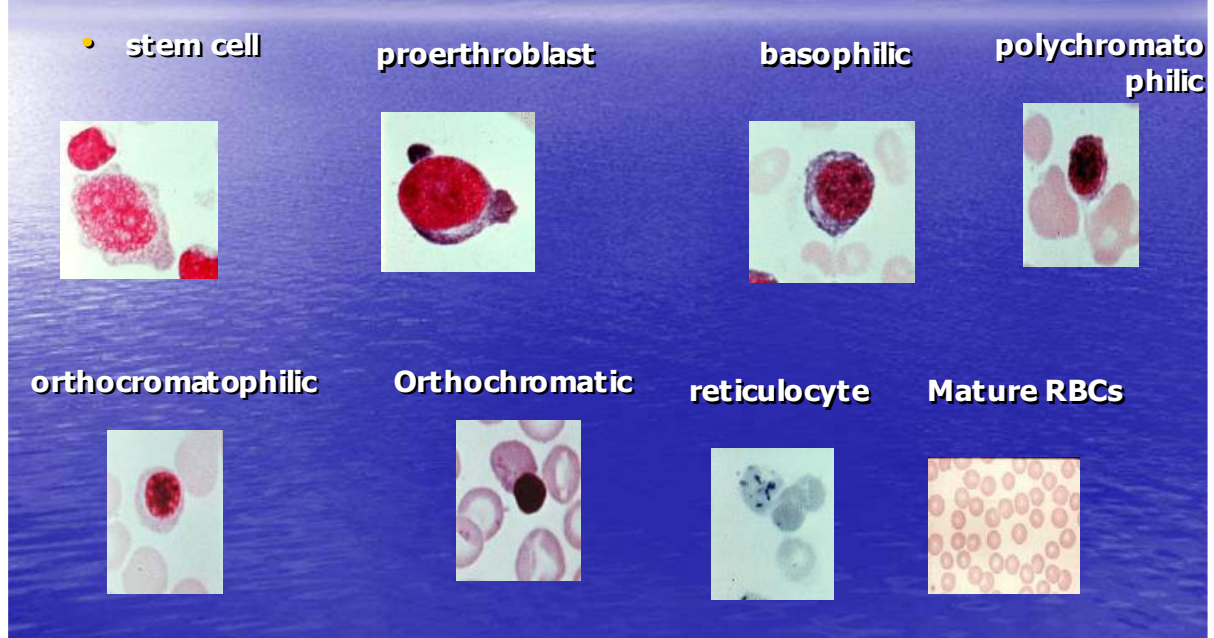
Numerous substances are necessary for creation of erythrocytes:

- Metals (iron, cobalt, manganese).
- Vitamins (B12, B6, C, E, folate, riboflavin, and thiamin)
- Amino acids.

Regulatory substances necessary for normal erythropoiesis include erythropoietin, thyroid hormones, and androgens.

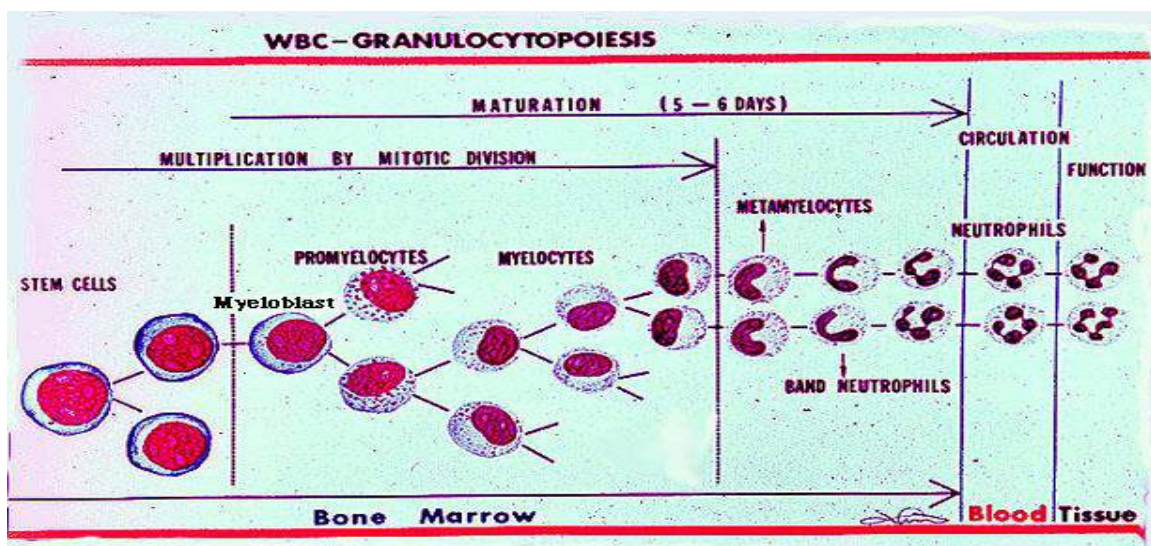
Stem cell $\longrightarrow$ erythroblast $\longrightarrow$ basophilic normoblast (early) $\longrightarrow$
polychromatic normoblast (intermediate) $\longrightarrow$ orthochromatic normoblast (late) $\longrightarrow$
reticulocyte $\longrightarrow$ mature red blood cell.

Erythropoiesis



Granulocytopoiesis:

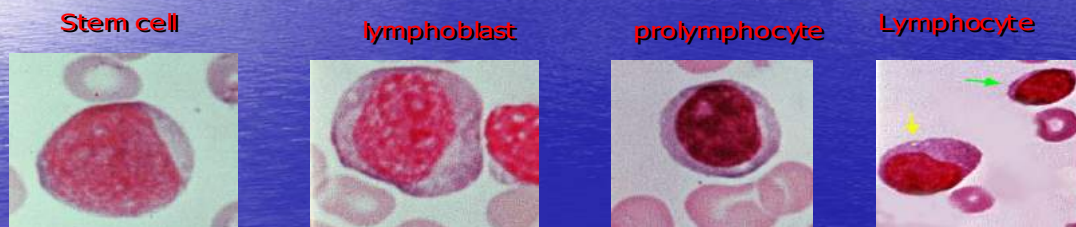
Stem cell $\longrightarrow$ myeloblast $\longrightarrow$ promyelocyte $\longrightarrow$ myelocyte $\longrightarrow$ metamyelocyte $\longrightarrow$ band cell $\longrightarrow$ neutrophil



Lymphopoiesis

Stem cell $\longrightarrow$ lymphoblast $\longrightarrow$ prolymphocyte $\longrightarrow$ lymphocyte

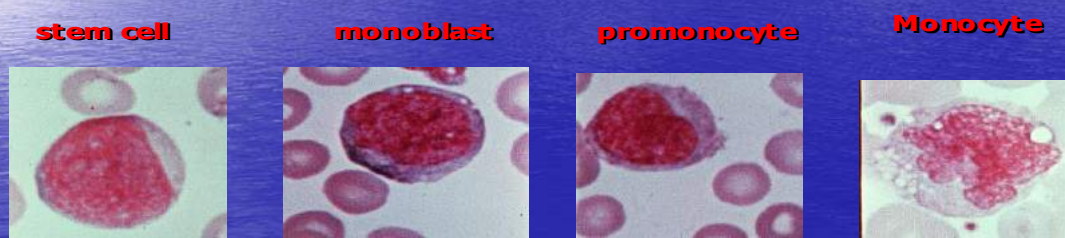
Lymphocyte Development



Monopoiesis:

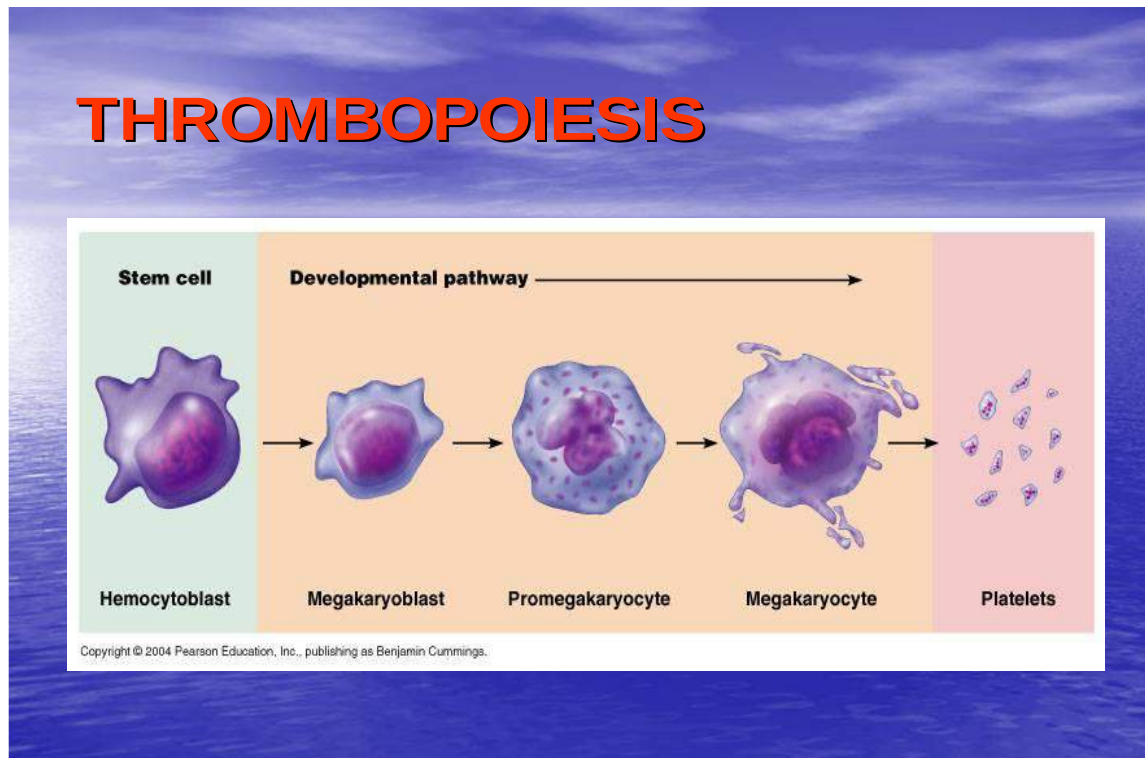
Stem cell $\longrightarrow$ monoblast $\longrightarrow$ promonocyte $\longrightarrow$ monocyte

Monocyte Development



Thrombopoiesis:

Stem cell $\longrightarrow$ megakryoblast $\longrightarrow$ promegakaryocyte
 megakryocyte $\longrightarrow$ platelet



Sites of formation of hematopoietic cells:

The process of hematopoiesis firstly starts at the extra-embryonic mesoderm in the yolk sac on day 10 of development.

Hematopoietic stem cell colonizes the liver at 5 weeks of gestation and remains the dominant hematopoietic organ throughout the fetal life.

That seeds the hematopoietic stem cells to the bone marrow at 8 weeks and the thymic rudiment at 8 weeks, and spleen at 12 weeks.

Liver stem cells differentiate in the thymus into mature T- lymphocyte which populate fetal lymph node, spleen and gut at 12 weeks and peripheral lymphoid tissue at 20 weeks.

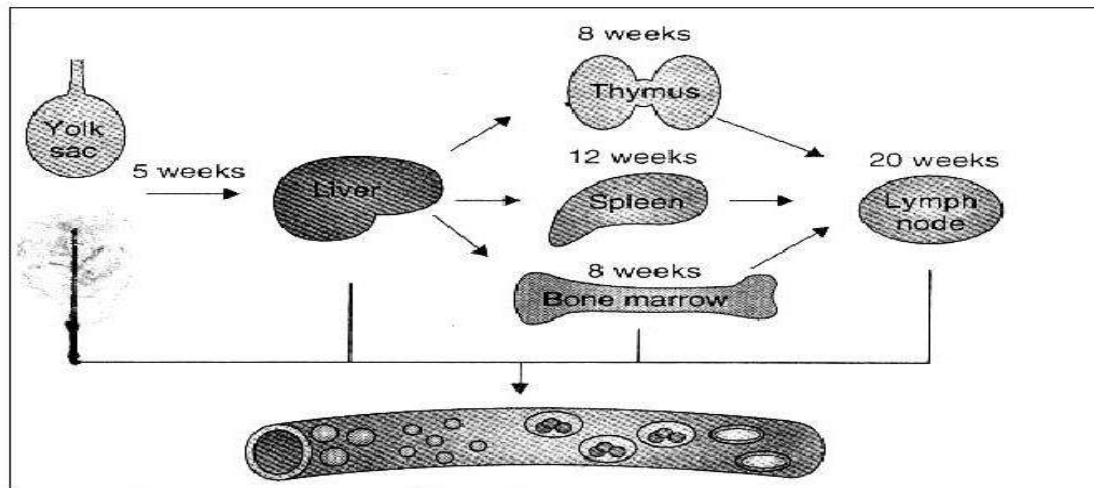


Figure I: Sites of formation of hematopoietic cells

The process of differentiation and self-renewal of the progenitor cells must be coupled to each other.

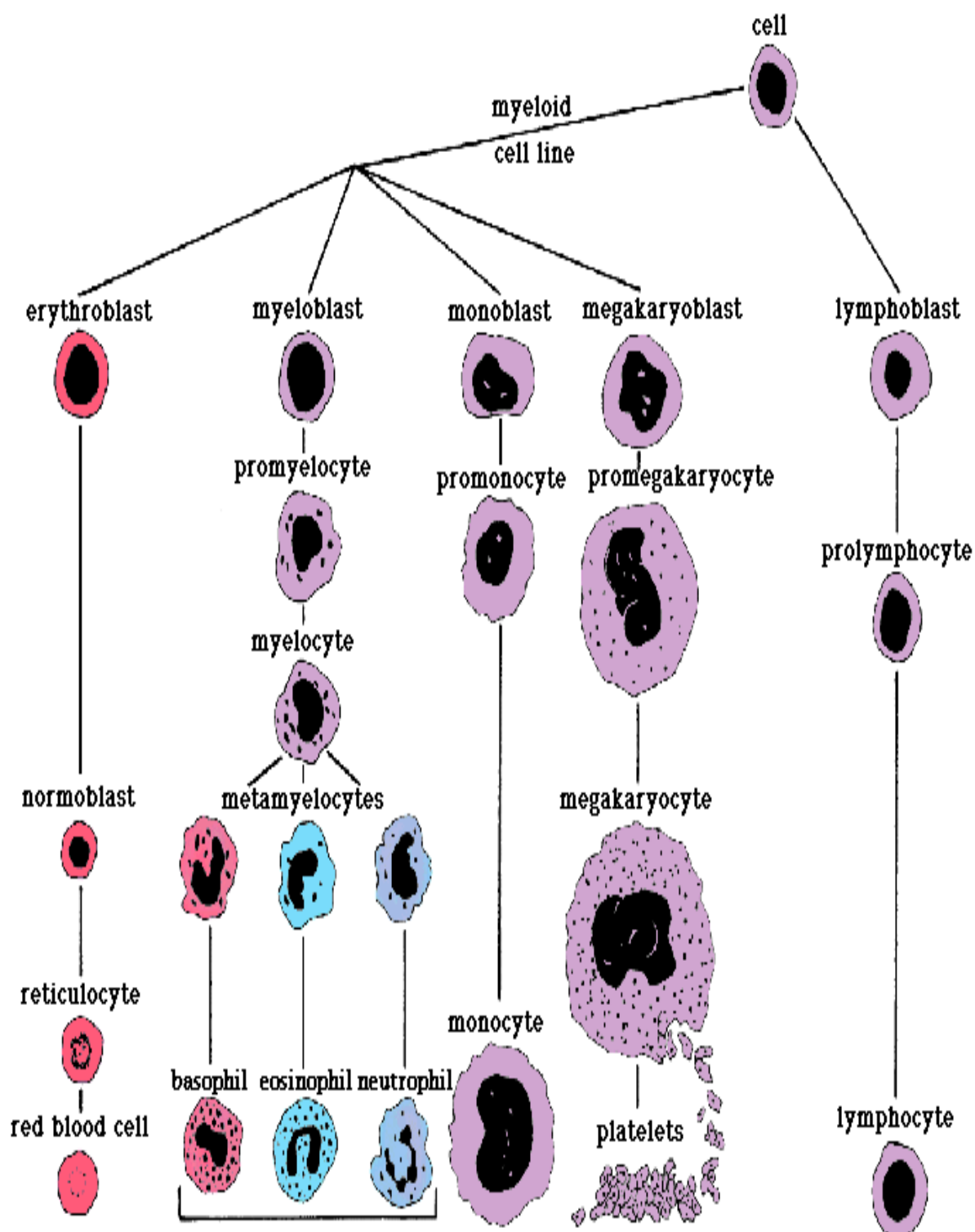
Excessive differentiation in the absence of self-renewal would rapidly lead to decline in the system, while excessive, prolonged self-renewal in absence of differentiation would lead overgrowth of primitive and functionally useless cells.

Control is best supplied at the local level by the effect of growth factors and regulatory molecules which are produced by the surrounding stromal cells supplying the extra cellular matrix (hematopoietic cell growth factor (HCGF).

The production of HCGF occurs locally under stringent control and is not released into the general circulation. However, modulators of mature cell function (i.e., erythropoietin) are produced in multiple sites and released into the circulation and play a systemic role. Thus, growth and development are determined by complex interactions among the developing hematopoietic cells, and regulatory molecules within the matrix.

Final cellular differentiation depends on short and long- range signals from the immediate environment and circulatory proteins, respectively.

Differentiation pathway of hematopoietic cells



The Anemias

Definition:

Reduction of the RBCs count or Hb% below the normal ranges for age and sex.

Classification:

I. Decreased or impaired production:

- A. Deficiency of substances required for Hb and red cell formation: Iron, folic acid, vitamin C, B12, and protein.
- B. Depression or inhibition of the bone marrow:
 - 1-Infection, chemical and physical agents, and metabolic products.
 - 2-Idiopathic bone marrow aplasia with or without congenital anomalies.
- C. Mechanical interference and replacement by abnormal cells: as leukemias.
- D. Miscellaneous: renal failure, hypothyroidism.

II. Blood loss: acute and chronic hemorrhage.

III. Excessive blood destruction (Hemolytic anemia)

A-Intracorpuseular defects:

- 1. Sick cell disease, Thalassemia, Spherocytosis and Elliptocytosis.
- 2. Hemolytic anemia due to enzyme deficiencies.

B-Extracorpuseular factors:

- 1. Auto immune hemolytic anemia
- 2. Miscellaneous: infection, chemical and physical agents, hypersplenism.

Physiologic Anemia of Infancy

Decrease Hb level to 10-11 gm% at 2-3 mo.

Causes:

1. Change of Hb.
2. Destruction of many RBCs.
3. Decrease iron store.
4. Decrease iron in diet.
5. Increase weight and expansion of blood volume (bleeding into the circulation).
6. Vit. E deficiency in premature.

Iron Deficiency Anemia (IDA)

Iron Metabolism

- Iron is digested in the stomach and absorbed in the ferrous form by the duodenal mucosa → attached to apoferritin.
- Iron is transported in the plasma in ferric state attached to transferrin.
- It is stored in two forms:
 - 1-Ferritin:** soluble, not visible in the tissues.
 - 2-Hemosiderin:** insoluble, visible, and stained the tissues.
- The daily iron requirements 8-15 mg/day. 10% of it will be absorbed (0.8-1.5 mg) daily.

Etiology of IDA

1-Inadequate supply of iron:

A-Deficient intake

B-Inadequate iron stores at birth:

1. Premature, twin, or multiple births.
2. Severe iron deficiency in the mother during pregnancy.

3. Fetal blood loss at or before delivery:
 - a) Fetal hemorrhage into maternal circulation or one to another.
 - b) Retroplacental bleeding.
 - c) Injury or early clamping of the cord.

2-Impaired absorption of iron

- A-Chronic diarrhea.
- B-Celiac syndrome.
- C-G.I.T. anomalies as hiatal hernia.

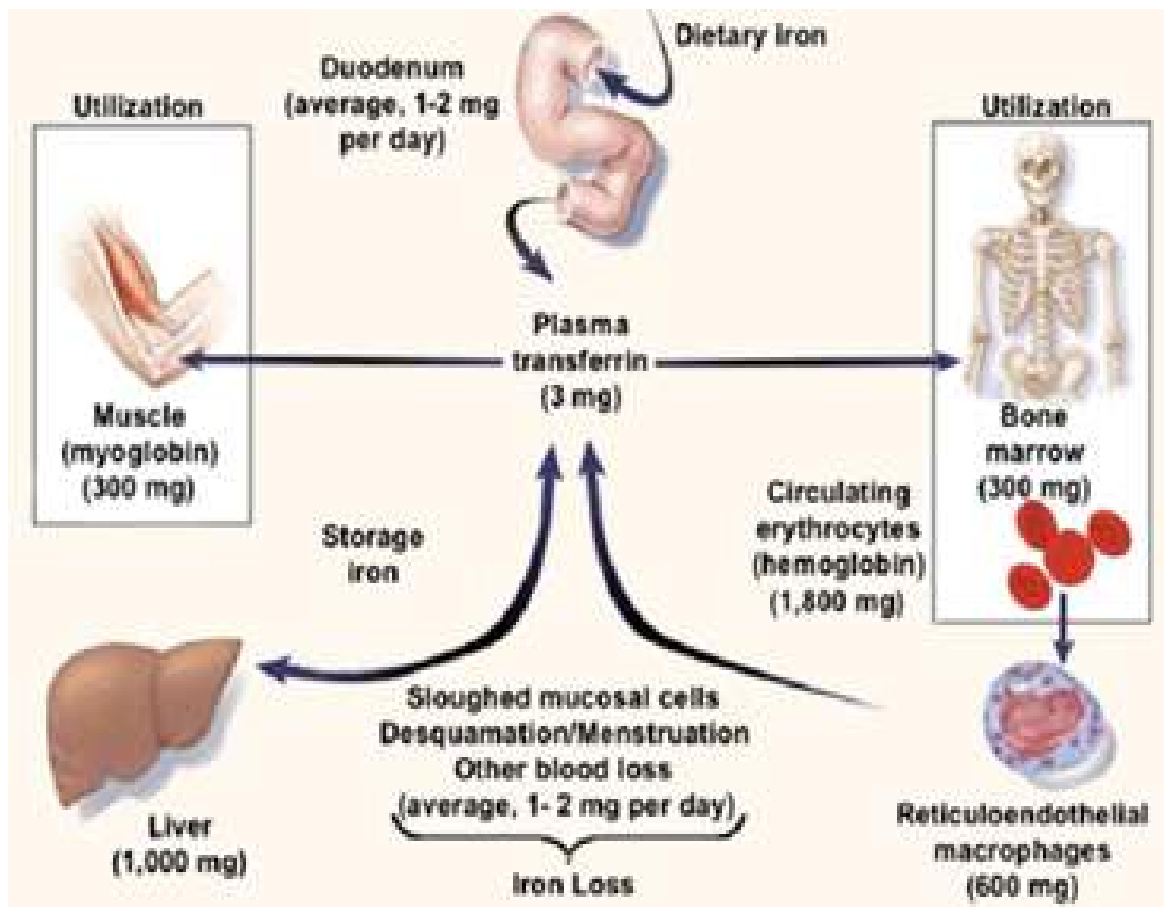
3-Excessive demands for iron.

- A. A-Blood loss e.g. hemorrhage and parasitic infestation.
- B. B-Increase growth rate e.g. premature and adolescence.

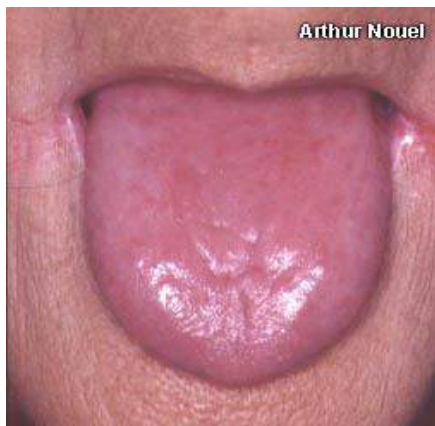
Clinical picture:

A. General manifestation of anemia:

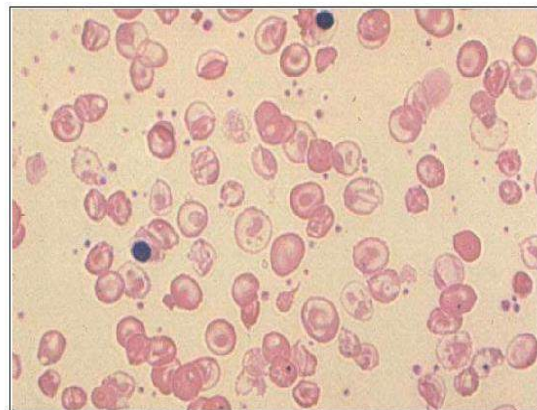
- Pallor
- General weakness
- Easy fatigability
- Headache
- Blurring of vision
- Spooning of the nails.



Iron Metabolism



Atrophic glossitis



Microcytic hypochromic

B. Gastrointestinal tract manifestations:

- Anorexia, pica, atrophic glossitis, dysphagia esophageal webs.
- Increased gastric acidity and malabsorption syndrome.

C. Central nervous system manifestations:

- Irritability, fatigue, conduct disorders, lower mental and motor developmental tests & scores, decreased attention span, breath holding spells, papilledema.

D. Cardiovascular system manifestations:

- Exertional dyspnea
- Tachycardia and Bounding pulse
- Hemic murmur
- Anemic heart failure in severe cases
- Cardiac hypertrophy
- Increase in plasma volume

Investigations for Diagnosis.**1-CBC shows:**

- Decreased Hb percentage.
- Decreased R.B.Cs numbers.
- Decreased hematocrite value.
- Decreased M.C.V (**Microcytic**).
- Decreased M.C.H. (**Hypochromic**).
- Decreased M.C.H.C.
- Reticulocyte within normal but may be increased in case of bleeding or after initiation of iron therapy.
- Increased red cell distribution width (RDW).

2- Iron profile in serum:

- Decreased **serum Ferritin** < 10 ng/ml (N: 35ng/ml)
- Decreased **serum Iron** (N =50-180 µg%).

- Increased **Total Iron Binding Capacity (TIBC)** (N = 250-350 µg %).
- Increased **serum Protoporphyrin** (N=1.9 ug /g Hb)

4-Stool analysis: searching for **parasitic infestation** and **occult blood**.

5-Therapeutic test: give iron 6 mg/kg/day and closely monitor the percentage of reticulocytic count after 72 hours, if it increased, the case is iron deficiency anemia.

6-GIT endoscopy: in resistant cases to exclude causes of GIT bleeding.

D.D from other causes of microcytic hypochromic anemia:

- 1- Thalassemia
- 2- Lead poisoning
- 3- Vitamin B6 deficiency
- 4- Sideroblastic anemia.
- 5- Chronic inflammation
- 6- Copper deficiency

Treatment:

1-Oral iron therapy:

Dose: 6mg/kg/day elemental iron. Should be continued for 1- 3 months after correction of Hb to the normal for the age and sex to replenish iron stores.

Oral iron preparations:

- A. Ferrous sulphate drops for infants (20% elemental Fe)
- B. Ferrous fumarate, sulphate, or gluconate for children (30, 20, 10% elemental iron respectively).

Failure of response to oral iron therapy can be due to:

- 1- Insufficient dose.
- 2- Inadequate duration.
- 3- Irregular intake.
- 4- Absorption may be interfered with as in GIT diseases.
- 5- Continuous loss of iron as in chronic hemorrhage.

6- Incorrect diagnosis.

2- Parental iron therapy (either IM or IV infusion):

Parental therapy is not recommended as first line treatment in pediatrics it's indicated only after failure to respond to oral iron and after exclusion of other causes of treatment failure

3- Packed RBCs transfusion:

5-10 ml/kg packed R.B.Cs. given in case of severe anemia (Hb less than 5 gm/dl) for fear of anemic heart failure or in presence of infection that prevent absorption, binding, and utilization of iron.

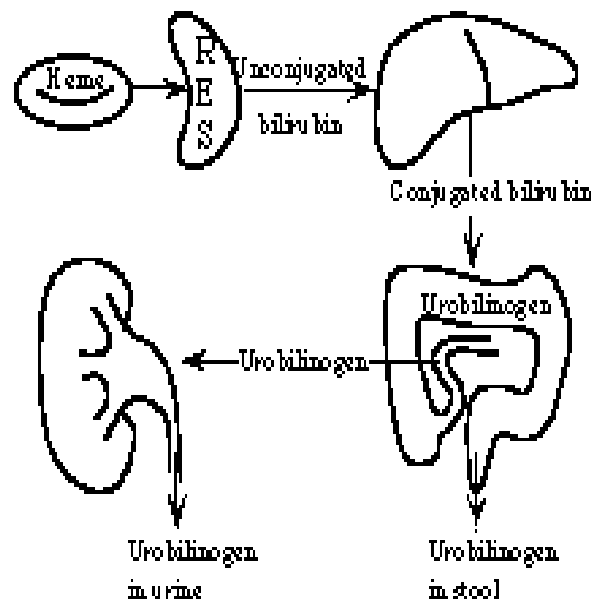
Hemolytic Anemia

Definition:

Increase of R.B.Cs. destruction more than 1% per day or short life span of R.B.Cs. less than 100 days

General laboratory manifestations:

- Hemoglobinemia and hemoglobinuria with increase urobilinogen.
- Hyperbilirubinemia and jaundice.
- Increase reticulocyte, normoblast and positive abnormal cells.
- Decrease life span-special tests e.g. autohemolysis and osmotic fragility test.
- Pigmented gallstones.



Causes of hemolytic anemia:

1-Intrinsic abnormality of the red cell: (corpuscular causes)

A. Membrane defects:

- Hereditary spherocytosis.
- Elliptocytosis.
- Ovalocytosis.
- Pyknocytosis.

B. Enzymatic defects:

- G.6.P.D. enzyme.
- Pyruvate kinase.
- Hexokinase enzyme.

C. Hemoglobin defects:

- Thalassemia
- Sickle cell anemia

2-Extrinsic abnormalities (Extracorpuscular causes):

A. Immunologic disorders:

1-Passively acquired antibodies: hemolytic disease of the newborn including:

- RH isoimmunization.
- ABO isoimmunization.

2-Active antibody formation:

- Idiopathic autoimmune hemolytic anemia .
- Secondary to:
 - SLE.
 - Infection.
 - Malignancy e.g lymphoma.
 - Drugs.

B. Non immunologic disorders:

- Toxic from drug and or chemicals.
- Infection as malaria and clostridium.

Hemolytic Anemia Due To Enzyme Deficiency

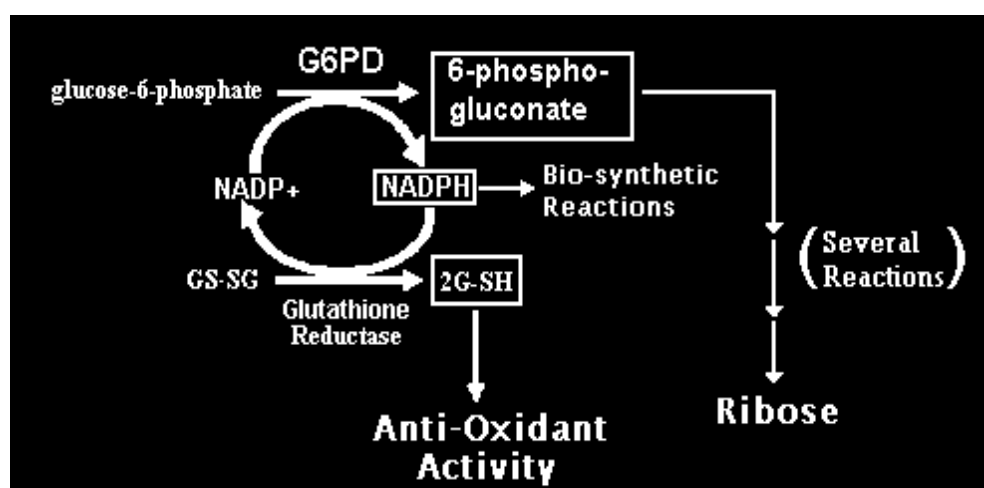
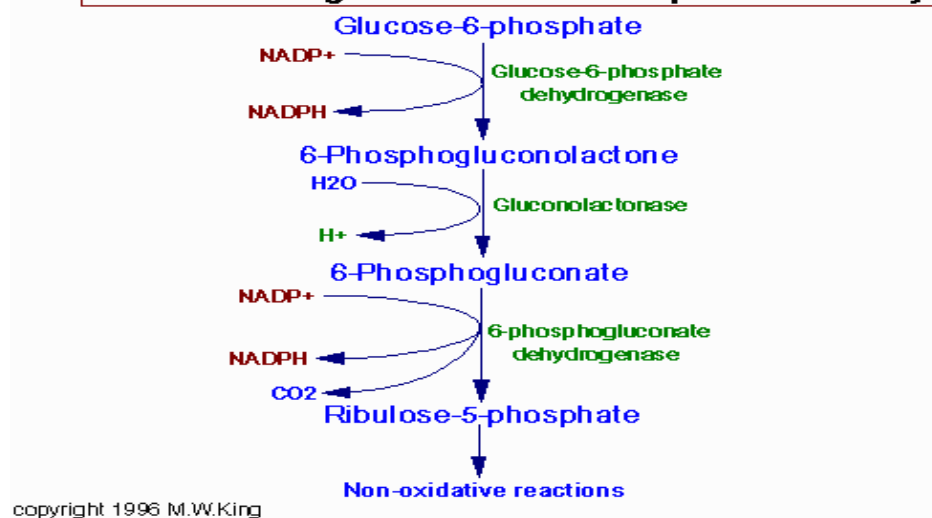
[G6PD deficiency]

G6PD deficiency is an *X-linked disease* that occurs mainly in males but may occur in the female in milder degree.

As many as 3% of the world's population is affected; most frequent among African Americans and those of Mediterranean origin.

Hemolysis occurs in susceptible patients after the administration of a number of drugs and chemicals due to glucose 6 phosphate dehydrogenase enzyme deficiency.

Oxidative Stage of Pentose Phosphate Pathway



Precipitating Factors:

I. Drugs & chemicals:

1. Antipyretics, all except paracetamol.
2. Antibiotics: e.g chloramphenicol, sulphonamide, macrodantin.
3. Anti-malarial drugs.
4. Drugs containing sulpha
5. Vitamins e.g synthetic vitamin k.
6. Organophosphorus compounds e.g insecticides
7. Naphthalene



II. Diet:

- An ingredient in the fava beans (vicia fava=favisim)

III. Diseases:

- As diabetic ketoacidosis and hepatitis

Clinical Picture:

- The disease may manifest at any age according to the time of exposure to the precipitating factors previously mentioned

I- It may be one of the causes of **neonatal** hyperbilirubinemia

II-**Acute** hemolysis (Favism)

- Development of the anemia after the intake of above-mentioned drugs or fava beans by 24-48 hour but may be shorter.
- The hemolytic attack presented by acute onset of a clinical triade of:
 - I. Intense pallor
 - II. Jaundice
 - III. Dark red urine.
- May be accompanied by fever, nausea, vomiting, or epigastric pain.

- Due to the acute nature of the condition, anemic heart failure is common at time of presentation due to sudden drop of Hb.
- Severity of hemolysis may be related to:
 - 1- Nature of precipitating factor.
 - 2- Amount of ingested materials.
 - 3- Severity of enzyme deficiency.

Laboratory Data:

1. Normocytic, normochromic anemia.
2. Reticulocytosis.
3. Hemoglobinemia, hemoglobinuria and very low or absent serum haptoglobin.
4. G.6-P.D. enzyme assay is decreased (*diagnostic test*).
5. Liver function tests to exclude hepatitis as a precipitating factor of hemolysis.

Treatment:

1. -Removal of the offending agent.
2. -Packed red cell transfusion in cases with Hb less than 9 gm/dL at a dose of 5-10 ml/kg. Fractionated transfusion of smaller doses over a longer duration is indicated in cases presented with anemic heart failure
3. -I.M. injection of desferioxamine 20-40 mg/kg single dose (as an antioxidant not chelator).

Hemoglobinopathies

Thalassemia Syndromes

Definition

Thalassemia is genetic disorder with absence of or defect in genes responsible for production of different hemoglobin chains (hemoglobinopathy).

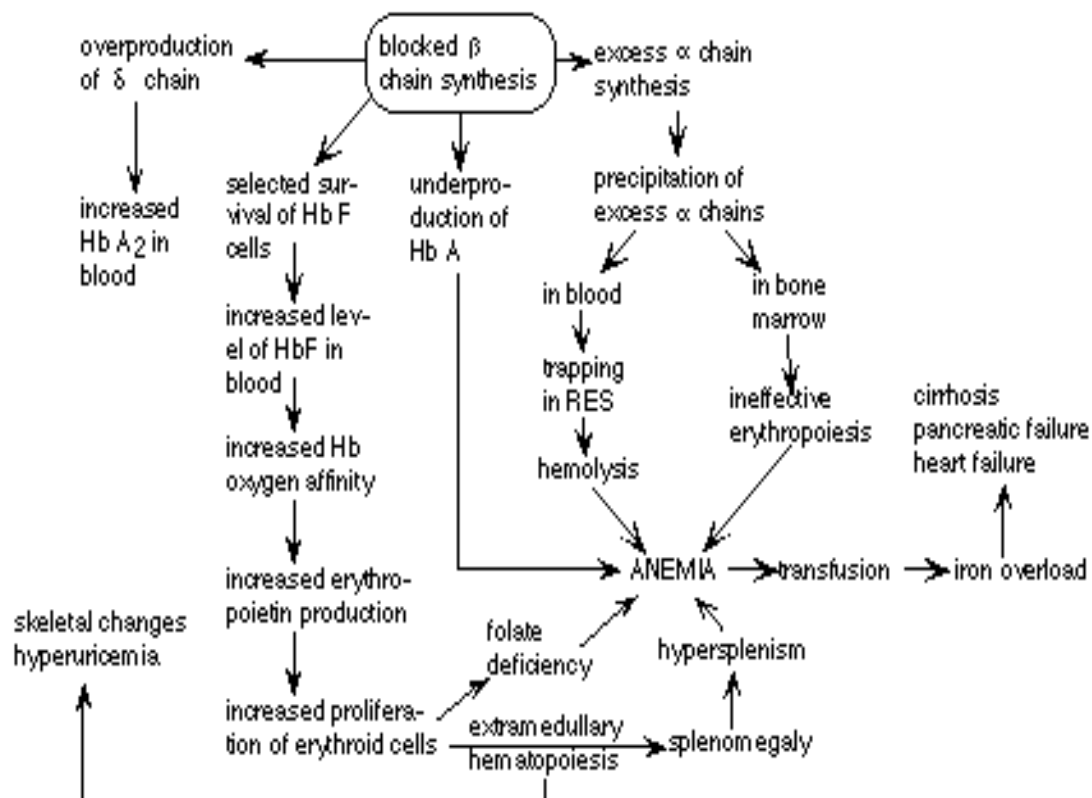
Mode of transmission

Thalassemia is an **autosomal-recessive** disorder that requires the inheritance of two defective genes from both parents who are usually carriers of the disease.

The carrier rate of beta thalassemia in Egypt is high (around 10%). The risk of thalassemia increases with consanguinity and positive family history.

Pathophysiology of β - thalassemia major:

- Normal postnatal hemoglobin (Hb A) is composed of two alpha and two beta polypeptide chains.
- In beta thalassemia there is partial or complete deficiency in the synthesis of the beta chain of the Hb molecule.
- Consequently, there is a excessive free alpha chains, and gamma chain production remains activated, resulting in defective Hb formation.
- This unbalanced polypeptide unit is very unstable; when it disintegrates, it damages the RBCs, causing severe anemia.
- To compensate for the hemolytic process, excess erythrocytes is formed (erythroid hyperplasia).
- Excess iron from hemolysis of supplemental RBCs in transfusion and from the rapid destruction of defective cells is stored in various organs which are marked in the liver, spleen and pancreas, thyroid, adrenals and heart (hemosiderosis).



Classifications of thalassemias:

Normal hemoglobin molecule consists of two alpha chains and two beta chains. Genes on chromosome 16 are responsible for alpha subunits, while genes on chromosome 11 control the production of beta subunits.

A lack of a particular subunit determines the type of thalassemia so:

- 1- **In alpha thalassemia:** There is decreased alpha chain synthesis with no decrease in beta chain. The excess beta chains aggregate and precipitate within the erythrocytes to form insoluble inclusion bodies.
- 2- **In beta- thalassemias:** There is decreased beta chain synthesis with no decrease in alpha chain. The excess alpha chains aggregate and precipitate as insoluble inclusion bodies inside RBCs. Beta- thalassemias may be clinically classified into 3 forms, each of which has varying level of severity depends on the mutations involved in the genes.

B - Thalassemia minor

β -Thalassemia minor or beta thalassemia trait is associated with decreased beta chain synthesis and is the heterozygous form of the disease, So the abnormality involves only one gene, which generally produces little effect on the child with a slight pallor and slight enlargement of the spleen, mild anemia (microcytic hypochromic).

 β - Thalassemia intermediate

There is moderate degree of anemia and hepatosplenomegaly. Children with β - Thalassemia intermediate can maintain the hemoglobin over 7g/dl and the clinical manifestations are intermediate between thalassemia major and thalassemia minor.

 β - Thalassemia major

Genetically, thalassemia major is classified as homozygous recessive thus there is a **25% chance with each pregnancy** that two parent who are both affected with β - Thalassemia trait will have a child with β -Thalassemia major.

Clinical manifestation of β - thalassemia major:

The patient usually becomes symptomatic from 6-12 months of age. If transfusion is possible, the affected children grow and develop normally and have no physical signs. The inadequately transfused child develops the typical features of the disease.

Manifestations of anemia:

Pallor, anorexia, easy fatigability, dyspnea on effort, dizziness and may be hemic murmurs and cardiac enlargement and cardiac decompensation.

Manifestations of hemolysis:

as jaundice, dark urine and dark stools and enlarged spleen.

Manifestations of increased medullary erythropoiesis:

Massive expansion of the marrow of the face and skull producing characteristic thalassemic facies with protrusion of the maxillae and teeth, depression of the nasal

bridge, and slanting of the eyes with an epicanthic fold. Thinning of cortex, widening of medullary space result primarily from hypertrophy and expansion of erythroid marrow such changes may lead to pathologic fractures and skeletal deformities.

Manifestations of extramedullary hemopoiesis:

Hepatosplenomegaly leading to abdominal enlargement.

Manifestations of complications:

1-Hemosiderosis:

Increase in tissue iron without associated tissue damage.

2-Hemochromatosis:

Excess iron storage with resultant cellular damage. The mechanism for tissue destruction resulting from iron storage is not known. Hemosiderosis and hemochromatosis also produce further enlargement of the liver, spleen, liver cirrhosis, cardiac complications, and endocrinal abnormalities.

3-Cardiac complications:

Pericarditis, myocardial siderosis which leads to arrhythmias and chronic congestive heart failure may occur.

4- Liver cirrhosis and failure.

5- Pulmonary hemosiderosis:

Mild abnormalities of pulmonary function are common. Some patients experience mild to moderate small airways obstruction and hyperinflation. Others may present with hemoptysis.

6- Pigmentation of the skin:

Bronzed skin discoloration due to combination of hemochromatosis, pallor and jaundice.

7- Endocrinal glands:

Hemosiderosis and hemochromatosis affects various glands as pancreas and pituitary leading to glucose intolerance, diabetes mellitus, growth retardation and diminished gonadotropins, parathyroid gland leading to tetany, gonads with lack of puberty, thyroids leading to hypothyroidism and adrenal glands leading to adrenal insufficiency.

8- Complications of repeated blood transfusions :

Mismatched blood transfusion, transmission of infectious agents, circulatory overload, and allergic reactions.

9-Pathological fractures of bones:

Hyperactivity of the bone marrow with bone expansion leads to thinning of bone cortex and pathological fracture.

10-Vitamin E, C and folic acid deficiency

11-Infections:

Lymphocytes and neutrophils dysfunction has been noticed leading to decrease in phagocytic activity against some microorganisms as salmonella and yersinia enterocolitica. In addition, splenectomy is a major predisposing factor to the increased risk of infection.

12-Pigmented gall stones:

Due to high rates of bilirubin formation. A cholecystectomy is usually indicated if biliary colic or obstructive jaundice occur.

13- Rare complications: as chronic leg ulcers and aplastic crisis.

Investigations of thalassemia

A. Hematological investigations:

- *Complete blood picture (CBC) shows:*

1-**Microcytic hypochromic** anemia.

2-Increased reticulocyte count.

3-Normoblast (immature RBCs) are increased.

5-**Target cells** on blood film.

▪ **Iron status**

1-Increased serum ferritin.

2-Increased serum iron.

3-Decreased total iron binding capacity.

▪ **Hemoglobin electrophoresis**

This is the diagnostic test for beta thalassemia. There is a compensatory **increase in Hb F**.

Hemoglobin electrophoresis is also important in carrier screening. Beta thalassemia carrier has Hb A2 equal to or greater than 3.5%.

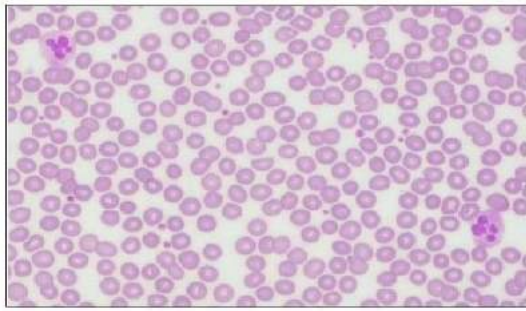
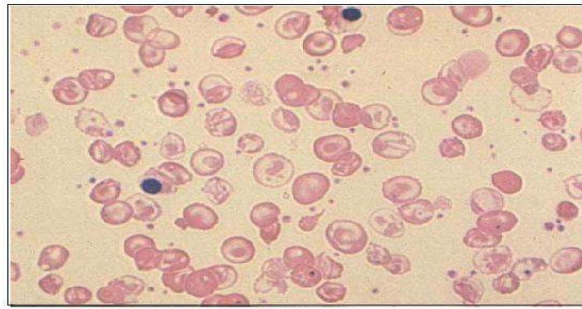
▪ **Liver function tests**

1-Increased serum indirect bilirubin to 2-4 mg /dl.

2-Increased S.G.O.T. and S.G.P.T. due to hepatic damage due to iron overload or associated hepatitis infection from repeated transfusion.

B. RADIOLOGIC INVESTIGATIONS:

- **Plain x ray skull:** There is maxillary overgrowth, prominent widening of the diploic spaces, with hair standing on end appearance.
- **Abdominal Ultrasonography:** Searching for hepatosplenomegaly and gall stones.
- **Echocardiogram:** For cardiac function assessment.

**Normal blood film****Thalassemia****Thalassemic Facies****x-ray: skull**

Demonstrates the maxillary overgrowth and shows prominent widening of the diploic spaces, with the "hair-on-end" appearance

Treatment of thalassemia major:

1-Transfusion therapy:

This is the main line of treatment. The aim of transfusion is to maintain the hemoglobin level between 8 – 9.5 gm/dl. Once Hb falls below 8 gm/dl, transfusion of 5-10 ml/kg packed RBCs is indicated.

2-Splenectomy:

➤ Indications:

I-Hypersplenism

- Suspected by increased needs for transfusion more than 240 ml/kg/year packed RBCs.
- Diagnosed by:
 - Splenomegaly
 - Pancytopenia,
 - Hyperactive BM
 - Correction by splenectomy

II -Huge spleen:

Diagnosed when the lower pole of the spleen reaches the level of the umbilicus.

➤ Precautions:

- Age >5 years.
- Preoperative vaccination with Hemophilus Influenza, meningococcal and pneumococcal vaccines.
- Postoperative long acting penicillin every 2 weeks 25-50,000 u/kg

3-Chelation therapy:

Injectable iron chelators: e.g Desferroxamine (Desferal)

- 20-40 mg/kg/day.
- 5-6 nights/week
- Over 8-12 hours/day
- Subcutaneous infusion by infusion pump

Oral iron chelators :e.g

- Deferiprone (L1 50-90 mg/kg/day)
- Deferasirox (JADENU 14-28 mg/kg/day)

4- Bone marrow transplantation (BMT):

- **BMT** is currently the only curative treatment, any transfusion-dependent patient who has an HLA matched doner should be offered BMT as a curative option of treatment.

5- Gene therapy: still under clinical trials

Prognosis of β - thalassemia major:

It depends on the type of inherited illness and its severity. Most children treated with blood transfusion and early chelation therapy survives well into adulthood.

The most common causes of death are:

- 1- Heart failure due to myocardial iron overload.
- 2- Liver failure due to liver cirrhosis caused by iron overload.
- 3- Liability to post-splenectomy infection may be another cause of death.

SICKLE CELL ANEMIA

Pathophysiology:

Sickle cell disease is an autosomal disease in which there is a single base substitution in the segment of nuclear D.N.A., which codes for the B-globin chain valine is substituted for glutamic acid in the sixth position → Hb S or Hb-6 valine.

When sickle hemoglobin is deoxygenated, it polymerizes and forms long rods that distort the cell, converting it from biconcave disc into sickle shape causing repetitive vaso-occlusive complications and chronic hemolytic anemia.

Clinical manifestation:

The general clinical picture of chronic hemolytic anemia plus:

1-Vaso-occlusive crisis:

Extremely painful, transient episodes that result from ischemic damage to tissue. Infection, acidosis, fever, and dehydration may precipitate vaso-occlusive episodes. Dactylitis or the hand foot syndrome is the first manifestation of the disease in 30% of patients.

2-Sequestration crisis:

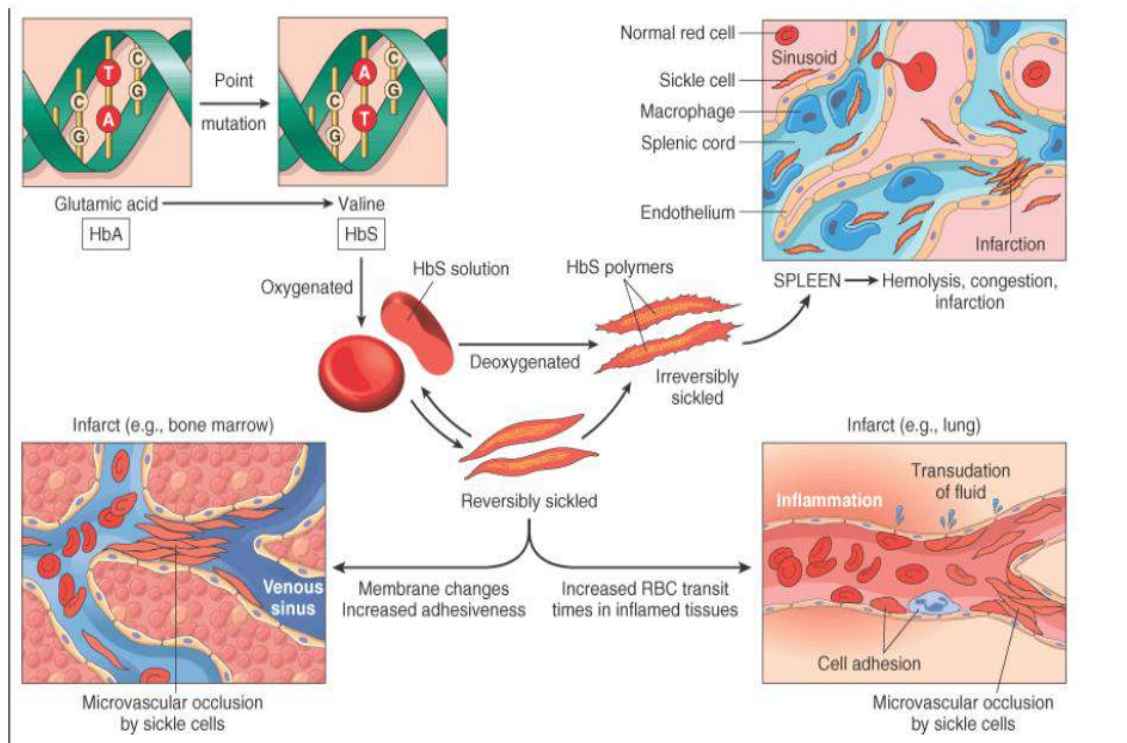
Sudden onset of pallor with rapidly enlarging abdomen, rapid pulse, hypotension and massive splenomegaly are present on examination.

3-Aplastic crisis:

Following or during infectious illness especially viral disease (parvovirus B19).

4-Hyperhemolytic crisis:

May be due to associated G6PD deficiency.



Sickle cell anemia

Treatment:

General line of treatment as thalassemia plus:

General measures:

- 1- Folic acid:
- 2- Prophylactic transfusion: Decreases frequency of crisis but require desferoxamine to prevent iron overload.
- 3- Avoidance of precipitating factors:
 - As sudden exposure to cold.
 - High altitude.
 - Occupation that require heavy manual work.
- 4- Vaccination: Especially with Pneumococcal and Hemophilus influenza vaccine.

Specific treatment:

1-Painful crisis

- Keep the patient warm
- Adequate hydration 2250 ml/m²/day.
- Alkalization 88 meq NaHCO₃/L.
- Exchange transfusion is indicated in:
 - 1- Anemic crisis.
 - 2- Acute chest syndrome.
 - 3- Prolonged painful crisis.
 - 4- Priapism.
 - 5- Pregnancy.
 - 6- Prior to surgery.
 - 7- Cerebrovascular accidents.

2- Drugs that decrease hemolysis by increasing fetal Hb

- Hydroxy urea
- Ara-C
- Interferon
- Erythropoietin
- Piracetam

3- Drugs that have anti-sickling effect

- Ca-channel blockers as verapamil and nifedipine.
- Vitamins as pyridoxine (B6).
- Minerals as Zinc.

4- Treatment of other crisis

Aplastic, sequestration and hyperhemolytic, by blood transfusion

5- Bone marrow transplantation

Aplastic Anemia

Definition:

It is failure of the bone marrow to produce blood cells or produces too few of all three types of blood cells: RBCs, WBCs, and platelets.

Etiology of aplastic anemia:

The exact cause of aplastic anemia is unknown. Aplastic anemia may be congenital (associated with congenital anomalies) or acquired.

Nearly 50 to 75 % of childhood acquired aplastic anemia occurs sporadically for no known reason and the condition is called *idiopathic aplastic anemia*.

About 25-50% of acquired aplastic anemia may be related to previous disorders and are called *secondary aplastic anemia*. It may be secondary to:

- **Virus infections** as hepatitis, EBV, CMV, parvovirus B19, or HIV.
- **Drugs** as chloramphenicol, anticonvulsants, chemotherapy.
- **Toxins** as heavy metals, Benzene, environmental toxins and insecticides.
- Exposure to **radiation**.
- **Autoimmune disease** as SLE

Some inherited conditions may predispose to congenital aplastic anemia as:

- Fanconi anemia.
- Dyskeratosis congenita.
- Shwachman-Diamond syndrome.
- Reticular dysgenesis.
- Amegakaryocytic thrombocytopenia.

Pathophysiology of aplastic anemia.

Aplastic anemia is a condition that results from injury to the stem cell, normal stem cells can divide and differentiate into all blood cell types. Consequently, when

stem cells are injured, there is a reduction in all blood cell production. The cause of injury is mostly unknown but is thought to be an autoimmune process.

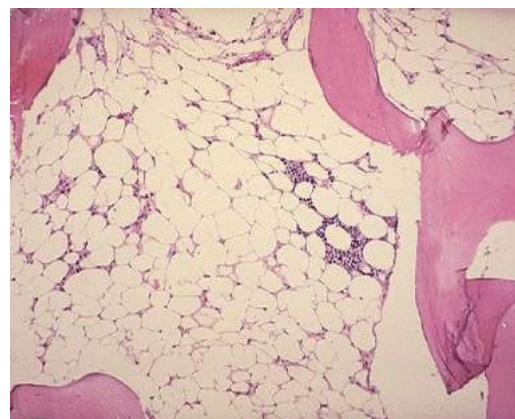
Clinical Manifestations

▪ Symptoms and signs

The disease may be **acute** or **chronic**, almost always progressive and usually gets worse unless the cause is removed. It can affect anyone: male or female, children or adults, any race or socio-economic status.

▪ Symptoms arises as a consequence of BM failure:

- Pallor, headache, dizziness, lack of energy, easy fatigue due to **anemia**.
- Recurrent infections as sinusitis, urinary tract infection, respiratory tract infection, oral moniliasis due to **leukopenia**.
- Easy bruising, purpura, mucus membrane bleeding due to **thrombocytopenia**.
- Other symptoms related to the cause.



Diagnosis of aplastic anemia

- Complete medical history.
- Thorough clinical examination.
- Investigations:

1- Complete blood picture :

Pancytopenia (anemia, thrombocytopenia and leucopenia) with reticulocytopenia.

2- Bone marrow aspiration and/or biopsy:

Examined for the number, size, and maturity of blood cells and/or abnormal cells. It mostly shows: Great reduction in the number of cells in the BM, RBCs, platelets and granulocytes with a normal appearance of the few remaining cells.

3- Tests to exclude specific causes of aplastic anemia :

- Ham test to rule out paroxysmal nocturnal hemoglobinuria.
- B12 and folate levels
- Hepatitis A,B, C serology
- Cytogenetic study to rule out Fanconi's anemia

Severity of aplastic anemia:

- **Severe aplastic anemia** = Hypocellular BM for age + two of following 3 criteria:
 - Platelet count of less than $20,000/\text{mm}^3$
 - Absolute reticulocyte count of less than $40,000/\text{mm}^3$
 - Absolute neutrophil count of less than $500/\text{mm}^3$.
- **Mild or moderate aplastic anemia** when pancytopenia is not severe enough to meet the above criteria.
- **Very severe aplastic anemia** when ANC count is less than $200/\text{mm}^3$.

Treatment of aplastic anemia

- 1- When aplastic anemia is diagnosed, all drugs or medications the patient is on should be stopped if possible.
- 2- In secondary aplastic anemia, removal of the causative agent is critical, and in some cases can lead to recovery.
- 3- Treatment depends upon the severity. Mild aplastic anemia may be treated with supportive care or may require no treatment. Moderate aplastic anemia often receives transfusions $\pm$ drug therapy $\pm$ stem cell transplantation. Severe aplastic anemia is a life-threatening condition and requires immediate treatment to stabilize the disease till performing bone marrow transplantation.

- **Isolation:** To prevent infection, patients must often be isolated from even healthy people. Necessary visitors may have to wear masks and gown and must always thoroughly wash hands before touching the patient.
- **Activity:** Activity must be restricted to reduce symptoms of anemia, avoid falls or accidents that may cause bleeding.
- **Antibiotics:** To control infection, appropriate intravenous antibiotic therapy as soon as fever or other signs of infection appear.

4- **Blood component transfusion:**

- 1) Red Cells transfusion: To correct anemia. However, with repeated transfusions, patients accumulate toxic amounts of iron with iron overload which may be fatal.
- 2) Platelets: To correct thrombocytopenia and prevent fatal hemorrhage. However, transfused platelets survive only a few days.
- 3) White Cells: Which cannot be effectively supplied by transfusion. The life span of white cells obtained from donors is so short (a few hours) that routine transfusion is technically impossible.

Blood and platelet transfusions should be leukocyte depleted by use of leukocyte depletion filter or washed prior to administration and if possible, irradiated as well and given as infrequently as possible.

Transfusions should not come from close family members until after BMT has been done or ruled out since this may interfere with the effectiveness of BMT.

5- **Bone marrow transplantation:**

Is now being used more frequently for patients with matched donor. If a patient does not have a perfect match within the family, a matched unrelated donor may be tried.

6- **Immunosuppressive therapy:**

- A) **Antithymocyte globulin** is a horse serum that contains antibodies against human T cells. It is used to suppress the body's immune system, allowing the BM to

resume its blood-cell generating function as patient's immune system is fighting against itself in aplastic anemia.

B) **Other medications** to suppress the immune system as cyclosporine ± androgens, cyclophosphamide, and corticosteroids may be used.

7- **Hematopoietic growth factors:**

As granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), Interleukin-3, Stem cell factor (SCF), IL-6 and IL-11 which may increase platelet and WBCs. Erythropoietin which increases RBCs production, but most patients with aplastic anemia already have a very high erythropoietin level.

Complications of aplastic anemia:

1. Infection
2. Severe bleeding as cerebral hemorrhage
3. Complications of treatment.
4. Death may be caused by bleeding, infectious complications of BMT, rejection of BMT, or severe reaction to ATG.

Prognosis of aplastic anemia:

Untreated aplastic anemia is rapidly fatal. Only mild to moderate cases may achieve long-term stable recoveries using transfusions or drug treatments, while in severe cases, BMT is the only chance for a cure with a long-term survival rate of 80%.

HEMORRHAGIC BLOOD DISEASES

Introduction

Blood within the vascular tree remains fluid throughout life. If a blood vessel injured a rapid localized response of blood clot formation will occur.

Hemostasis

Hemostasis is an active process that clots blood in areas of blood vessel injury.

The main components of the hemostatic process are the:

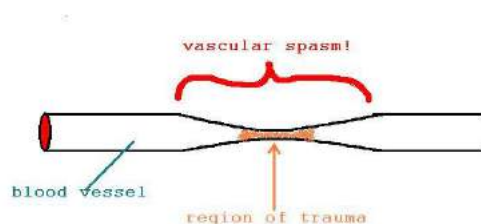
- Vessel wall integrity
- Adequate numbers of platelets
- Properly functioning platelets
- Adequate levels of clotting factors

The intact vascular endothelium is the primary barrier against hemorrhage. The endothelial cells that line the vessel wall normally inhibit coagulation and provide a smooth surface that permit rapid blood flow.

After vascular injury the process of hemostasis will start

I-Vascular phase

- Vascular vasoconstriction
- Due to:
 - Local axon reflex
 - Serotonin release



II-Platelet phase (1ry phase)

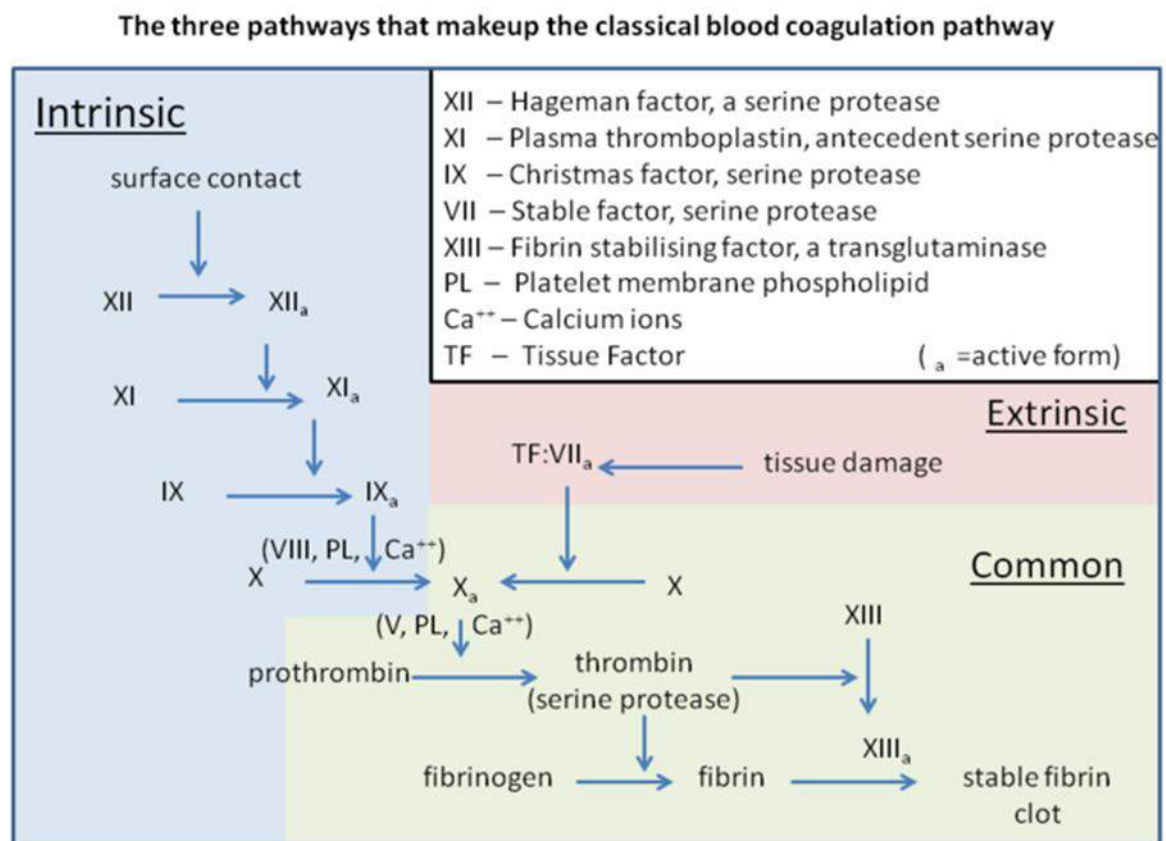
When the subendothelial tissues are exposed:

- Platelet adhesion (vWF+PG1b)
- Platelet activation
- Platelet release reaction (ADP-Thromboxane E2- serotonin)

- Platelet aggregation (PGI₂, PGII_a, fibrinogen)
- Platelet plug formation

III- Plasma phase

Normal scheme of coagulation mechanism



Tests for evaluation of homeostatic mechanism:

1-Primary hemostatic mechanism (platelet phase)

Hess test, bleeding time, Platelet counts and platelet function tests.

2-Secondary hemostatic mechanism (plasma phase)

By thrombin time (TT): For assessment of common pathway:

TT is the time taken for plasma to clot after addition of bovine thrombin → fibrinogen → fibrin.

Normal= 15-20 seconds

By prothrombin time (PT): To measure the function of the extrinsic and common coagulation pathways. PT is the time taken for plasma to clot after addition of thromboplastin and Ca.

Normal = 12-14 seconds.

By partial thromboplastin time (PTT): To detect significant deficiencies of all the intrinsic and common coagulation factors. PTT is the time taken for plasma to clot after being activated by incubation with kaolin then Ca and platelets or lipid substitute for platelets called partial thromboplastin.

Normal= 25-40 seconds.

COAGULATION DISORDERS

Inherited coagulation disorders

- Hemophilia A and B
- VonWillebrand disease
- Other factor deficiencies

Acquired coagulation disorders

- Liver diseases
- Vitamin K deficiency/warfarin overdose
- DIC

HEMOPHILIA- A

Etiology:

An X - linked recessive disease caused by decreased level of factor VIII in the plasma.

Clinical manifestation:

Depend on the level of deficiency of factor VIII in the blood which ranged from severe (factor level activity <1%), moderate (factor level activity from 1 – 5%) and mild with (factor level activity >5%).

Clinical manifestation may appear in the neonatal period in the form of hematoma after injection, bleeding after circumcision. After trauma excessive bruising and persistent bleeding will occur, hemarthrosis commonly occur. Internal bleeding as spontaneous hematuria, G.I.T. bleeding and intracranial hemorrhage may also present.

Diagnosis

1. APTT: Prolonged
2. F VIII: Decreased
3. PT, TT, bleeding time, platelet count, vWF, fibrinogen are normal

Treatment:

1-Prevention of trauma

2-Avoid aspirin

3- When there is bleeding

A-Local cold application and pressure

B-Replacement therapy by:

- Factor VIII concentrates 25-50 I.U. /kg/12 h

- Fresh frozen plasma (1ML=1 IU)
- Cryoprecipitate one bag/5kg (bag=75:125 IU).

4-Gene therapy

Purpuras

Definition:

It is a group of the blood disorder characterized by skin hemorrhage. With or without bleeding from the mucus membranes and internal hemorrhage.

Types and causes:

I-Thrombocytopenic purpura:

❖ *Decreased production:*

- Hypoplastic or aplastic anemia.
- Bone marrow infiltrate e.g. leukemia, and metabolic disorders.
- Drugs (cytotoxic, sulphonamide, chloramphenicol, antiepileptic)
- Physical agents as irradiation.
- Chemical agents as benzene.

❖ *Increased destruction:*

- Idiopathic (Immune) thrombocytopenic purpura.
- Allo-immune (post-transfusion and allo-immune neonatal thromocytopenic purpura).
- Hypersplenism.

❖ *Sequestration*

- Splenic sequestration.
- Cavernous hemangioma.

II-Non thrombocytopenic purpuras (non ITP):

1-Allergic or (Henoch- schonlein purpura)

2-Thrombasthenia (platelet function disorders)

- Disorders of adhesion
- Disorders of platelet secretion (release reaction)
- Storage pool deficiency
- Disorders of aggregation

Idiopathic Thrombocytopenic Purpura (ITP)

Definition:

Immune thrombocytopenic purpura (ITP) is a syndrome characterized by thrombocytopenia, shortened platelet survival, presence of platelet auto-antibodies in the plasma and increased count but decreased productivity of megakaryocytes in the bone marrow.

Etiology of ITP:

A history of preceding infection, usually viral, is noted within the preceding three weeks in 50-80% of cases. Nonspecific upper respiratory infections are the most common cause in post-infectious cases. In about 20% of cases a specific infection can be identified, such as varicella, pertussis, cytomegalovirus, parvovirus or bacterial infection. The disease appears to be related to sensitization by infection and thrombocytopenia is due to an immune mechanism.

Pathogenesis

ITP is an autoimmune disease in which IgG antibodies are responsible for thrombocytopenia. Most ITP patients have an increased level of IgG on the platelet surface.

Clinical picture:

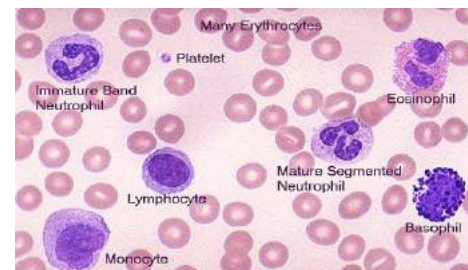
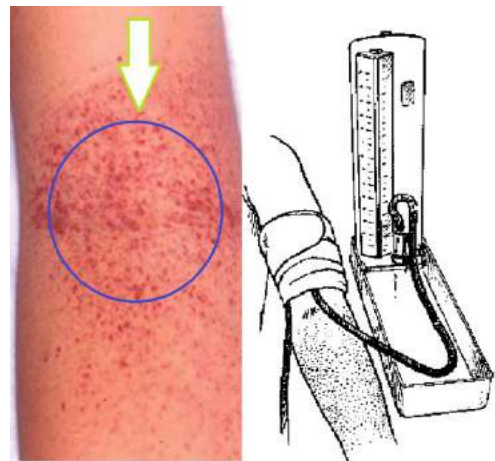
- Spontaneous appearance of purpura and ecchymosis
- Bleeding from mucous membranes: epistaxis, bleeding per gum, bleeding per rectum
- Bleeding from wounds
- Internal hemorrhage in severe cases

Clinical types include:

- A. Acute ITP: within the first 6 months of diagnosis
- B. Persistent ITP: thrombocytopenia for 6 to 12 months from initial diagnosis
- C. Chronic ITP: thrombocytopenia for more than one year
- D. Recurrent ITP: thrombocytopenia after complete recovery of the previous attack

Investigations:

- 1. Hess test: Positive
- 2. Bleeding time: Prolonged (N: 4-8 minutes).
- 3. CBC: Decrease platelet count below 150,000 / mm³.
- 4. Bone Marrow examination: Increase megakaryocytes count with decrease productive capacity (weakly productive or sterile).

**Course:**

Remission in 75%- chronic form in 10%

Differential Diagnosis:

Other causes of purpura especially aplastic anemia, allergic purpura and leukemia

Treatment:**Supportive management:**

- Restriction of physical activity and complete avoidance of all contact sports and playground activities.

- All medication with antiplatelet activity should be avoided including aspirin, and non-steroidal anti-inflammatory drugs.
- Avoid intramuscular injections.
- Avoidance of surgery if thrombocytopenia is present.

Indications of treatment:

- Mucus membrane bleeding.
- Platelets less than 30,000/cmm.
- Progressive purpura.
- Persistent of purpura more than 3 months.
- Extensive purpura involving all body with ecchymosis.
- Recurrent purpura.

1-Corticosteroid therapy:

Prednisone 2mg/kg/day for three weeks.

Mechanism of action

- Decrease antibody formation.
- Bone marrow stimulant.
- Increase stability of blood vessels.

2-I.V.Anti-D therapy

Is a plasma derived gamma immune globulin containing a high titer of antibodies to Rh antigens of red blood cells for IV injection?

Mechanism of action

Block Fc receptors of reticulo endothelial cells with antibodies coated autologous red blood cells

Dose: 50-75 ug/kg IV over a 3-to-5-minute period.

3-Intravenous immunoglobulin:

Dose: 400 mg/kg/day for 5 days (I.V. infusion).

Indication

Same indication of corticosteroid plus failure of response to steroid

Mechanism

- Block Fc receptors of reticulo-endothelial system.
- Anti-viral activity.
- Protect platelet destruction by antibodies.
- Decrease antibody formation.

4-Splenectomy for :

- Chronic thrombocytopenia more than one year.
- Severe cases do not respond to corticosteroids, IV anti-D, and IVIG.
- Girls near menarche.

Precautions before splenectomy:

- Age >5 years.
- Preoperative vaccination by pneumococcal and Hemophilus influenza vaccines.
- Platelet transfusion during operation.
- Post-operative long-acting penicillin.

5-Immunosuppressive drugs:

- Vincristine, cyclophosphamide, azathioprine.

6- Monoclonal antibody therapy: Anti-CD20 (Rituximab)

Mechanism of action: Eliminate auto reactive B cells.

Dose: 375mg/ m² IV weekly for 4 weeks

7-Plasmapheresis

8-Platelet transfusion

In severe cases for fear of internal hemorrhage till other lines of therapy act and emergency operations.

Dose: 1 unit /5kg. **NB:** life span of transfused platelet in case of ITP is very short (hours) due to presence of antibodies that destroy platelets.

Henoch – Schoenlein Purpura

Etiology:

The exact etiology is unknown. The disease often follows an upper respiratory tract infection with beta hemolytic streptococci, and is considered as a form of allergic vasculitis, and that explains its alternative name “anaphylactoid purpura”.

Clinical manifestation

1. Skin:

Recurrent attacks of maculopapular eruption in the buttocks and lower limbs in addition to petechial and purpuric eruption.



2. Abdominal manifestation:

Abdominal pain, bleeding per rectum, intussusception.

3. CNS manifestation

Headache, convulsion, coma

Subarachnoid or cerebral hemorrhage may occur.

4. Renal manifestation

Hematuria, renal colic, nephritis or nephrotic syndrome

5. Joint manifestation

Arthralgia and arthritis

Investigations:

- Platelet count: normal.
- Renal function tests must be done to exclude the renal complications.

Treatment:

- Symptomatic treatment.
- Antibiotics for infection.
- NSAID for arthritis.
- Antihistaminic and elimination of the offending agent if detected.
- Corticosteroids are commonly used with fair results.

Indications of corticosteroid

1. CNS manifestations.
2. Renal manifestation if nephrotic syndrome.
3. GIT manifestation if presents with bleeding per rectum.
4. Joint manifestation if there is contraindication to NSAID or if there is poor response.

Dose and duration:

1-2 mg/kg/day for 5-7 days except in nephrotic syndrome in which it is given for prolonged period.

Childhood Leukemias

Leukemias are the most common childhood malignancies, accounting for 33% of pediatric malignancies. It represents a clonal expansion and arrest of maturation at a specific stage of normal myeloid and lymphoid hematopoiesis.

Types of leukemia:

Acute leukemia (97% of childhood leukemias).

- 1-Acute lymphoblastic leukemia (ALL): 75% of all cases.
- 2-Acute myeloid leukemia (AML): 20% of all cases.
- 3-Acute undifferentiated leukemia (AUL): < 0.5%
- 4-Acute mixed lineage leukemia (AMLL)

Chronic leukemia (3% of childhood leukemias).

- 1-Chronic Myeloid Leukemia
- 2-Chronic lymphocytic Leukemia (very rare in Pediatrics).

Acute lymphoblastic leukemia

Definition:

Uncontrolled growth and proliferation of immature lymphoid cells or excessive accumulation of lymphoblasts (immature lymphocytes).

Epidemiology:

ALL is the most common malignancy in children. It accounts for 25% of all childhood cancers and 75% of childhood leukemias.

Age:

Peak onset of ALL occurs between 2-10 years and 10% occur in infants less than 1 year.

Sex:

Male to female ratio is 2:1 with exceptions of infant leukemia, where there is a female predominance.

Race:

ALL is 2 folds higher in whites than in blacks.

Social distribution:

Higher incidence occurs among middle and high socio-economic classes.

Geographic distribution:

The incidence is highest in Egypt, USA (whites). Intermediate rates exist in most European countries, while the lowest rates occur in USA (blacks), India and Kuwait.

Leukemia clustering:

Occurrence of greater number of cases of leukemia than expected within geographical area or time period.

Etiology of leukemia

It remains unknown but many factors may be associated with ALL.

Genetic factors:

Evidences of contribution of genetic factors are: Higher incidence of leukemia among children with Down syndrome, occurrence of familial leukemia, higher incidence of leukemia in siblings of affected children and higher incidence among monozygotic twins

Viral infection:

As EBV in ALL (L3) and endemic Burkitt's lymphoma, Human T Lymphotropic viruses I and II and Retroviruses in T-cell leukemia.

Environmental factors:

Exposure to ionizing radiation may cause acute leukemia as radiation induces chromosomal aberrations and interfere with immunologic defenses and thus predispose to malignancy.

Chemical carcinogens:

Chronic exposure to Benzene, Herbicides, and Pesticides, drugs as Chemotherapy, Chloramphenicol and maternal use of Contraceptives, Cigarettes and Alcohol may have possible association with ALL.

Immune deficiency:

Children with congenital immune deficiency diseases or patients receiving immunosuppressive drugs have an increased risk of ALL.

Clinical features of ALL

Symptoms may be insidious and slowly progressive over weeks to months or may be acute and explosive.

1. Hematological effects of BM invasion:

These are pallor due to anemia, purpura, bleeding due to thrombocytopenia, fever and infection due to neutropenia

2. Manifestations of lymphoid system invasion:

Hepatosplenomegaly and lymphadenopathy.

3. Bone and joint involvement:

Bone pain occurs in 25% of patients. It may be due to leukemic infiltration of the periosteum, bone infarction or infection, expansion of BM cavity, subperiosteal hemorrhage.

4. Gastrointestinal involvement:

It may presents with bleeding from GIT due to thrombocytopenia or leukemic infiltrates of GIT.

5. Renal involvement:

May present with hematuria, hypertension and renal failure which may be due to tumor lysis syndrome or leukemic renal infiltration.

6. Manifestations of CNS invasion:

- Increased intracranial pressure as headache, vomiting, blurring of vision, papilledema.
- Cerebral involvement with hemiparesis, cranial nerve palsies, convulsions.
- Cerebellar involvement with ataxia, hypotonia and hyporeflexia.
- Posterior pituitary involvement with diabetes insipidus.
- Hypothalamic syndrome presented by polyphagia with excessive weight gain, hirsutism and behavioral disturbances.
- Spinal cord chloromas with back and leg pain, numbness, weakness, paraplegia, bladder and bowel sphincter problems.

7. Genital tract involvement:

Testicular involvement causing painless testicular swelling and less commonly ovarian involvement.

8. Cardiac infiltration:

Symptomatic heart disease occurs in < 5% of cases with leukemic infiltrate and hemorrhage of myopericardium.

9. Lung involvement:

Lung may involve with leukemic infiltrates, hemorrhage, pleural effusion or anterior mediastinal mass.

Laboratory investigations

Complete blood picture:

Normocytic, normochromic anemia and reticulocytic count is usually low. Thrombocytopenia may be present. WBCs may show Leucocytosis, Leucopenia or hyperleucocytosis and blast cell may be present.

Bone marrow examination:

Although blast cells in BM is normally less 5%, diagnosis is confirmed only when bone marrow contains $\geq 30\%$ blast cells. Definitive diagnosis of type of leukemia is made by morphologic assessment, Immunophenotyping and cytogenetic study of BM aspirate.

Morphology of ALL

French American British (FAB) classification divides ALL into L₁, L₂ and L₃ while Egyptian modification of FAB (FAB-E) divides ALL into: L₁ / L₂ with morphological features in between L₁ and L₂, L₂ / L₃ with features in between L₂ and L₃ and leukemic phase of lymphoma, which is a separate group with its own features .

Immunophenotyping of ALL

Determination of cell of origin of leukemia which may be:

(1) B cell ALL (85%):

Classified according to the degree of maturation into early pre-B, pre B- and mature B-ALL.

(2) T cell ALL (15%):

Classified into early, intermediate and late stages T-cell ALL.

CSF Examination:

CSF analysis and cytology should be done. Cell count > 5 per HPF, with blast cells on cyto-centrifuge preparation, are diagnostic of CNS infiltration.

Biochemical analysis:

- Increased serum uric acid, due to increased catabolism of purines.
- Hypercalcemia due to leukemic infiltration of bone, or release of parathormone like substance from lymphoblast.
- Hyperphosphatemia as a result of leukemic cell lysis and it may induce hypocalcemia.
- Serum LDH is increased during acute phase and relapses and normalize during remission of the disease.
- Blood urea and serum creatinine may be increased.

Radiographic investigation:

- Radiograph of the chest may show lung infiltration, infection or anterior mediastinal mass
- Plain x ray for long bones may showes lytic areas, periosteal elevation and diffuse osteoprosis.
- Abdomenal Ultrasound for evaluation of liver, spleen, kidney and para-aortic lymph nodes.
- CT scan is useful in detecting enlargement of retroperitoneal, mesenteric lymph nodes and leukemic masses of CNS.

Differential diagnosis of ALL

- 1-AML: Morphology, cytochemistry and immunophenotyping can differentiate
- 2- Leukemic phase **of lymphoma**: Bone marrow is infiltrated with cells morphologically indistinguishable from those of ALL. Morphology, immunophenotyping and cytogenetic studies are used in difficult cases.
- 3- Aplastic anemia: ALL may present with aplastic picture due to inhibition of normal hematopoietic progenitors by leukemic cells, BM biobsy can differentiate.

4-Small round cell tumors as neuroblastoma or retinoblastoma may mimic the clinical and laboratory features of ALL when infiltrate bone marrow, demonstration of the primary tumor usually solve the problem.

5-Some infectious diseases may mimic ALL because of the presence of fever, lymphadenopathy, hepatosplenomegaly, blood cytopenia and atypical lymphocytes. Proper interpretation of cellular morphology of the atypical lymphocytes and BM examination should prevent any confusion.

6-Osteomyelitis and rheumatologic disease when ALL presents with bone-ache and arthralgia.

Treatment of ALL

I-General supportive care:

Newly diagnosed cases must be prepared for chemotherapy by improving general condition through treatment of:

Fever: May be due to release of pyrogenic cytokines from leukemic cells as IL-1, IL-6 and TNF so fever resolves in most patients after institution of chemotherapy or due to infections so, empirical antibiotics is initiated.

Thrombocytopenia: Is corrected by platelets transfusion to raise platelet count above 20.000/mm³.

Anemia: Is corrected with packed RBCs transfusion.

Neutropenia: Is treated using empiric use of antibiotics and hematopoietic growth factors as G.CSF and G.M.CSF.

Hyperleukocytosis:

Therapy is directed towards prevention of tumor lysis syndrome by:

- Hydration therapy with 3 L/m²/day in the form of 5% dextrose in 0.25 normal saline.
- Alkalinization therapy with NaHCO₃ 40 mEq/L.

- Allopurinol (Xanthine oxidase enzyme inhibitor which help the conversion of xanthine and hypoxanthine to uric acid) 300 mg/m²/day.
- Leukapheresis using blood cell separator.
- Exchange transfusion with blood containing average WBCs count.

II- Specific anti-leukemic therapy :

It includes induction, CNS directed therapy and maintenance therapy. Consolidation may be added to high-risk group of patients.

(1) Induction therapy:

Its goal is to induce complete remission with no clinical evidence of leukemia, peripheral blood values within normal, BM of normal cellularity with <5% blasts and no extramedullary disease. It includes corticosteroids, vincristine, asparaginase and anthracycline for 6 weeks. Failure of induction therapy occurs in < 5% of patients treated with current regimens. Mortality rate during induction is $\leq 3\%$.

(2) CNS directed therapy

The use of 2400 CGY in 16 fractions of 150 CGY over 4 weeks plus five concurrent doses of triple intrathecal therapy including methotrexate, Ara-C and hydrocortisone is the standard form of CNS directed therapy.

(3) Maintenance therapy

Combination of daily 6-mercaptopurine and weekly methotrexate constitutes the usual continuation regimen. This therapy is effective in producing long term disease control in 60 to 80% of low and standard risk ALL. More intensive therapy is required for high risk patients. Duration of maintenance treatment, should be continued until leukemic cells are eliminated which is about 2.5-3 years after the start of therapy.

(4) Bone Marrow transplantation

It involves the administration of high dose chemotherapy in lethal dose to normal bone marrow $\pm$ total body irradiation and then intravenous infusion of BM obtained

from a compatible donor or transplantation of cord blood stem cells which do not require the same degree of histocompatibility. The donated cells after infusion into the patient will multiply and replace the patient's deficient marrow.

Prognostic factors of ALL

1-Age:

Prognosis is poor when age is < 2 years and > 10 years at diagnosis and worst prognosis is found in infant < 1 year.

2-Sex:

Higher relapse rate is evident in boys than girls.

3- Race:

Black children have lower remission and higher relapse rates due to higher incidence of high initial WBC count, mediastinal mass, L₂ morphology and lower socioeconomic status.

4-Onset of leukemia

The more slowly the onset, the more durable the remission that follow institution of therapy.

5- Leukemic cell burden

Which can be assessed by evaluation of extramedullary disease as the degree of hepatosplenomegaly and lymphadenopathy.

6- CNS involvement:

CNS infiltration is associated with lower rate of remission induction, a higher risk of relapse and a shorter survival.

7- Nutritional status:

Malnourished children may have less tolerance and receive sub-optimal doses of chemotherapy.

8- WBCs count:

Initial WBCs count is the most significant factor. There is a linear relation between WBCs count and outcome. High WBCs counts are associated with bulky extramedullary disease and high risk of CNS or testicular relapses.

9- Hemoglobin concentration:

Hb<10 gm/dl is associated with higher remission induction, lower relapse, and longer survival rates while normal hemoglobin level is associated with bulky extramedullary disease and high percentage of blasts.

10- Platelet counts:

Patients with low platelet counts below 20.000/m³ have shorter duration of remission. Leukemia associated with petechial hemorrhages may predispose patients to testicular and CNS relapses.

11- Lactate dehydrogenase enzyme (LDH):

Higher LDH levels are associated with shorter remission.

12-Blast morphology:

L₁ is associated with more favorable prognosis, than L₂ morphology, which has poor prognosis. L₃ have the worst prognosis.

13- Immunophenotyping:

B cell ALL have worst prognosis. Mature B ALL has extremely poor prognosis. Pre-B cell ALL is worse than early pre-B ALL.

T cell ALL has poor prognosis, but after adjustment for its association with the high initial WBCs count, T-cell become weak independent predictor of treatment outcome. Mature T-cell have poorer outcome than early T.

14- Response to treatment:

Failure to reduce leukemic mass rapidly permits the emergence of clones of lymphoblasts resistant to drugs so early responders with < 5% blasts in bone marrow on day 7 have the best prognosis.

LYMPHOMA

Lymphomas are abnormal growth of lymphocytes within the lymphatic system which includes lymph nodes, spleen, thymus, tonsils and bone marrow. Two major types of lymphomas are known, Hodgkin's Disease (HD) and (Non-Hodgkin's lymphoma) NHL.

Epidemiology:

Lymphomas are the third most common childhood cancer after leukemias (33%) and brain tumor (25%). It accounts for 20% of pediatric malignancies.

Age:

Peak incidence of NHL occurs around 5-15 years, while three forms of HD have been identified including childhood form (≤ 14 years), young adult form around (15-34 years) and older adult form (55-74 years).

Sex:

Male are mostly affected than female by both HD and NHL.

Race:

Lymphomas are higher in blacks than in whites. This may reflect a difference in susceptibility or in exposure to environmental factors.

ETIOLOGY OF LYMPHOMAS:

Remains unknown but may be due to many factors as:

Genetic factors:

Evidences are: Occurrence of familial lymphomas and higher incidence in relative of affected children.

Viral infection:

As EBV, Human T Lymphotropic virus and HIV.

Environmental factors:

Exposure to ionizing radiation induces chromosomal aberrations and interfere with immunologic defenses and predispose to malignancy.

Chemical carcinogens:

Hydantoin may be associated with development of benign Pseudo-lymphomas which resolve when the drug is discontinued also Herbicides and Chemotherapy may have possible association with lymphomas.

Immune deficiency:

Children with congenital immune deficiency diseases or receiving immunosuppressive drugs, patients with autoimmune diseases and organ transplants have an increased risk of lymphomas.

Clinical features of lymphomas:**1. Lymphadenopathy (90%):**

The most common symptom of both HD and NHL is enlargement of lymph nodes anywhere in the body. Cervical lymph nodes are mostly involved followed by axillary, inguinal, mediastinal and retroperitoneal lymph nodes. Affected LN are painless, not tender, firm and discrete.

2. Mediastinal Lymphoma (30-60%):

Mediastinal mass is often present in 60% of cases of HD and 30% of NHL.

3. General manifestations (30%):

Occurs mostly in HD and includes the following criteria:

- Night sweat
- Unexplained Weight loss > 10% over 6-month period
- Unexplained recurrent fever with temperature > 38°C.

4. Jaw lymphomas (20-70%)

Occurs in 20 % of cases of American Burkitt's lymphomas and in 70% of cases of African Burkitt's lymphomas.

5. BM involvement (5%)

Bone marrow involvement is focal, so manifestation of bone marrow infiltration is late in both types of lymphomas.

6. Abdominal lymphoma

Intestinal lymphoma with nonspecific gastrointestinal symptoms, vague abdominal pain, frank bleeding, obstruction or perforation are commonly associated with small intestinal NHL. Hepatosplenomegaly is frequently present in NHL but rarely encountered in HD.

7. Neurologic manifestations

As headache, cranial nerves palsy is usually late manifestation in HD and may occur in high grade NHL.

Classification of Hodgkin's disease

Diagnosis is based upon the recognition of tumor giant cells (Reed sternberg cells) containing two or more nuclei and two or more inclusion like nucleoli surrounded by lymphocytes, histiocytes, plasma cells, eosinophils and fibroblasts either singly or in combinations and according to these cells it is classified into:

- Nodular sclerosis (50%)
- Mixed cellularity (30%)
- Lymphocytic predominance (10-20%)
- Lymphocytic depletion (<5%).

Staging of Hodgkin's disease

Stage I

Single lymph node involvement or single extra lymphatic organ or site.

Stage II

Two or more lymph node region involvement in one side of the diaphragm.

Stage III

Two or more lymph node region involvement in both side of the diaphragm or splenic involvement.

Stage IV

Diffuse or disseminated involvement of one or more extra lymphatic organs other than lymph node, spleen, thymus, appendix, and Peyer's patches as liver, lung and bone.

Sub classification

A: Denotes no specific symptoms

B: Denotes specific symptoms as:

- Unexplained Weight loss > 10% over 6-month period.
- Unexplained recurrent fever with temperature > 38.
- Night sweat.

Bulky disease based on:

- Mediastinal mass > one third of thoracic diameter or
- LN mass ≥ 10 cm in diameter or
- ≥ 4 nodal regions involved.

Classification of NHL

High grade Lymphoma (rapidly growing):

Most of childhood NHL.

- **Immunoblastic lymphoma**
- **Lymphoblastic lymphomas**
- **Small non cleaved cell lymphoma**
 - Burkitt's
 - Non Burkitt's

Intermediate grade lymphomas

- Large cell lymphoma
 - Cleaved
 - Non cleaved
- Small, cleaved cell lymphoma

Low grade Lymphomas

- Small lymphocytic lymphomas
- Follicular lymphomas.

This is malignant lymphoma of lymph node, invading the capsule and extending into the surrounding tissue. Note that the follicles are numerous and irregularly sized.

Staging of non-Hodgkin's lymphoma:

Stage I

Single lymph node or extra nodal involvement with exception of abdomen or mediastinum.

Stage II

Two or more lymph node region or extra nodal sites in one side of the diaphragm
Primary abdominal tumor which is grossly (>90%) resected.

Stage III

Two or more lymph node region or extra nodal sites in both side of the diaphragm.
Extensive primary abdominal tumor (< 90% resected).

Primary intrathoracic tumor (mediastinal, pleural or thymic).

Stage IV

Disseminated involvement of extra lymphatic organs as bone marrow or CNS.

Investigation of lymphoma

Complete blood picture:

Bone marrow examination:

Bilateral bone marrow aspirate and biopsy is required as bone marrow infiltration is focal and not diffuse as in case of leukemia.

CSF Examination:

CSF analysis and cytology.

Biochemical analysis:

ESR, LDH, uric acid, serum electrolyte, liver and renal function tests.

Radiographic investigation:

Plain x ray and CT of the chest may detect mediastinal mass.

Plain x ray for long bones and bone scan for skeletal lesions.

Abdominal ultrasound and CT to detect retroperitoneal and mesenteric lymph nodes enlargement.

Lymphangiography may show enlargement of the lymph nodes and abnormal architecture in lymph nodes of normal size.

Lymph node biopsy (Histopathology)

At least one complete lymph node must be excised preferably the largest and most central one especially maxillary or cervical.

Immunophenotyping of lymphomas

- **B cell lymphoma:**

It is classified into early pre-B, Pre B- and mature B cell lymphoma

- **T cell lymphoma:**

It is classified into early, intermediate and late Tcell lymphoma.

Treatment of lymphoma

Non-Hodgkin's lymphoma:

Chemotherapy is the main line of therapy non-Hodgkin's lymphoma as it is disseminated disease from time of diagnosis.

Stage I and II is treated with six cycles of COMP (cyclophosphamide, oncovin, methotrexate and prednisone).

Stage III and IV is best treated based on histological subtypes:

Lymphoblastic and large cell lymphoma is treated with multidrug therapy for 2 years.

Small non cleaved cell lymphoma is treated with intensive multidrug therapy for 3-6 months.

Hodgkin's disease

Radiotherapy: Involved field radiation is integral part of treatment.

Chemotherapy including the following:

- MOPP (Mustard, Oncovin, Procarbazine and Prednisone).
- ABVD (Adriablastine, Bleomycin, Vinblastine and Decarbazine).

Other lines of treatment of lymphomas:

- Immunotherapy: Monoclonal antibodies labeled with toxins or radioisotopes are injected tumor cells.
- Bone marrow transplantation.

Prognosis of lymphomas:

Cure rate is 50 - 90 % depending in international prognostic index which include age, stage, number of extra nodal sites, performance status and LDH.

Complication of leukemia and lymphomas

1-Hyperleukocytosis:

Excessive WBCs obstruct circulation in the brain, lung and other organs by forming white thrombi in small veins.

2-Leukopenia:

Leucopenia predisposes the patient to opportunistic infections.

3-Coagulopathy:

It is due to thrombocytopenia, consumption of coagulation factors.

4-Organ infiltration:

Any organ may be infiltrated leading to its dysfunction.

5-Cerebro vascular accidents:

Causes are hyperleukocytosis, coagulopathy, or drugs induced as asparaginase which cause inhibition of synthesis of coagulation factors.

6-Psychological disturbances:

Survivors of ALL and lymphoma are likely to have more behavioral problems, impaired attainment of social skills.

7-Metabolic disturbances:

As tumor lysis syndrome in which there is acute lysis of tumor cells resulting in release of potassium, phosphates and urates causing acute renal failure due to their precipitation in the acidic environment of the kidney.

8- Secondary neoplasm:

CNS tumors are the most common then leukemia and lymphomas

9- Late effects of treatment:

A-CNS and endocrinal toxicity:

B-Hepatic, Cardiac and Genito- urinary toxicity.

BLOOD TRANSFUSION

Blood banking: The blood must be kept in the fluid state, living tissue, metabolically viable, free from bacterial infection. The blood kept in the fluid state by the addition of acid citrate dextrose (ACD).

Blood donation

1-Careful donor selection with donor interview.

- Age: not less than 17 years
- Pulse: between 50-100 beat / minute without irregularities.
- Blood pressure: systole <180mmHg, diastolic <100mmHg.
- Temperature: < 37.5C
- Hemoglobin: >12g/dl, Hct >38%
- Site of vein puncture must be free of lesions and infections.

2-ABO grouping, Rh typing and cross matching

3-Laboratory screening test for HBsAg, HIV, HTLV1, HTLV2, HC.

Blood grouping

Blood grouping means the determination of the antigens of a specific group on the red cells and the antibodies relevant to this group in the normal serum.

An individual's red cell group is determined by suspending washed red cells with diluted anti-A, anti-B, anti A+B and anti Rh (D). But automated machines are increasingly used. Agglutination indicates a positive test. Serum is simultaneously incubated with group A, B and O cells to confirm the presence of the expected naturally occurring ABO antibodies.

Blood group	Antigens on RBCs	Antibodies in serum
A	A	Anti B
B	B	Anti A
AB	AB	Non
O	O	Anti A & anti B

Reaction of cells tested with		Reaction of serum tested against		Interpretation
Anti A	Anti B	A cells	B cells	ABO Group
-	-	+	+	O
+	-	-	+	A
-	+	+	-	B
+	+	-	-	AB

Compatibility of BLOOD TYPES

	Donor							
	O-	O+	B-	B+	A-	A+	AB-	AB+
Recipient	AB+	+	+	+	+	+	+	+
	AB-	+	+	+	+	+	+	+
	A+	+	+	+	+	+	+	+
	A-	+	+	+	+	+	+	+
	B+	+	+	+	+	+	+	+
	B-	+	+	+	+	+	+	+
	O+	+	+	+	+	+	+	+
	O-	+	+	+	+	+	+	+

Compatibility testing

Compatibility testing (cross-matching) entails suspension of red cells from a donor pack with recipient serum, incubation (at room temperature and 37°C) to allow reactions to occur, and examination for agglutination.

Transfusion Modalities:

Whole blood:

Whole Blood is rarely given to patients because it is wasteful and sometimes harmful to give blood components that are not needed. Whole blood transfusions are necessary when very large amounts of blood have been lost, otherwise blood components are given.

Component therapy

To face an individual case needs as:

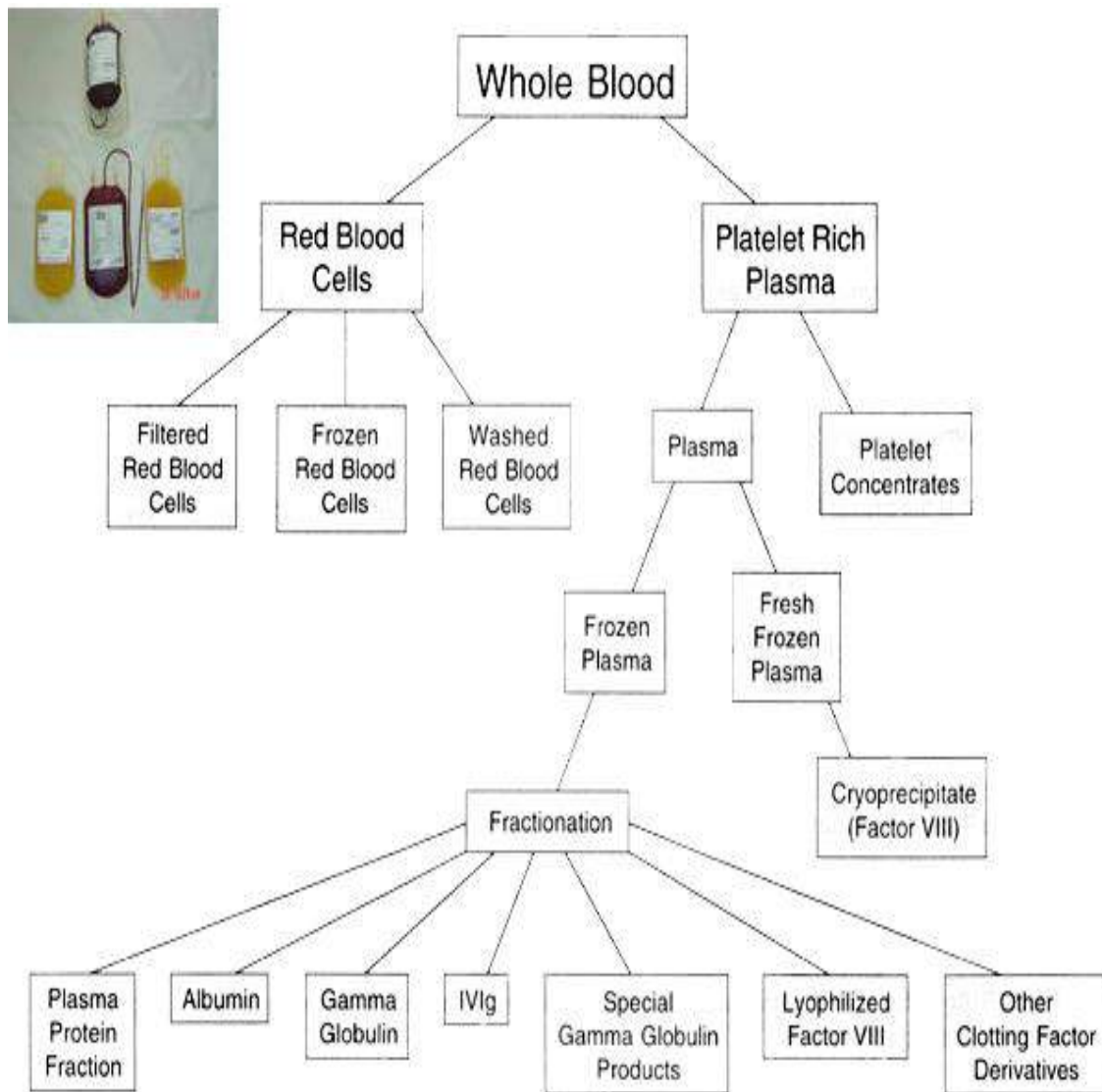
- ❖ **Red Blood Cells:** Carry oxygen and are needed by surgical patients or those with anemia.
- ❖ **Platelet Rich Plasma:** Is an intermediate stage in the production of platelet concentrate and plasma components.
- ❖ **Frozen Red Blood Cells:** Have been frozen to extend their storage period. Very rare blood types are frozen to insure they are always on hand.
- ❖ **Washed Red Blood Cells:** Have been washed to prevent reactions in some sensitive patients.
- ❖ **Filtered Red Blood Cells:** Have been filtered to prevent reactions in some sensitive patients and removal of contaminated WBCs with cytomegalovirus.
- ❖ **Irradiated red blood cells:** To deplete the cytotoxic T cells to avoid graft versus host disease in immunocompromised children.
- ❖ **Platelet Concentrates:** Are needed by patients to control bleeding in thrombocytopenia and platelet function disorders.
- ❖ **Plasma:** Is the yellow liquid portion of blood. It is also a source of proteins that stop bleeding by forming blood clots.

Frozen Plasma to be manufactured into derivatives is stored and shipped in the frozen state.

Fresh frozen plasma must be processed and frozen within eight hours of the whole blood donation to preserve the less stable clotting proteins as **Cryoprecipitate:** Which is a part of the plasma, containing two important clotting factors found in whole blood. It is used to treat two common clotting disorders.

Fractionation is the process of breaking plasma down into "fractions." When plasma gets mixed with certain chemicals, proteins can be separated and processed into products which are stable and easily stored. Some of the more common fractions are as follows:

- ❖ **Albumin:** Used in the treatment of certain kidney and liver diseases. Because of the relative simplicity of storage and administration, it is also used for emergency cases, such as accident or shock victims, particularly where facilities for administering blood are not available or where time does not permit its use.
- ❖ **Plasma Protein Fraction:** Similar to albumin; the two products are often used interchangeably.
- ❖ **Gamma Globulin:** Contains the antibodies in plasma and is able to modify or prevent measles and other infectious diseases, such as some varieties of hepatitis.
- ❖ **HBIG, RHIG, VZIG:** Are gamma globulin products prepared from the plasma of donors with high levels of specific desirable antibodies.
- ❖ **Lyophilized Factor VIII concentrates:** Are used for the treatment of Hemophilia A.
- ❖ **Other Clotting Factor Derivatives:** Contain concentrated amounts of specific clotting factors and are used in certain less common clotting disorders.



Complication of the blood transfusion:

1-Transmission of infectious diseases

- Bacterial, e.g., Yersinia, Treponema, Brucella, Salmonella.
- Protozoa, e.g. malaria, Toxoplasma, microfilaria.
- Viral infections which may be:

Plasma-borne viruses

- Hepatitis B, hepatitis C.
- Hepatitis A (rarely)
- Other unidentified hepatitis viruses

- HIV-1 and HIV-2 (also cellular)
- Parvovirus

Cell associated viruses

- Cytomegalovirus
- Epstein-Barr virus
- HTLV-I and HTLV-II

2- Transfusion reactions

Untoward reaction due to infusion of blood or one of its components:

Acute transfusion reactions

- ***Immune***
 - Febrile reaction
 - Allergic reaction
 - Anaphylactic reaction
 - Haemolytic transfusion reaction
- ***Nonimmune***
 - Circulatory overload
 - Air embolism
 - Metabolic complication (hyperkalemia, hypomagnesemia, and citrate toxicity)
 - Hypothermia
 - Acid base changes.

Delayed transfusion reactions

- ***Immune***
 - Immune sensitization (allo-antibodies)
 - GVHD in immunocompromised
 - Immunocompromizing effect
- ***Nonimmune***
 - Iron overload and Hemosiderosis

Minimizing the blood transfusion

- Maintenance of cardiac output by: crystalloid solution, colloid solution (dextran, gelatin, hydroxylethy starch) act from 4-24 hours, human albumin act for 4 days.
- Do not delay an emergency operation (bleeding case) regardless of preoperative Hb level.
- Minimizing blood loss by preoperative planning, induced hypothermia, hypotensive anesthesia, and meticulous hemostasis.
- Minimizing the oxygen consumption by mild hypothermia, neuromuscular blocking agent.
- Minimizing phlebotomies by transcutaneous pulse oximeter, pediatric micro sampling, multiple test per sample.
- Maximizing blood production by growth factors as: GM-CSF, G-CSF for neutropenia and erythropoietin hormone for anemia.
- Drug modifiers: hydroxyurea to increase fetal hemoglobin in sickle cell anemia,
- Desmopressin in Von-Willbrand disease.

Hemapheresis (Apheresis)

Definition:-

Apheresis is defined as the separation of whole blood into its components. During this procedure, a selected component is removed, and the remaining elements are recombined and returned to the donor or patient.

Purpose:-

- 1) To collect a blood product generally intended for transfusion when performed on a donor.
- 2) To provide a therapeutic effect when performed on a patient.

Types: -

Apheresis can be divided into two broad classifications: -

- A. Collections: platelets, plasma, RBCs, leukocytes including stem cells (for donation).
- B. Therapeutic: can be divided into two types: -

a) Depletion (cytapheresis)

- i) **Platelets apheresis:** is performed mainly for thrombocytosis with risk of thrombosis and hemorrhage (platelet count greater than million).
- ii) Leukocytes is depleted mainly for hyperleukocytosis (in leukemia).
- iii) RBCs is depleted mainly in polycythemia vera.
- iiii) RBCs exchange is performed mainly for sickle cell disease.

b) Plasma Exchange: - Is the removal of a large volume of plasma containing antibodies causing acute disease or organ damage and replacement by an appropriate fluid such as fresh frozen plasma or albumin.

Indications:

- Hyper viscosity syndrome associated with Hyperglobulinemia
- Acute myasthenia gravis

- Guillain-Barre syndrome
- Chronic relapsing inflammatory polyneuropathy
- Thrombotic thrombocytopenic purpura
- Familial hypercholesterolemia
- Immune complex vasculitis e.g. systemic lupus erythematosus
- Hemophilia with inhibitors
- Poisons and drugs

Bone Marrow Transplantation (BMT)

Definition

BMT is a procedure in which the recipient's unhealthy bone marrow is ablated then replaced by healthy hematopoietic stem cells (HSCs) either from a donor (allogenic BMT), or from the patient himself (autologous BMT). Thus, it can be also termed hematopoietic stem cell transplantation (HSCT).

Sources of hematopoietic stem cell:

1. Bone marrow
2. Peripheral blood stem cells
3. Umbilical cord blood

Types of BMT:

1-Autologous BMT: Reinfusion of the patients' previously stored HSCs.

In cancer patients without bone marrow involvement, the bone marrow is removed and cryopreserved prior to ablative cancer chemotherapy. In case of BM involvement, the marrow is removed during remission and the residual malignant cells are removed by the use of monoclonal antibodies directed against the tumor.

2-Syngeneic BMT: BMT from an identical twin.

3-Allogeneic BMT: BMT from HLA identical sibling or, less often, from a matched unrelated donor.

Indications for BMT and HSCT

Malignant disorders:

1. Acute leukemias: High risk, resistant to chemotherapy or relapsed cases
2. Chronic myeloid leukemia

3. Relapsed lymphomas
4. Advanced solid tumors e.g stage IV neuroblastoma

Non-malignant disorders:

5. Hematological disorders:
 - Severe aplastic anemia: congenital or acquired
 - Thalassemia
 - Sickle cell anemia
6. Immune deficiency syndrome
7. Metabolic disorders e.g. glycogen storage disease

Procedure of BMT:

- A. Pretransplant evaluation: Evaluation of both the patient and donor to exclude any other diseases that may affect BMT. In this stage HLA matching between donor and recipient is carried out in allogenic BMT for proper donor selection.
- B. Conditioning: It means preparation of the recipient's bone marrow to receive the transplanted HSCs. It involves ablation (destruction) of the affected bone marrow using chemotherapy and/or radiotherapy.
- C. Harvest of HSCs
- D. Infusion of HSCs
- E. Engraftment: It means establishment of new functioning bone marrow arising from the transplanted HSCs.

Complications of BMT:

1. Infectious complications:

During conditioning and before engraftment of the bone marrow the patient is immunocompromised. Liability to bacterial, viral, and fungal infections is increased. Such infections can be life threatening.

2. Graft rejection:

If the body immune system is strong enough to attack the transplanted HSCs, this will lead to destruction of the cells and graft failure. It can be prevented by proper selection of HLA matched HSCs and good conditioning.

3. Graft versus host disease (GVHD):

This is the opposite to graft rejection. In GVHD the immune cells present in the donor's marrow attack the recipient who is already immune-deficient. GVHD can be either acute or chronic. It can be prevented by the use of immunosuppressant medications.

Practice Questions

(Choose one correct answer)

- 1- Diagnosis of Henoch-Schoenlein purpura depends mainly on:
 - a) abdominal pain.
 - b) special distribution of purpuric spots.
 - c) platelet count.
 - d) arthritis.
- 2- Definition of anemia is:
 - a) decrease hemoglobin percent below the normal for age and sex.
 - b) decrease red cell count only.
 - c) decrease the hematocrite value.
 - d) decrease of the RBCs count or Hb% below the normal ranges for age and sex.
- 3- Aplastic crisis in sickle cell anemia is due to:
 - a) sickling of the red cells.
 - b) Parvovirus B19 infection.
 - c) pyruvate kinase enzyme deficiency.
 - d) associated G6PD deficiency.
- 4- The commonest type of leukemia in children is:
 - a) acute lymphoblastic leukemia.
 - b) acute non-lymphoblastic leukemia.
 - c) chronic lymphocytic leukemia.
 - d) acute mixed lineage leukemia.
- 5- Hemophilia-A occurs due to deficiency of :
 - a) factor VIII.
 - b) factor IX.
 - c) factor X.
 - d) factor XI.
- 6- Corticosteroid therapy is indicated in ITP in :
 - a) girls near menarche.
 - b) ITP with splenomegaly.
 - c) platelet count less than 30000/ cmm.
 - d) chronic purpura > 1 year.
- 7- The indication of corticosteroids in Henoch-Schonlein purpura is :
 - a) skin manifestations.
 - b) CNS manifestations.
 - c) uncomplicated joint manifestations.
 - d) abdominal pain.



Chapter 15

Nephrology and Urology

Objectives:

1. Discuss nephrotic syndrome.
2. Correlates between the clinical presentations and the special nature of both nephrotic and nephritic syndrome.
3. Understand the process of acute kidney injury.
4. Formulate a management plan for urinary tract infections.
5. Enumerate common renal and urinary tract developmental abnormalities.

Contents:

1. Nephrotic Syndrome.
2. Acute Poststreptococcal Glomerulonephritis.
3. Acute Kidney Injury.
4. Urinary Tract Infections.
5. Common Renal and Urinary Tract Developmental Abnormalities.

Nephrotic Syndrome (NS)

- **The nephrotic syndrome is a clinical complex characterized by:**
 1. Heavy proteinuria ($>40 \text{ mg/m}^2/\text{h}$)
 2. Hypoalbuminemia ($< 2.5 \text{ g/dl}$)
 3. Generalized massive edema
 4. Hyperlipidemia (Total cholesterol $> 250 \text{ mg/dl}$)
 5. Recurrence
- **The nephrotic syndrome can be classified according to the etiology into:**
 - A. **Primary (Idiopathic) nephrotic syndrome:** where the etiology is unknown.
 - B. **Secondary nephrotic syndrome:** where nephrotic syndrome is secondary to another disease.
 - C. **Congenital nephrotic syndrome.**

A. Primary (Idiopathic) NS

It is the most prevalent glomerular injury in childhood.

It forms **90%** of cases of nephrotic syndrome in childhood.

The categories of primary NS are:

- Minimal change disease (MCD) **85%**.
- Focal segmental glomerulosclerosis (FSGS) **10%**.
- Mesangial proliferative nephropathy (MPN) **5%**.

B. Secondary nephrotic syndrome

- It forms **10%** of childhood nephrotic syndrome. **It occurs as a consequence of:**

1. Following glomerulonephritis e.g. acute post streptococcal glomerulonephritis.

2. Systemic diseases involving the kidney as in:

- Henoch - Schonlein Purpura (HSP).
- Systemic Lupus Erythematosus (SLE).
- Hodgkin's Lymphoma.
- Juvenile Diabetes Mellitus (JDM).

3. Infections:

- Hepatitis B virus.
- Infective endocarditis.
- Malaria.
- Bilharziasis.
- Syphilis.

C. Congenital nephrotic syndrome:

- Occurs in the **first 3 months** of life.
- It may be **hereditary** disease (Finnish type) or secondary to congenital infection (Toxoplasmosis or syphilis).

Pathophysiology:

The underlying abnormality in nephrotic syndrome is an increase in permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The cause of the increased permeability is not well understood.

- In minimal change disease, it is possible that T-cell dysfunction leads to alteration of cytokines, which causes a loss of negatively charged glycoproteins within the glomerular capillary wall. The role of immune-mediated process in the etiology of MCD was supported by the response to immunosuppressive drugs.
- In focal segmental glomerulosclerosis, a plasma factor, perhaps produced by lymphocytes, may be responsible for the increase in capillary wall permeability. Alternately, mutations in podocyte proteins (podocin, α -actinin 4) are associated with focal segmental glomerulosclerosis

Minimal Change Disease (MCD) (Nil disease)

- It is the **most common** form of nephrotic syndrome in childhood.
- MCD is common **in boys**, with male to female ratio of 2:1.
- Age: It is a disease of young children with a peak incidence from **2 to 5 years** of age.

Etiology: The etiology of MCD remains unknown.

Pathology:

1. **Gross picture:** In MCD the kidneys are large pale and smooth.
2. **Light microscope (LM):** The glomeruli appear normal. With no immune deposits by immunofluorescence
3. **Electron microscope (EM):** Fusion of the foot processes of the epithelial cells lining the glomerulus, and some irregularity of the thickness of the basement membrane. These changes are reversible. (*See fig.1*)

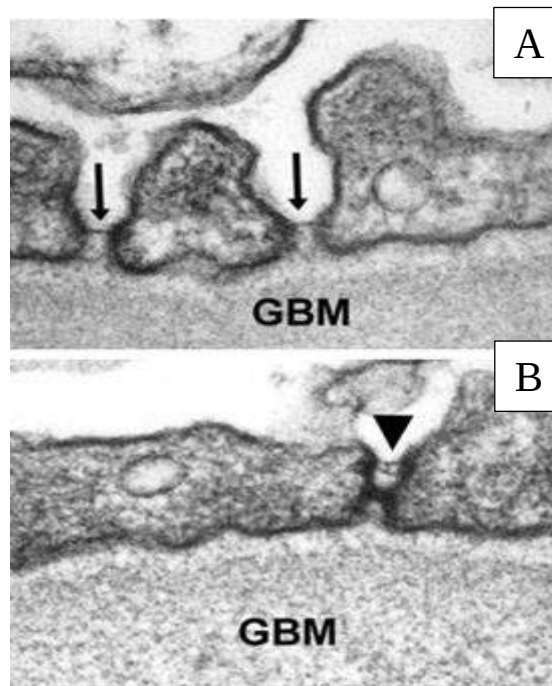


Figure 1: (A) EM picture of the normal glomerular filtration barrier, the arrows show the glomerular slit diaphragm between foot processes of podocytes. **(B)** EM of the glomerular filtration barrier in MCD, The arrow shows fusion of the foot processes and collapsing of slit diaphragm (GBM, glomerular basement membrane)

Pathogenesis:

The glomerular leakage of serum proteins mainly albumin results in:

1. Hypoalbuminemia.

2. **Edema:** It is the increase in the extra vascular (interstitial) component of the extracellular fluid volume. **It results from:**

- i. The hypoalbuminemia and the decrease in the oncotic pressure of the blood (underfill theory).
- ii. Decrease in plasma volume leads to the activation of the renin angiotensin - aldosterone axis with salt and water retention (overfill theory).

3. Hyperlipidemia:

- i. It is mainly due to increase in serum cholesterol and triglycerides.
- ii. This is due to increased liver synthesis of cholesterol and triglycerides and also due to the decrease in peripheral catabolism of lipids.

4. Increased susceptibility to infection: This is due to:

- i. Decrease in serum immunoglobulins and complement, which are lost in urine.
- ii. Edema fluid acts as good bacterial culture media.
- iii. Protein deficiency and decreased bactericidal activity of leukocytes.
- iv. Defective opsonization of bacteria due to Loss of properdin factor B in urine

5. Hypercoagulability:

- i. Due to increased plasma levels of certain coagulation factors such as factor V, VII and fibrinogen. While plasma level of antithrombin III is decreased. In addition to increased blood viscosity.
- ii. Tendency for thrombosis is less common in children.

Clinical Picture:

The onset is usually gradual in a child of 2-5 years of age often following influenza like syndrome.

1. Edema:

- It may be mild at first around the eyes (periorbital edema). Then progresses to become generalized with increase in body weight and decreased amount of urine.
- Generalized edema may be severe up to anasarca (Hydrothorax and ascites) leading to dyspnea.
- Gastrointestinal disturbances as nausea, vomiting, diarrhea and abdominal pain due to edema of gastrointestinal wall.

2. Hematuria, hypertension and renal dysfunction are rare.

Diagnosis:

A. Clinical presentations.

B. Laboratory investigations:

1. Urine analysis:

a. Proteinuria:

- Normally urine contains very minute amount of protein up to 4 mg/m² /hour.
- Significant proteinuria is the presence of > 4 and less than 40 mg/m² /hour.
- Heavy proteinuria or proteinuria of nephrotic range is the presence of > 40 mg/m² /hour or > 1 g/ m² /day.
- So, for the diagnosis, the urine must contain proteinuria of nephrotic range.

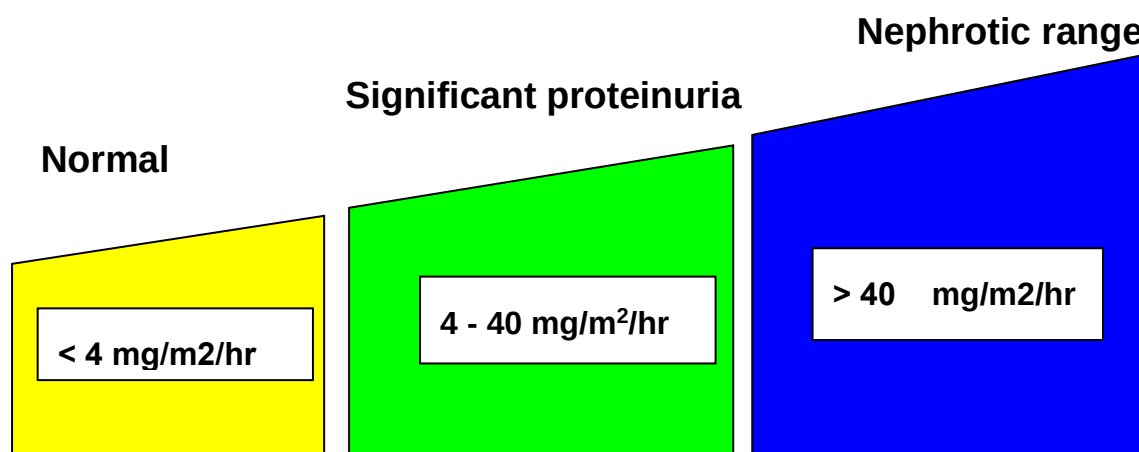


Diagram shows degrees of proteinuria in children

- b. The urine contains number of cellular, granular, hyaline and lipoid casts, microscopic hematuria may be present.

2. Blood:

- a. Decreased serum proteins, mainly serum albumin. Edema usually starts when serum albumin is ≤ 2.5 g/dl.
- b. Increase in serum cholesterol (>250 mg/dl) and triglycerides.

- c. Total serum Ca level is diminished owing to the decrease in albumin- bound fraction.
- d. The serum complement 3 (C3) level is normal.
- e. Increased ESR and anemia are usually present.
- f. Renal function tests are normal in MCD.

3. Renal biopsy: It is indicated if other pathology rather than MCD is suspected as:

- i. Age of onset less than one year or more than 10 years in the first presentation
- ii. Presence of hypocomplementemia.
- iii. Raised BUN and serum creatinine not responding to volume and albumin correction.
- iv. Steroid resistant, steroid dependent and multiple relapses.
- v. Presence of persistent hypertension and gross hematuria.

Complications of nephrotic syndrome:

1. Infections:

- Bacterial and viral infections are common due to increased liability of nephrotic patients to infection and the use of steroid therapy.
- The most common organisms are pneumococcus and gram -ve (E. coli).
- Peritonitis is the most common site of infection but pneumonia, Skin infection (cellulitis) and urinary infections are not uncommon.
- Steroid therapy reduces the clinical signs of infection and its flaring, so we must treat infections before starting steroid therapy.
- All children with nephrotic syndrome should receive polyvalent pneumococcal vaccine (if not previously immunized). Children with a negative varicella titer

should be given varicella vaccine. These vaccines ideally administered when the child is in remission or on a low dose of alternate-day steroids.

- Nonimmune nephrotic children in relapse exposed to varicella should receive varicella-zoster immunoglobulin within 72 hr of exposure.
- Influenza vaccine should be given on a yearly basis.

2. Hypovolemic shock:

It occurs in severe cases with massive proteinuria, septicemia and aggressive diuretic therapy especially if serum albumin below 1.5 g/dl.

3. Arterial and venous thrombosis:

- Due to hypercoagulability state, it is less common in children than adults.
- Its possibility increases when associated with dehydration, septicemia and serum albumin below 1.5 g/dl.
- Its manifestations occur according to the site of blood vessels (BV) thrombosis as intestinal obstruction (mesenteric BV), skin gangrene (cutaneous BV) hemiplegia (central nervous BV) or severe hematuria (renal BV).

4. Muscle wasting: Due to hypoproteinemia and the steroid therapy.

5. Side effect of therapy:

a. Side effects of steroid therapy:

- Cushingoid obesity, cutaneous striae, poor wound healing.
- Flaring of viral or T.B infection.
- Osteoporosis and delayed growth.
- Systemic hypertension, hyperglycemia.
- Toxic manifestations as: Papilledema, fits and severe osteoporosis.

b. Other immunosuppressive drugs:

- Cyclophosphamide (Depressed immunity, cystitis, sterility and alopecia)
- Cyclosporine (Nephrotoxicity, gum hyperplasia and hirsutism).

6. Acute Kidney failure: It occurs after aggressive diuretic therapy due to hypovolemia and decreased renal perfusion, severe hypoalbuminemia and septicemia.

Differential diagnosis:

Nephrotic syndrome must be differentiated from:

I. Acute post streptococcal glomerulonephritis.

II. Generalized edema.

- Nutritional as PEM and wet Beri Beri.
- Cardiac edema as in cases of right sided or congestive heart failure and constrictive pericarditis.
- Hepatic edema, in late cases of chronic liver diseases with ascites.
- Allergic edema as in angioneurotic edema.

III. Other causes of nephrotic syndrome. A diagnosis other than MCNS should be considered in the presence of age <1 yr, presence of family history of NS, extrarenal findings (arthritis, rash, anemia), hypertension, acute or chronic renal insufficiency, and gross hematuria.

Treatment:

1. Hospitalization: No indication for hospitalization except:

- First time for teaching the mother and to observe the response of the child to steroid therapy.
- Presence of severe infection, electrolyte disturbance or hypertension.
- Severe cases with anasarca.
- Acute kidney failure.

2. **Activities:** Encourage normal activity except in the presence of respiratory distress, anasarca, hypertension, shock and impaired renal function.

3. **Diet:** Well-balanced diet with an adequate protein content (recommended daily allowance). Low salt diet (1 to 2 g / day). Fluid Restriction is indicated in cases with severe edema.

4. **Therapy:**

a. **Antibiotic therapy:** Treatment of infection has the priority: the suitable antibiotic after culture and sensitivity should be given before starting steroid therapy.

b. **Steroid therapy:**

- Prednisone is given in a dose of 2 mg/kg/day (maximum 80 mg/day divided into 2 - 3 doses) for :

- In initial episode : 4 consecutive weeks
- In case of relapse: till urine becomes free of protein, and remains as such for 5 days.

- Then we shift prednisone to alternate day therapy: 1.5 mg/kg as single morning dose every other day for 4 - 6 weeks to lower the possibility of relapse. The dose is then slowly tapered and discontinued over the next 2- 3 months.

- **Steroid responder:** when urine becomes protein free within four weeks of steroid therapy.

- **Steroid resistant:** when urine did not become protein free after six weeks of daily full dose steroid therapy.

- **Steroid dependent:** when proteinuria reappears after shifting to alternate day therapy or on stopping the alternate day therapy.

c. **Other immunosuppressive drugs:** Used alone or with steroid therapy in:

- Steroid resistant.

- Steroid dependent.
- Frequent relapses.
- Occurrence of toxic complications of steroid therapy (osteoporosis, fits, papilledema and hypertension).
- e.g.:
 - **Cyclophosphamide**: 2 - 3 mg/kg/day for 8 - 12 weeks.
 - **Chlorambucil**: 0.1 - 0.15 mg/kg/day for 12 weeks.
 - **Cyclosporine**: 5 mg/kg/day for 6- 12 months.
 - **Mycophenolate mofetil (MMF)**: 1200mg/m²/day for 6- 12 months.

d. Diuretics:

- Used in cases with severe edema with salt free human albumin.
- The dose of furosemide as diuretic 2 mg/kg/day.
- Salt free human albumin 0.5 - 1 g/kg/day slow IV infusion.

Prognosis:

- The majority of children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older.
- It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop end stage renal disease (ESRD).
- Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, with a much poorer prognosis, leading to ESRD.

Acute Poststreptococcal Glomerulonephritis (APSGN)

- It is the **most common form of nephritis** in childhood.
- **Characterized by sudden onset of:**
 - Gross hematuria.
 - Significant proteinuria.
 - Mild to moderate edema.
 - Hypertension.
 - Variable degrees of impaired renal function.

Etiology:

- APSGN follows infection of the upper respiratory tract (Pharyngitis, nasopharyngitis, or otitis media) or skin infection (impetigo, acne, or erysipelas) with certain nephritogenic strains of group A beta - hemolytic streptococci.
- A seasonal variation in the incidence of attacks of APSGN due to either streptococcal pharyngitis (winter and early spring) or streptococcal pyoderma (summer and early fall) has been observed.
- Epidemics of nephritis have been described in association with both throat (Serotype 12) and skin (Serotype 49) infections.
- A latent period between the preceding streptococcal infection and the onset of APSGN of 7 to 21 days (average 10 days) in throat infection and 14 to 28 days (average 20 days) in pyoderma is usually present.

Pathology:

- The kidneys are symmetrically slightly enlarged, pale, and dotted with small punctuate hemorrhages on the cortical cut surface. On light microscopical examination:
- Glomeruli appear enlarged and relatively bloodless.
- There is proliferation of capillary endothelium.
- Diffuse mesangial proliferation with increase in mesangial matrix with polymorphonuclear leukocytes in glomeruli (Glomerular hypercellularity).
- In severe cases crescents and interstitial inflammation are seen.
- Immunofluorescence microscopy reveals deposits of immunoglobulin (IgG) and complement (C3) on the basement membrane.
- The tubular cells are swollen, granular with fatty and hyaline deposits.
- All these changes start to disappear within 3 weeks and completely disappear after 6 - 8 weeks.

Pathogenesis:

1. Decreased glomerular filtration rate (GFR).
2. Increased permeability of glomerular capillaries leading to escape of RBCs (hematuria) and passing of serum albumin (albuminuria).
3. Edema: Due to salt and water retention and circulatory overload leading to the expansion of extracellular fluid compartment.
4. Hypertension: In addition to salt and water retention and circulatory overload (circulatory congestion), renal ischemia also shares in getting hypertension, hypertensive heart failure, hypertensive encephalopathy and retinal exudate and hemorrhages are the complications of hypertension.

5. Impaired renal function: Decreased renal perfusion due to narrowing of glomerular capillaries leads to oliguria, retention of potassium, non-protein nitrogen and results in acute kidney failure.

Clinical presentation:

- Age at onset is **3 - 10 years**.
- More common in **males**, male to female ratio 2: 1.
- **Asymptomatic cases:** The disease may be so mild to be passed unnoticed.

1. General manifestations: anorexia, nausea, fever (usually low grade) and abdominal pain (loin pain).

2. Urinary manifestations:

a. Hematuria:

- Occurs in 100% of cases
- Ranges from microscopic to gross hematuria.
- Gross hematuria occurs in 50% of cases.
- Most of RBCs are lysed causing tea color, cola color, smoky urine or dark red colored urine.
- Gross hematuria persists for 1 - 14 days.

b. Decreased urine volume and oliguria in cases of acute kidney failure (AKF).

3. Edema:

- Present in over 75% of cases.
- Mild to moderate edema.
- Usually starts in the face in the morning.
- Severe edema occurs in: CHF, and secondary nephrotic syndrome.

4.Hypertension:

- Mild to moderate hypertension but may be severe enough to cause hypertensive HF and hypertensive encephalopathy.
- Occurs in 50% - 60% of cases.
- It occurs during acute phase (first 3 weeks).
- Blood pressure usually returns to normal within two weeks.

5.Manifestations of complications:

a. **Hypertensive heart failure:**

- Due to circulatory congestion and the hypertension.
- Dyspnea and congested pulsating neck veins, cardiomegaly, tachycardia, pulmonary edema, hepatomegaly and increasing generalized edema.

b. **Hypertensive encephalopathy:** The child gets severe headache, nausea, vomiting, drowsiness, papilledema and convulsions may occur.

c. **Acute kidney failure:** The child develops progressive oliguria and even anuria with increasing edema, with nausea, vomiting, drowsiness and even convulsions may occur.

Investigations:

A. Urine Analysis:

1. Decreased volume or even oliguria.

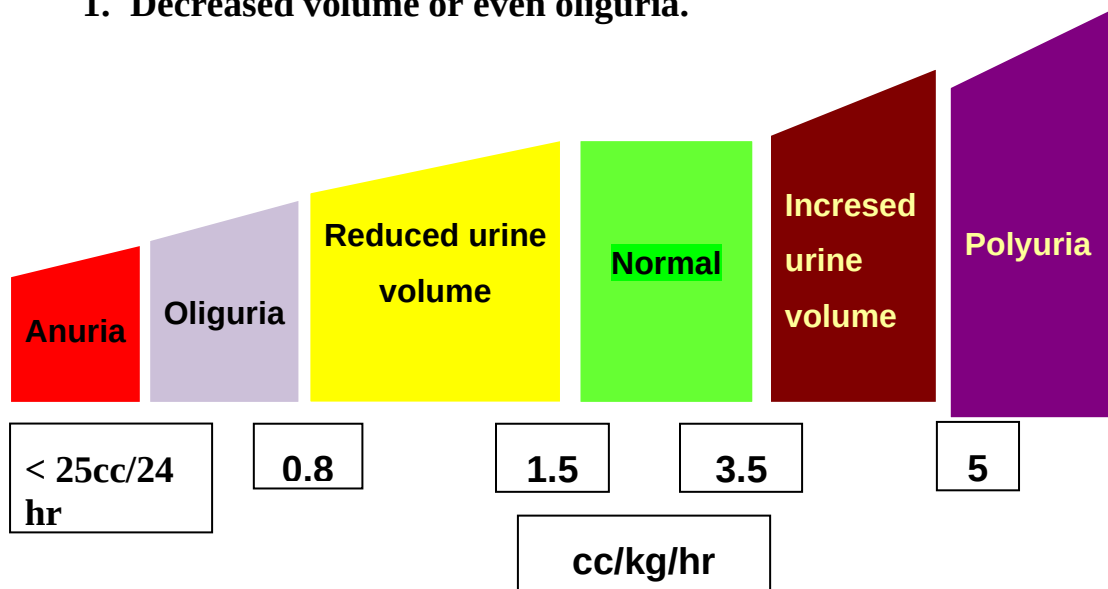


Diagram shows normal and abnormal urine volumes in children

- Normal urine output is (1.5 to 3.5 cc/kg/hr).
 - Reduced urine volume (0.8 - 1.5 cc/kg/hr) is normal variation occurs in dehydration, starvation and hot weather
 - Oliguria is urine output less than 0.8 cc/kg/hr and anuria is severe oliguria with 24-hour urine volume less than 25 cc in children.
 - Increased urine volume (3.5 – 5 cc/kg/hr) is normal variant occurs in cold weather, recovery from edema and excessive drinking.
 - Polyuria (5 or more cc/kg/hr.).
2. Specific gravity increase to 1020 or more.
 3. Gross or microscopic haematuria.
 4. RBCs are dysmorphic.

5. RBC's casts

6. Some WBCs and granular casts.

7. Significant proteinuria ($>4 \text{ mg/m}^2/\text{hr}$ and less than $40 \text{ mg /rn}^2/\text{ hr}$).

B. Blood:

- Anemia mild normochromic normocytic anemia due to hemodilution.
- Increased ESR
- Blood chemistry
 - ✓ Hyperkalemia
 - ✓ Increased blood urea nitrogen and serum creatinine.
 - ✓ Metabolic acidosis
 - ✓ Hyperchloremia
- Decreased serum complement (C3) during the first 3 weeks and returns to normal within 6-8 weeks
- Antibody titers to streptococcal antigens:
 - ✓ Increase in antistreptolysin O titer (ASOT) but not in APSGN after pyoderma.
 - ✓ Increased in antideoxyribonuclease B (ADNA ase - B).
 - ✓ But no correlation between the severity of renal insult and the titer levels.
- Leukocytosis.

C. Positive throat culture for streptococci.

D. Chest X-ray: Reveals pulmonary congestion, cardiomegaly and pulmonary edema in severe cases.

E. Renal biopsy: It is indicated in:

- i. AKF.
- ii. RPGN.

- iii. 2nd nephrotic syndrome.
- iv. Persistent hypocomplementemia.
- v. Recurrent gross hematuria.
- vi. Persistent hematuria and proteinuria.

Differential Diagnosis:

1. Other glomerular diseases:

- Nephrotic syndrome.
- Acute post-infectious glomerulonephritis (APIGN) following pneumococcal, gram -ve bacteria or viral infections.
- Anaphylactoid purpura.
- SLE.
- IgA nephropathy.

2. Other causes of hematuria:

- Congenital polycystic kidney.
- Trauma. Blunt trauma and urinary stones and crystalluria (oxaluria).
- Infection: Urinary tract infection, Renal T.B, and Urinary Bilharziasis.
- Blood diseases: Coagulation defects (Hemophilia), Thrombocytopenia (I.T.P.), and Sick cell anemia,
- Malignancy: Leukemia, and Renal tumors (Wilm's tumor).
- Drugs: Anticoagulants (Heparin).

Prognosis:

- It is benign self - limited disease with complete recovery in over 95% of children with APSGN.
- Early mortality rate is 0.5%.
- Prognosis is better in childhood than in adulthood.

Prevention:

- No available vaccine.
- Avoid contact with children suffering from streptococcal throat or skin infections.
- Avoid overcrowding during cold weather.
- Adequate skin hygiene during summer.
- Antibiotic prophylaxis is not justified.

Treatment:

A. General treatment:

1. **Hospitalization:** Indicated in:

- Severe gross hematuria.
- Presence of hypertension.
- Occurrence of complications.

2. **Rest:** Bed rest for the period of gross hematuria, hypertension or complications.

3. **Diet:**

- Dietary salt and water restriction.
- Salt: 1 - 2 g/day.

- Water: equal to insensible water loss (400 cc/m^2 + urinary output of previous day - the planned weight loss). So getting negative fluid balance. This helps reduction of hypertension and edema.

B. Specific treatment:

- **A 10 days course of penicillin** is given to the patient and any culture positive family members, to eradicate streptococcal infection.
- **Diuretics:** as furosemide, at first is given I.M or I.V. in dose 1-2 mg/kg, followed by a dose of 1-2 mg/kg/day orally.
- **Anti-hypertensive drugs:**

Indicated if blood pressure is 140/90 or more.

- **There are 2 types of drugs:**

A. Emergency:

Used when the blood pressure (BP) is very high, leading to acute organs damage and the goal is to decrease BP by 20-25% in first 8 hours as:

- ✓ Nifedipine (Ca channel blocker): 0.25-0.5 mg/kg/dose sublingual hourly when needed.
- ✓ Nitroprusside (Vasodilator): 0.5- 2 $\mu\text{g/kg}$ /min IV infusion.
- ✓ Hydralazine (Vasodilator): 0.1-0.4 mg/kg/dose, slow IV hourly when needed.
- ✓ Labetalol (α - β blocker): 0.25 - 1 mg/kg/dose, IV hourly when needed then IV infusion (1-3 mg/kg/hr).
- ✓ Furosemide (Loop diuretic): 0.5-2 mg/kg/dose IV / 6hr.

B. Maintenance:

- ✓ Amlodipine (Ca channel blocker): 0.1-0.4 mg/kg/day orally.
- ✓ Atenolol (β blocker): 1-2 mg/kg/day orally.
- ✓ Furosemide (Loop diuretic) in dose of 1- 6 mg/kg/day orally.

- ✓ Captopril (Angiotensin converting enzyme inhibitor): 1- 6 mg/kg/day orally.

C. Treatment of complications:

i. Hypertensive heart failure:

- Reduction of high blood pressure especially with diuretics.
- In the absence of organic myocardial disease digitalization will offer no beneficial effects.

ii. Hypertensive encephalopathy:

- Reduction of high blood pressure.
- Control of convulsions by diazepam 0.3 mg/kg/dose IV and phenobarbitone sodium in dose of 3-5 mg/kg/day IV to prevent convulsions.

Acute Kidney Injury (AKI)

It is a clinical syndrome in which a sudden decrease in the renal function results in retention of nitrogenous waste products and disturbance in water, electrolytes and acid - base balance. The term AKI has largely replaced acute renal failure (ARF), reflecting the recognition that smaller decrements in kidney function that do not result in overt organ failure are of substantial clinical relevance and are associated with increased morbidity and mortality. The term AKF is now reserved for severe AKI, usually implying the need for renal replacement therapy.

Etiology:

1. **Pre - renal:** Where there is decrease in renal perfusion and subsequent decrease in GFR as in:
 - Hypovolemia: hemorrhage, severe dehydration, burns and nephrotic syndrome.
 - Hypoxia: neonatal asphyxia, severe chest infection and post cardiac surgery.
 - Hypotension: cardiac failure, severe septicemia and cardiomyopathy.
2. **Renal:** as in APSGN, hemolytic uremic syndrome (H.U.S), Henöch-Schonlein purpura (H.S.P.) pyelonephritis and nephrotoxins as aminoglycosides.
3. **Post - renal:** Due to obstruction of urinary tracts as in:
 - i. Ureteropelvic junction obstruction.
 - ii. Bladder neck obstruction.
 - iii. Urethral stricture.
 - iv. Spina bifida.
 - v. Posterior urethral valve.

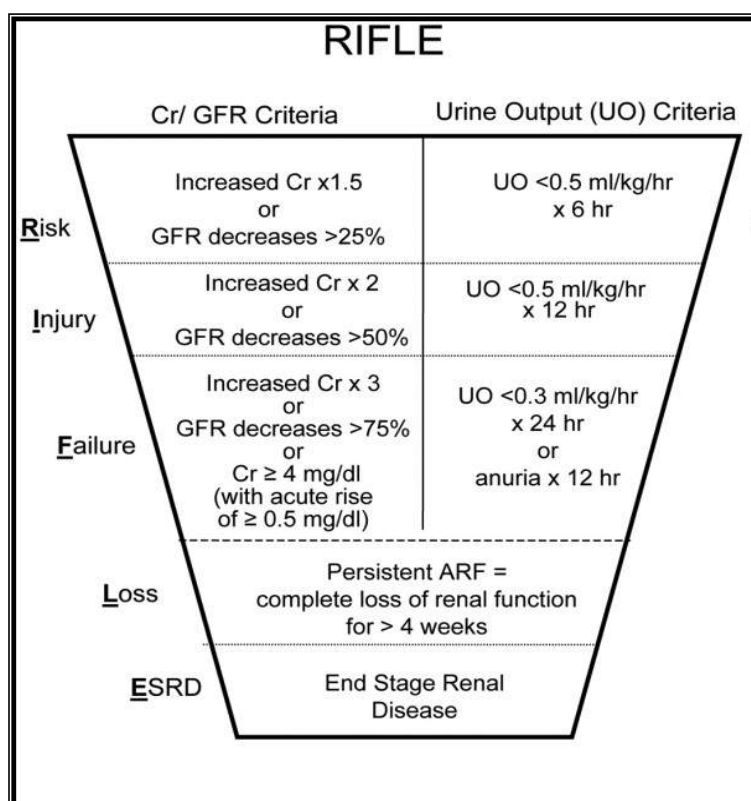


Figure 2: Stages of AKI by RIFLE criteria

Clinical presentations:

- A carefully taken history is critical in defining the cause of AKF. An infant with a 3-day history of vomiting and diarrhea most likely has prerenal ARF caused by volume depletion. A 6 yrs. old child with a recent pharyngitis who presents with periorbital edema, hypertension, and gross hematuria most likely has intrinsic AKF related to acute post-infectious glomerulonephritis. A critically ill child with a history of protracted hypotension and exposure to nephrotoxic medications most likely has acute tubular necrosis (ATN)
- The physical examination must be thorough, with careful attention to volume status. Tachycardia, dry mucous membranes, and poor peripheral perfusion suggest inadequate circulating volume and the possibility of prerenal AKF.

Peripheral edema, rales, and a cardiac gallop suggest volume overload and the possibility of intrinsic AKF from glomerulonephritis or ATN. The presence of a rash and arthritis may suggest systemic lupus erythematosus (SLE) or Henoch-Schönlein purpura nephritis. Palpable flank masses may suggest renal vein thrombosis, tumors, cystic disease, or urinary tract obstruction.

Investigations:

- 1. Retention of waste products:** as urea and creatinine (Normal serum BUN is 5 - 18 mg / dl and normal serum creatinine 0.3 - 0.7 mg /dl).
- 2. Biochemical disturbance:**
 - Hyperkalemia: serum K >6 mEq /L (Normal serum potassium from 3.5 - 5.5 mEq / L).
 - Hyponatremia: serum Na<130 mEq /L (Normal serum sodium:135-145 mEq/ L).
 - Metabolic acidosis: pH< 7.35 (Normal pH: 7.35 - 7.45).
 - Hypocalcemia: Total serum Ca <9 mg/dl (Normal serum calcium is 9 - 11 mg/dl).
- 3. Radiology:**
 - Chest radiography may reveal cardiomegaly and pulmonary congestion (fluid overload).
 - Renal ultrasonography may reveal hydronephrosis and/or hydroureter, which are suggestive of urinary tract obstruction
- 4. Urinary indices:** may be useful in differentiating prerenal AKF from intrinsic AKF. Patients whose urine shows an elevated specific gravity (>1.020), elevated urine osmolality (UOsm > 500 mOsm/kg), low urine sodium (UNa < 20 mEq/L), and fractional excretion of sodium (FENa) <1% most likely have prerenal ARF. Those with a specific gravity of <1.010, low urine osmolality (UOsm < 350

mOsm/kg), high urine sodium ($\text{UNa} > 20 \text{ mEq/L}$), and $\text{FENa} > 1\%$ most likely have intrinsic AKF.

5. **Renal biopsy:** may be required to determine the precise cause of AKF in patients who do not have clearly defined renal cause.

Treatment:

- **Post renal AKF:** insert a catheter and consult urology surgeon.
- **Pre-renal ARF:** correct volume depletion by the same component lost as blood transfusion in hemorrhage, IV fluids in dehydration, plasma transfusion in burns and IV human albumin in hypoalbuminemia, to improve the renal perfusion. In addition control of infections in cases of septicemia.
- **Fluid balance:** In case of AKF renal and postrenal fluid must be calculated as:
[Insensible water loss ($400 \text{ cc./m}^2/\text{day}$) + urine volume of the previous day + any ongoing losses as nasogastric or chest tube drainage + $75 \text{ cc./m}^2/\text{day}$ for each degree centigrade rise in body temperature]
- **Diuretic therapy:** should be considered only after the adequacy of the circulating blood volume has been established. Furosemide ($1\text{--}6 \text{ mg/kg/day}$) may be administered.
- **Hyperkalemia is corrected by:**
 - i. Elimination of any dietary exogenous potassium.
 - ii. Calcium gluconate 10%: to antagonize the effect of excess K^+ on myocardium in dose of 0.5 c.c./kg IV over 5-10 minutes.
 - iii. B_2 agonist inhalation.
 - iv. Sodium bicarbonate 8.4%: for shifting K^+ into cells as it decreases the metabolic acidosis. The dose is $1\text{--}2 \text{ c.c./kg IV}$.
 - v. Glucose and insulin: For shifting K into cells .the I.V. glucose 0.5 g/kg and regular insulin 0.1 unit /kg .

vi. Ion exchange resins: Remove K^+ from body, 1g/kg/dose either orally or per rectum.

vii. Dialysis.

▪ **Hyponatremia:**

i. Fluid restriction. ii. Dialysis.

▪ **Metabolic acidosis:** (pH below 7.25)

i. Sodium Bicarbonate 8.4%: 1-2 mEq/Kg/dose slow IV.

ii. Dialysis.

▪ **Dialysis:**

It is either peritoneal dialysis (PD) or hemodialysis (HD) indicated in:

- Circulatory overload and pulmonary edema.
- Uremic encephalopathy.
- Persistent hyperkalemia unresponsive to conventional measures or serum $K^+ \geq 7$ mEq/L.
- Intractable metabolic acidosis.
- Persistent hyponatremia.
- Severe CHF and intractable hypertension.

Urinary Tract Infections (UTI)

Urinary tract infections are common in infancy and childhood, only exceeded by respiratory tract and gastrointestinal infections. It occurs in as many as 5 % in girls and 1- 2 % in boys.

Etiology:

The causative organism in 80% of cases is *Escherichia coli* (E. coli), and the rest 20% by *streptococcal fecalis*, *proteus*, *kiebsiella* and *pseudomonas*.

Predisposing factors:

1. Age and sex:

- During first year of life, U.T.I is more common in boys than in girls, as congenital anomalies of urinary tract are more common in boys.
- During childhood, UTI is more common in girls than in boys in ratio 5:1 due to the short urethra in females.

2. Congenital anomalies of urinary tract:

- Stasis or obstructive uropathies encourage UTI as in stricture ureters, stones or neurogenic bladder.

3. Malnutrition: PEM and vitamin A deficiency favor UTI.

4. Poor perineal hygiene: Wiping from back to front in females, Pinworm infestation

5. Frequent instrumentation of urinary tract.

6. Constipation.

7. Uncircumcised males.

8. Family history of recurrent UTI or renal anomalies.

Pathogenesis:

Urinary infections have been classified according to their anatomical location into:

1. **Lower UTI:** urethritis and cystitis.
2. **Upper UTI:** pyelitis and pyelonephritis. UTI is rarely limited to a single portion of urinary tract especially in infants and children.

Routes of infection:

1. Hematogenous: Hematogenous spread by blood stream from a distant focus, usually occurs in newborns and infants.
2. Ascending infection: Ascending infection via the urinary passages is the commonest route of infection in childhood.
3. Through lymphatic channels is rare in children.

Clinical Presentations:

A. Acute UTI:

1. In newborns:

Picture of septicemia as; fever, hypothermia, vomiting, diarrhea, poor feeding, jaundice, convulsions and failure to thrive.

2. In infants and preschool age:

- Diarrhea
- Vomiting
- Fever
- Irritability
- Dysuria.
- Strong smelling or bad smelling urine

3. In school aged children:

- Fever and vomiting.
- Abdominal, loin or suprapubic pain.

- Strong or bad urine smelling.
- Frequency, urgency and dribbling.
- Nocturnal enuresis.
- Asymptomatic bacteriuria occurs usually in school children.

B. Complications of recurrent or chronic UTI:

1. Failure to thrive.
2. Renal scarring which leads to; Hypertension, progressive deterioration of renal functions, progressive anemia and finally chronic renal failure.
3. Vesico-ureteral reflux and reflux nephropathy.

Diagnosis:

A. Clinical presentations

B. Investigations:

1. Urine examination usually reveals:

- Pyuria: presence of 5 or more pus cells (WBC's) per high power field of centrifuged urine sediment.
- Minimal significant proteinuria.
- Leukocyte casts in cases of pyelonephritis.
- Few RBC's (minimal hematuria) without RBC's casts.
- Leukocyte esterase: detects pyuria.
- Nitrites: will only be present in urine sitting in bladder >4 hours, with gram-negative bacteria.

2. Bacteriological examination of urine (Colony count):

- Urine may be obtained as a midstream, by catheter, sterile urine bag or by percutaneous suprapubic aspiration especially in neonates.

- The finding of 100×10^3 organisms per ml of single organism is indicative of active UTI. Less than 100×10^3 organisms/ml or if two or more different organisms are cultured, indicate contamination.

3. Renal functions:

Blood urea nitrogen and creatinine are impaired in chronic pyelonephritis with renal scarring.

- 4. In recurrent cases:** renal sonogram, intravenous pyelogram (IVP) and voiding cystourethrogram (VCUG) are indicated to exclude reflux nephropathy (RN). Also, renal scanning (DMSA) to detect any functional changes.

Treatment:

While waiting the result of urine culture; we must start with one of the sulfa drugs or ampicillin.

- If the culture reveals that these drugs are effective continue the treatment, otherwise switch to the antibiotic of choice.
 - Treatment should continue for a minimal of 2 weeks as urinary tract infections commonly recur, urine should be cultured after 1 -2 Weeks of cessation of treatment and repeated at increasing intervals for a period of 1-2 years.
- **Some drugs are commonly used in the treatment of UTI in children:**

Ampicillin	100 mg/ kg / day orally.
amoxicillin	50-100 mg/ kg/day orally.
Trimethoprim	5 mg/kg/day orally.
Nalidixic acid	25-50 mg/kg/day. Orally.
Gentamicin	5-7 mg/kg/day I. M. Injection
Cefaclor	25 mg/kg/day orally.

- **Prophylaxis in recurrent cases:**
 1. Nitrofurantoin 1- 2 mg/kg/day.
 2. Trimethoprim 1-2 mg/kg/day for 6 months.

Congenital Anomalies of the Kidneys and the Urinary Tract

A. Congenital anomalies of the kidneys:

1. Renal agenesis
2. Renal dysplasia and hypoplasia
3. Renal fusion and ectopia
4. Polycystic diseases of the kidney
5. Renal tubular disorders

- **Polycystic diseases of kidney:**

- 1. **Infantile type:**

- Autosomal recessive (**AR**) inheritance.
 - **Presented early** in life.
 - **Clinical picture:**
 - At birth, both kidneys are enlarged and renal failure
 - May present later in childhood by hypertension and chronic renal failure
 - Bad prognosis
 - **Diagnosis:** by clinical presentation, abdominal ultrasonography and CT.
 - **Treatment :**
 - Supportive: including fluid and electrolyte therapy and control of hypertension.
 - Renal replacement therapy: dialysis and renal transplantation

- 2. **Adult type:**

- Autosomal dominant (**AD**) inheritance.
 - Usually presented in **middle age** but can occur in any age even in neonates.
 - **Clinical picture:**

Hematuria, flank pain or mass.

Hypertension.

End stage renal disease (ESRD).

▪ **Diagnosis:** by the clinical presentation, abdominal ultrasonography and CT.

▪ **Treatment:**

Supportive, with hypertension control.

Renal replacement therapy: dialysis and renal transplantation.

B. Congenital anomalies of the urinary tract:

A large number of congenital abnormalities may be found in the urinary tract, especially in males. They are mainly of importance because they lead to either:

1. Urinary obstruction with increase of pressure in the pelvis of the kidney and renal tubules, and so interfere with the filtration function of the kidney.
2. retention of urine which predispose to recurrent and prolonged infections

• **These urinary tract anomalies are:**

1. Pelvi-ureteric junction obstruction.
2. Duplication of the renal pelvis and ureter.
3. Ureteral stenosis.
4. Congenital vesico-ureteral reflux.
5. Divarication of the bladder and ureter.
6. Congenital bladder neck obstruction.
7. Posterior urethral valve.

- **Posterior Urethral Valve (PUV) obstruction:**

Posterior urethral valves, which is seen in male infants, and is important to recognize early as prompt surgical treatment may prevent rapid progression to renal failure which is irreversible and may have already occurred prior to birth.

- **Diagnosis:**

- Antenatal diagnosis: could be done by the presence of hydronephrosis and enlarged bladder.
- May present in neonates as sepsis.
- In infants and children: the stream of urine is thin, interrupted with dribbling or even no urine with enlarged hypertrophied bladder.
- Diagnosis is confirmed by uretheroscopy or VCUG.

- **Treatment:**

- Before birth: insertion of supra-bladder catheter to drain the fetal urine into the amniotic fluid.
- After birth: prompt surgical treatment for the valve and prolonged post-operative observation.

Practice Questions**(Choose one correct answer)**

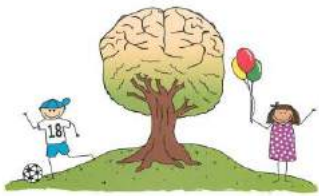
- 1- Minimal change disease (MCD) nephrotic syndrome represents:
 - a) 90% of all pediatric nephrotic cases.
 - b) 85% of all pediatric nephrotic cases.
 - c) 65% of all pediatric nephrotic cases.
 - d) 10% of all pediatric nephrotic cases.

- 2- Steroid resistant nephrotic syndrome means:
 - a) no remission on daily full dose steroids for 6 weeks.
 - b) no remission on alternative daily full dose steroids for 6 weeks.
 - c) no remission on daily full dose steroids for 4 weeks.
 - d) relapse on steroids withdrawal.

- 3- Renal biopsy is indicated in children with nephrotic syndrome when:
 - a) age at onset is > 6 y.
 - b) patients have microscopic hematuria.
 - c) age at onset is less than one year.
 - d) patients have relapse.

- 4- Acute post-streptococcal glomerulonephritis (APSGN) is characterized by:
 - a) relapsing course.
 - b) bright red hematuria.
 - c) low serum level of C3.
 - d) ESRD occurs in 10% of cases.

- 5- All of the following decrease serum level of potassium EXCEPT:
 - a) elimination of dietary potassium.
 - b) calcium gluconate 10% slowly IV.
 - c) sodium bicarbonate infusion.
 - d) glucose and insulin infusion.



Chapter 16

Neurology

Objectives:

1. Discuss seizures and describe the epidemiology and treatment of febrile and other seizure disorders.
2. Classify different types of cerebral palsy.
3. Correlates between the clinical presentations and the special nature of different types of cerebral palsy
4. Formulate a management plan for the child with Intellectual disability.
5. Understand causes and diagnostic criteria of Floppy Infant Syndrome.

Contents:

1. Seizures And Epilepsy.
2. Cerebral Palsy.
3. Intellectual Disability.
4. Floppy Infant Syndrome.

Seizures and Epilepsy

Convulsions are common in childhood. Nearly 5% of all children suffer one or more convulsions before 5 years of age, more than 50% of these are febrile convulsions.

Definitions:

A seizure: is a sudden, paroxysmal disruption of the brain's normal electrical activity accompanied by altered consciousness and/or other neurological and behavioral manifestations.

Seizures are not a disease in themselves. Instead, they are a symptom of many different disorders that can affect the brain.

Convulsion: This means a motor seizure and consists of abnormal involuntary muscular contractions which may be:

- Sustained (tonic).
- Interrupted (clonic).
- Brief, jerk-like (myoclonic).

Epilepsy: means recurrent seizures.

Causes of convulsions:

1- Acute convulsions:

- 1- Febrile convulsions.
- 2- Intracranial infections: meningitis, encephalitis, brain abscess.
- 3- Head injuries: birth trauma or later in life.
- 4- Intracranial hemorrhage due to birth or later trauma, hemorrhagic diseases, or vascular malformations.
- 5- Brain anoxia:

- a) Prenatal or perinatal asphyxia.
- b) Severe bronchopulmonary disease.
- c) Hyper-cyanotic attacks of congenital cyanotic heart disease.

6- Metabolic: hypocalcemia, hypomagnesemia, hypoglycemia, hyponatremia, alkalosis, post-acidosis.

7- Toxic agents as:

- Bacterial toxins of shigella, salmonella, tetanus.
- Poisons: insecticides, lead.
- Drugs: theophylline, corticosteroids, strychnine.

8- Intracranial neoplasm (brain tumor).

9- Cerebrovascular:

- Embolism (subacute bacterial endocarditis).
- Thrombosis (cyanotic heart disease, dehydration).
- Hypertensive encephalopathy.

2- Chronic (recurrent) convulsions i.e. epilepsy:

- a- Primary (idiopathic).
- b- Secondary.

FEBRILE CONVULSIONS

Definition: Febrile convulsions are tonic-clonic convulsions due to rapid rise of body temperature caused by extracranial infections.

Epidemiology:

- They are the most common seizure disorder during childhood. The incidence approaches 3-4 % of young children.
- They are age dependent and are rare before 6 mo and after 5 yr of age. The peak age of onset is approximately 14-18 mo of age.
- There is a strong family history of febrile convulsions in siblings and parents, suggesting a genetic predisposition. An autosomal dominant inheritance pattern is demonstrated in some families.

Types of febrile convulsions:

- 1- Typical (primary, simple or benign).
- 2- Atypical (secondary, complex or complicated).

The typical seizure is characterized by the following:

- Age from 6 mo. – 6 yr.
- Generalized tonic-clonic.
- Single during the same febrile illness.
- A few seconds to 10 minutes in duration.
- No neurological abnormalities in the child.
- EEG is normal in between the attacks.

The atypical seizure is diagnosed if one of the following is present:

1. A seizure persisting more than 15 min.
2. Repeated convulsions occur within the same day.
3. A focal seizure.

The risk factors for the development of epilepsy as a complication of febrile seizures include:

1. Atypical febrile seizure.
2. A positive family history of epilepsy.
3. Initial febrile seizure prior to 6 mo or after 6 yr of age.
4. Delayed developmental milestones.
5. An abnormal neurological examination.
6. Abnormal EEG in between the attacks.

The incidence of epilepsy is approximately 9 % when several risk factors are present compared with an incidence of 1 % in children who have febrile convulsions and no risk factors.

Management of febrile convulsions:

1. Aborting the attack of convulsion with diazepam 0.3 mg/kg slowly intravenously or rectally. This dose can be repeated after 10 minutes if needed.
2. Lowering the body temperature with tepid sponges (no ice or alcohol) and antipyretics.
3. Treating the cause of fever e.g antibiotics for otitis media.
4. Excluding intracranial infections by doing lumbar puncture and CSF examination if any doubt exists.

Prophylactic therapy:

Diazepam has been shown to be effective in preventing recurrences if given together with a potent antipyretic immediately at the onset of fever and continued until the patient has been afebrile for 24 hours. Diazepam dosage is 0.3 mg / kg orally every 8 hours (1 mg / kg / 24 hr).

Prolonged antiepileptic drug (AED) prophylaxis:

- i-** May be given for patients with secondary febrile convulsions with risk factors for epilepsy and with abnormal EEG.
- ii-** No need for long-term AED in primary febrile convulsions because these are ineffective and have many side effects.

EPILEPSY

Definition:

Recurrent seizures unrelated to fever or to an acute cerebral insult (two or more unprovoked seizures occur at an interval greater than 24 hr apart are needed for the diagnosis).

Epidemiology:

Epilepsy has a prevalence of 5-10/1000 population, 60% of cases occur in the pediatric age.

Etiology: Epilepsy is divided into two groups:

A- Idiopathic (primary):

- This is the main group and most of the patients (2/3 of cases) belong to it.
- It is called idiopathic because the etiology is unknown. The only important factor is heredity. In more than 90 % of cases a positive family history of epilepsy is present.

B- Symptomatic (secondary):

- The minority of patients belongs to this group (1/3 of cases).
- It occurs secondary to a brain lesion.
- **The common causes are:**
 - 1- Congenital conditions: e.g. congenital hydrocephalus, microcephaly, cerebral agenesis, and vascular anomalies.
 - 2- Post-infectious: following encephalitis, meningitis and brain abscess.
 - 3- Post traumatic.
 - 4- Post hypoxic.

- 5- Post-hypoglycemic.
- 6- Post-toxic (e.g after kernicterus).
- 7- Degenerative brain diseases.
- 8- Parasitic e.g. toxoplasmosis.
- 9- General causes: e.g. Tetany, Uremia

Classification of epileptic seizures:

A classification useful in delineating childhood epilepsy is shown in **table 1**.

TABLE 1- International classification of seizures

I- Partial (Focal) Seizures

1. Simple partial (consciousness is retained)
 - Motor -Sensory -Autonomic -Psychic
2. Complex partial (consciousness is impaired):
3. Partial seizures with secondary generalization

II. Generalized Seizures

1. Absence:
 - Typical - Atypical
2. Generalized tonic-clonic:
 - Tonic
 - Clonic
 - Tonic-clonic
3. Myoclonic
4. Atonic (Akinetic)

III-Unclassified seizures

The best example is subtle neonatal seizures

1- Partial (focal) seizures

- Arise from a focal area in brain (cortical or subcortical).
- Give focal manifestations related to the area of origin.
- No loss of consciousness.
- May be associated with a preceding aura which indicates a focal onset of the seizure (usually absent in infants and young children).
- EEG: focal abnormalities.
- **Partial seizures may be:**
 1. **Simple** (with no loss of consciousness).
 2. **Complex** (consciousness is impaired).

2 - Generalized seizures

- Arise from subcortical structures (thalamus and brain stem)
- Give generalized manifestations (both cerebral hemispheres are involved)
- Consciousness is lost
- EEG: generalized abnormalities
- Generalized seizures may be:
 1. Tonic-clonic (grand mal)
 2. Absence (petit mal)
 3. Myoclonic
 4. Atonic (akinetic)

3- Partial with secondary generalization

- Arise from focal area

- Starts with localized manifestations followed by secondary spread to the other side and loss of consciousness
- EEG: focal abnormalities with secondary generalization.

Pathogenesis:

- The normal, spontaneous electrical activity of the brain can be recorded by the electroencephalogram (EEG).
- In epilepsy there is paroxysmal increase in the electrical activity of the brain. For this reason epilepsy has been described as “paroxysmal cerebral dysrhythmia”.
- The zone of origin of the abnormal electrical activity is called the epileptogenic focus which may be:
 - a) Centrencephalic (subcortical)
 - b) Cortical.

GENERALIZED TONIC-CLONIC SEIZURES

(Grand mal epilepsy)

May occur at any age. Three clinical stages may be detected to occur successively:

1- Proconvulsive stage (occurs in few cases): As pallor, irritability or behavioral changes. Parents may be familiar with these changes.

2- Convulsive stage:

The attack usually occurs without warning. The consciousness is suddenly lost and the child falls to the ground.

a) Tonic phase: during this phase there is sustained contraction of the muscles, apnea, cyanosis and tongue biting.

b) Clonic phase: during this phase there is repetitive contraction of muscles, frothing at the mouth, and at the end of the attack relaxation of sphincters occur leading to bedwetting and sometimes defecation..

The convulsive stage lasts from one to several minutes.

3- Post-ictal stage:

After the attack, the patient falls asleep or suffers from headache, depression and confusion and on rising he is completely normal.

Precipitating factors of generalized tonic-clonic seizures in children:

1. Excessive fatigue.
2. Lack of sleep.
3. Infectious illnesses and fever.
4. Emotional stress.
5. Drugs as theophylline, psychotropic drugs, methylphenidate.
6. Sensory stimuli such as flashing lights, visual patterns, sounds including music and startling by noise or touch.
7. Sudden withdrawal of AED.

Recurrence rate:

- Very low after a single fit.
- About 50% if the child had more than one fit.

ABSENCE (petit mal)

- Usually in children more than five years old, more in females.
- There is sudden loss of voluntary motor activity.

- The child loses consciousness but doesn't lose postural tone (does not fall).
- There is a blank star and rapid eye blinking.
- This lasts around 30 seconds and then the child resumes his / her pre-seizure activity
- No postictal confusion.
- The attack can be induced by hyperventilation
- Has a characteristic EEG pattern (3 per second spike and wave pattern).
- May be associated with poor school performance.
- Etiology: idiopathic (genetic).
- Good response to ethosuximide and sodium valproate with good prognosis.
- 60% of children experience remissions by late adolescence.

MYOCLONIC SEIZURES

- The attack is characterized by short involuntary muscle contractions usually of a localized group of muscles
- Upper limbs are more commonly affected
- More frequent in the morning after awakening
- Loss of consciousness may not be noticed due to very short duration.

INFANTILE SPASMS

- Also called infantile myoclonic seizures
- Occur in infants below 2 yr of age (usually begin between the ages of 4 and 8 mo).
- There are 3 types of infantile spasms: flexor, extensor, and mixed.

- Flexor spasms are more common. Usually occur in clusters or volleys, and consist of sudden dropping of the head, flexion of the arms, flexion of the legs to the abdomen and crying (like colic).
- Extensor spasms produce extension of the trunk and extremities.
- Mixed spasms consist of flexion in some volleys and extension in others.
- Disappear before the 4th yr of life to be followed by another type of seizure.
- 10-20 % are idiopathic, and the remainder are symptomatic.
- Symptomatic infantile spasms are related to severe prenatal, perinatal, and postnatal factors.
- Have a characteristic EEG pattern (hypsarrythmia).
- May or may not be associated with mental retardation
- Good response to ACTH or prednisone

ATONIC (Akinetic) SEIZURES

(Drop attack)

- Is characterized by sudden loss of muscle tone and fall to the ground.
- In infants it takes the form of sudden drop of the head forward.
- It may be associated with momentary loss of consciousness.
- No tonic or clonic movements

SIMPLE PARTIAL (FOCAL) SEIZURES

- They may be motor (muscle contractions), sensory (numbness, auditory hallucinations, flashes of light) or autonomic (sweating, tachycardia or abdominal pain,...).

- The motor seizure may start locally in a part of the body and then spreads to adjacent parts (with jacksonian march) or may involve the whole limb from the start (without jacksonian march).
- Weakness of the affected limb may follow temporarily (Todd's paralysis).
- The patient remains conscious.
- No postictal phenomenon follows the event.

COMPLEX PARTIAL SEIZURES

(Psychomotor seizures)

Complex partial seizure (CPS) is also called temporal lobe epilepsy.

- Complex = motor + sensory + autonomic
- The early part is often remembered as a dreamy state
- Motor manifestations (**automatism**):
 - In infants : automatic behavior consists of masticatory movements as lip smacking, chewing, swallowing, and excessive salivation.
 - In older children: automatic behavior consists of semi-purposeful, incoordinated movements including Picking and pulling at clothing or bed sheets, rubbing or caressing objects, and walking or running in a nondirective fashion.
- Sensory manifestations: hallucinations, disturbance of perception
- Autonomic manifestations: fear, anxiety, anger, aggression.
- CPS may be precipitated by sleep deprivation.
- The EEG usually shows a focal discharge in the anterior temporal lobe. In some children the abnormal discharge arises from the frontal, parietal, or occipital lobes.

- Temporal lobe epilepsy may be associated with visual field defects due to involvement of optic radiations in the temporal lobe.
- Spreading of the epileptiform discharge during CPS can result in secondary generalization with a tonic-clonic convulsion.

Diagnosis of epilepsy:

1. This is essentially on clinical basis, through history from the parents and observation by the pediatrician.
2. Investigation of the suspected cause e.g. metabolic studies, CSF examination, MRI.
3. EEG: if positive is confirmatory. It may be normal in more than 30 % of epileptic children. A normal EEG does not exclude epilepsy.

Sometimes prolonged video monitoring of the EEG may be needed to prove the occurrence of seizures.

Differential diagnosis:

Epilepsy should be differentiated from “recurrent events” that mimic epilepsy in childhood. The most common are:

1. Breath holding attack.
2. Syncope.
3. Pseudoseizures (Psychogenic).

Prognosis:

70 % outgrow their seizure tendency with remission.

30 % may have recurrences especially during the first year after withdrawal of treatment.

Recurrence risk factors:

- Age of onset less than 2yr
- Neurological dysfunction
- Mental retardation
- Seizure type: infantile spasms
- Difficult control with polytherapy
- Abnormal EEG at stoppage of treatment

TREATMENT OF EPILEPSY**1- General treatment:**

- An epileptic child should, as far as possible, live a normal life
- The child should attend school
- The patient should avoid situations of obvious dangers e.g. swimming and working at a height
- The parents should avoid the precipitating factors
- Moderate exercise is desirable but violent ones may precipitate fits

2- During the attack of convulsion:**A- First aid:**

- Put the patient in semi prone position with the head turned to one side
- Suctioning and cleaning of the airways
- Do not thrust a tongue depressor or spoon handle into clenched teeth.
- Do not try to restrain the patient.

B- Give oxygen if the patient is cyanosed.

C- Correct the cause if it is evident (e.g. glucose in hypoglycemia and calcium in cases of tetany).

D- If the cause is not evident or not readily correctable, **give diazepam**, 0.3 mg/kg slowly intravenously. This dose can be repeated after 10 minutes.

3- Long term therapy with AEDs:

A- Indications:

AED therapy is indicated only if the patient had more than one fit.

For a patient with isolated fit (i.e a single afebrile fit), AED therapy is indicated only if:

- The patient is neurologically abnormal
- The presence of a focal brain lesion
- Positive family history of epilepsy
- Abnormal EEG

B- Rules:

- Only one drug, known to be effective for the seizure type, should be used in a small dose that is increased gradually at intervals of two weeks till the fit is controlled or the maximum dose is reached.
- If the drug is ineffective, start a 2nd one in a similar way, and once seizures are controlled, start gradual withdrawal of the first one.
- The dose must increase with the increase in age and weight.
- Avoid double or triple drug therapy as far as possible.
- Treatment is continued for at least 2-seizure free years and discontinued gradually over 3-6-month period.

C- Follow up:

- I- Because most serious adverse effects of anticonvulsant drugs develop during the initial 2-3 mo of therapy, screening of **complete blood count and liver function studies** should be done every month for the first 3 months. Subsequently, routine blood tests are ordered only when clinically indicated.

II- Routine Serum monitoring of anticonvulsant levels is not recommended.

D- Common AEDs are:

1- Conventional AEDs (Table 2):

Table 2: Conventional antiepileptic drugs

<u>Drug</u>	<u>Seizure type</u>	<u>Oral dose (mg/kg/day)</u>	<u>Most common side effects</u>
<u>Phenobarbital</u>	GTC. Partial Status epilepticus	<u>2 - 6</u>	Drowsiness. Hyperactivity. Impaired cognition.
<u>Phenytoin</u>	GTC Partial Status epilepticus	<u>5 - 8</u>	Hirsutism. Gum hypertrophy. Ataxia. Skin rash. Impaired cognition. Rickets.
<u>Carbamazepine</u>	Partial GTC	10 - 30	Drowsiness. Liver dysfunction. Hematological abnormalities
<u>Sodium valproate</u>	GTC Partial Absence Myoclonic	10 - 60	Weight gain. Alopecia. Tremor. Liver dysfunction. Hematol. abnormalities.
<u>Ethosuximide</u>	Absence	20 - 40	GIT disturbances. Skin rash. Liver dysfunction. Leucopenia.
<u>Clonazepam</u>	Absence Myoclonic Infantile spasm Partial seizures Akinetic Lennox-Gastaut syndrome	0.05 – 0.2	Drowsiness. Irritability. Behavioral abnormalities. Depression. Excessive salivation.

GTC= Generalized tonic clonic

- Valproate: is a broad spectrum AED.
- Carbamazepine: is more preferable in partial seizures.
- Phenobarbital and phenytoin are less frequently used now due to their effects on cognition.

2- Second line AEDs: e.g oxcarbazepine, topiramate, vigabatrin, lamotrigine, levetiracetam

STATUS EPILEPTICUS (SE)

Definition:

Status epilepticus is defined as a continuous convulsion lasting greater than 30 min, or The recurrence of serial convulsions between which there is no return of consciousness.

Etiology:

1. A prolonged febrile convulsion in a child < 3 yr old, is the most common cause
2. Rapid withdrawal of AED at any age
3. Idiopathic SE: a seizure develops in the absence of an underlying CNS lesion or insult
4. Symptomatic SE: a seizure occurs in association with a longstanding neurological disorder or a metabolic abnormality

Treatment:

A- Airway patency: by suctioning, semi prone position ± put airway tube

B- Breathing: should be adequate

C-Circulation: should be insured

D- Drugs: all drugs should be given IV. AEDs are tried in the following order:

1. Diazepam (0.3mg/kg) is used initially.

2. Phenytoin infusion: IV loading dose 20 mg/kg slowly over 30 min, followed 12 hours later by maintenance dose of 5-8 mg/kg /day in two divided doses.
3. Phenobarbital: IV loading dose 20 mg/kg slowly over 30 min, followed 12 hours later by maintenance dose of 3-5 mg/kg /day in two divided doses.
4. Diazepam IV infusion 2 mg / hour.
5. General anesthesia and assisted ventilation is given if the above-mentioned measures fail.

CEREBRAL PALSY (CP)

CP is a non-progressive permanent motor disorder (affecting muscle power, tone, movements, coordination or posture) due to brain insult, which occurs during early brain growth (from conception to 3 yr of age).

It may or may not be associated with epilepsy, mental retardation, visual / hearing impairment, and / or language delay.

Incidence: 2 / 1,000 population.

Etiology:

CP results from damage affecting motor areas of brain (motor cortex, basal ganglia, cerebellum) due to:

1- Prenatal factors (10-20 % of cases):

- Intrauterine infection: TORCH, other viruses
- Prenatal anoxia
- Fetal irradiation
- Congenital CNS malformations
- Primary microcephaly
- Placental insufficiency

2- Natal factors (40-60 % of cases):

- Birth trauma
- Neonatal anoxia

3- Postnatal factors (20-30 %):

- Kernicterus
- Intracranial infections e.g. meningitis, encephalitis
- Brain trauma

- Dehydration
- Cerebral anoxia
- Vascular lesions e.g. cerebral hemorrhage and thrombosis

Early detection of CP in high risk neonate:

- Poor suckling ability
- Increased or decreased muscle tone
- Abnormal reflexes
- Irritability

Detection of CP later in life:

1- Delayed motor development (e.g. lack of head control at 3 months)

2- Abnormal motor development:

- Baby is stiff on handling
- Early handedness (before one year) may be early sign of hemiplegic CP
- Very early neck support or persistent toe walking (may be early sign of spastic CP)
- Persistent hand clenching (after 3 months)
- Persistence of primitive reflexes (tonic neck reflex, Moro reflex, grasp reflex) beyond their age limit
- Absence of normal protective cortical reflexes as parachute reaction
- Floppiness, hypotonia, and involuntary movements

Clinical types of CP:

1- **Spastic CP:** lesion in pyramidal area.

2- **Extrapyramidal CP:** Lesion in basal ganglia.

3- **Ataxic CP:** lesion in cerebellum.

4- **Atonic CP:** an evolutionary stage in the development of spastic CP.

5- **Mixed CP.**

Spastic Cerebral palsy

- It is the commonest type of CP. It accounts for 70 % of cases.
- It is caused by affection of motor cerebral cortex and its connections (pyramidal area).
- There is increased tone (clasp knife), increased tendon reflexes, extensor planter responses, clonus, scissoring of legs.

Spastic quadriplegia, double hemiplegia and diplegia are commonly associated with:

1. Mental retardation
2. Seizures
3. Swallowing difficulties due to supranuclear bulbar palsies
4. Persistence of primitive reflexes.

Topographically it includes:

TYPE	AFFECTED LIMB	COMMENTS
Monoplegia	One limb	
Paraplegia	Both lower limbs	
Triplegia	Both lower limbs and one upper limb	
Hemiplegia	One side of the body	Upper limb is more affected than lower limb
Quadriplegia	Affection of 4 limbs + trunk	
Tetraplegia	4 limbs	All limbs are equally affected
Double hemiplegia	4 limbs	Upper limbs are more affected than lower limbs
Diplegia	4 limbs	Lower limbs are more affected than upper limbs

Extrapyramidal (Athetoid) Cerebral Palsy

- Accounts for 10 % of cases of CP.
- It is caused by a lesion of the basal ganglia, usually as a sequel of kernicterus.
- Early in life: Infants are characteristically hypotonic and have poor head control and marked head lag.
- At about one year of age, involuntary movements in the form of choreo-athetosis and dystonia appear and the muscle tone is increased (rigidity).
- Speech is typically affected owing to involvement of the oropharyngeal muscles.
- Seizures are uncommon, and intellect is preserved in most patients.

Ataxic Cerebral Palsy

- Accounts for 10 % of cases of CP.
- It is caused by affection of the cerebellum.
- Early in life: association of hypotonia, floppiness and weakness.

Later on it is characterized by:

- 1) Ataxia (disturbed gait)
- 2) Incoordination of movements
- 3) Ataxic speech
- 4) Intention tremors
- 5) Nystagmus may be present
- 6) Hypotonia and diminished deep tendon reflexes
- 7) Mental retardation is slight

Atonic Cerebral Palsy

It is characterized by:

- It will be changed into a spastic type after a period of time.
- Generalized hypotonia.
- Exaggerated deep tendon reflexes.
- Mental retardation.

Mixed Cerebral Palsy

- Accounts for 10 % of cases of CP.
- Usually one type is more manifest.
- The common mixed CP is spastic and athetoid type.

Differential diagnosis:

1. Degenerative CNS diseases
2. Spinal cord tumor
3. Muscular dystrophy

Investigations:

1. Brain CT scan or magnetic resonance imaging (MRI)
2. EEG
3. Tests for auditory and visual acuity

Associated disabilities with CP:

1- Epilepsy:

Occur in 30 % of cases.

It is of the symptomatic rather than the idiopathic type.

Treatment may need more than one drug and usually given for life.

2- Mental retardation, and learning problems:

60 % of children with CP have some degree of mental retardation.

However, many children with severe CP, especially the dystonic type may have normal intelligence.

3- Perceptual defects:

Visual impairment due to refractive errors, optic atrophy or visual cortical damage occurs in 20 % of cases.

Squint in 30 % of cases. Early treatment is needed.

Hearing loss of sensory neural type is common in 20 % of cases.

4- Speech disorders: common and may be due to

- Hearing loss
- Mental retardation
- Muscular incoordination

Management of CP:

Management of CP is a teamwork aiming at offering the child the best quality of life he can have and to reduce parent's stress.

This needs the cooperation of pediatrician, physiotherapist, orthopedist, speech therapist and nutritionist.

Treatment consists of:

1. Education: depends on the degree of brain affection

2. Drugs:

Muscle relaxants: (oral diazepam, baclofen, IM botulinum toxin type A, intrathecal baclofen). Anticonvulsant drugs if epilepsy is present.

3. Physiotherapy: to avoid contractures.

4. Use of some aids:

Sitting: special chairs.

Walking: special calipers.

Toilet: special seats.

5. Speech therapist

6. Orthopedic correction of deformities and contractures.

Intellectual disability (ID)

Definition: It is a deficit in intellectual and adaptive functioning presenting before 18 years of age.

The term improves upon and replaces the older term, mental retardation.

The term global developmental delay (GDD) is used to describe children younger than age three who fail to meet expected developmental milestones in multiple areas of intellectual functioning, and whose severity level of impairment cannot be reliably assessed; not all children with GDD will meet criteria for ID as they grow older.

Etiology:

Genetic and Environmental causes

I- Genetic causes:

A- Chromosomal abnormalities: Chromosomal aberrations are the most common known cause of ID.

e.g Down syndrome and other trisomies, Turner syndrome

B- Single-gene disorders:

- Inborn errors of metabolism: phenylketonuria, galactosemia.
- Neurocutaneous syndromes e.g. tuberous sclerosis.
- Cerebral malformation e.g. lissencephaly.

II- Environmental causes

A- Prenatal causes

- Congenital infections
- Environmental toxins or teratogens (eg, alcohol, lead, mercury, phenytoin, valproate).

- Radiation exposure
- Fetal anoxia or trauma.
- Placental insufficiency.

B- Perinatal brain insult:

- Extreme prematurity.
- Neonatal asphyxia.
- Intracranial hemorrhage.
- Birth injuries.
- Neonatal meningoencephalitis.
- Hypoglycemia.
- Hyperbilirubinemia.

C- Postnatal brain insult:

- Congenital hypothyroidism.
- CNS infections: meningitis, encephalitis, brain abscess.
- Brain trauma
- Hypoxia (eg, near-drowning)
- Environmental toxins: Poisoning e.g. CO, lead.
- Post-immunization e.g. after rabies or pertussis Vaccination.
- Psychosocial deprivation
- Malnutrition

CLINICAL FEATURES

Presenting symptoms —Language delay, behavior difficulties, immature self-help skills, or difficulty in learning.

Diagnostic criteria:

1. Subaverage intellectual functioning with an Intelligence quotient (IQ) of 70 or less when intelligence is tested .
2. Defect in adaptive behavior (ability to adapt to environment) taking in consideration his/her age and environment.
3. Onset of impairment before age of 18 years.

Assessment of Intellectual Function:

Many intelligence (psychometric) tests are available to judge the mental age of the child.

These tests assess verbal and performance functions.

The normal IQ is in the range of 90-110.

$$\text{IQ} = \frac{\text{Mental age} \times 100}{\text{Chronological age}}$$

In infant and children less than 3 years and in those with developmental, behavioral, or emotional problems, the developmental tests are used to judge the developmental age of the child.

These tests assess gross motor, fine motor, social-adaptive, and language functions.

This is used to calculate the developmental quotient (DQ).

Normally DQ is above 70.

$$\text{DQ} = \frac{\text{Developmental age} \times 100}{\text{Chronological age}}$$

Grades of Intellectual disability

IQ	Type	Comment
90 – 71	Borderline	- Not handicapped but have some learning problems. - Can function independently.
70 – 51	Mild (educable)	- May not be apparent till school age. In special schools, they can attain 4th – 6th grade reading level, able to function independently as adult.
50 – 36	Moderate (trainable)	- Cannot be learned to read or write but can talk Have maximal self-care skills if trained. - Can be trained to do simple tasks. - Able to function semi independently.
35 - 21	Severe	- Non-educable, non-trainable. - Minimal self-care, no language development.
20 - 0	Profound	- Non educable, non trainable. - No self-care, no language development.

Evaluation of the child with Intellectual disability /GDD:

History: prenatal, perinatal, and postnatal history; developmental history; and family history.

Physical examination and neurologic examination

Investigation:

1. Standardized intelligence tests: Intellectual function is measured by the administration of intelligence tests in children >3 yr of age .
2. Brain imaging: Plain x-ray, brain CT scan, MRI.

3. Chromosomal studies.
4. Thyroid function tests: Serum T3, T4, and TSH.
5. Serum for TORCH.
6. Blood lead level.
7. Metabolic screening: Urine for urine organic acids, serum amino acids, serum ammonia, and lactate.

Treatment:

1. Treat the cause if possible.
2. Interventions that should be applied early to improve short-term and long-term outcomes, including
 - Speech and language therapy
 - Occupational therapy
 - Physical therapy and rehabilitation, including mobility and postural support
 - Family counseling and support
 - Behavioral intervention
 - Educational assistance: Special schools for education and training.
3. Treat associated diseases e.g epilepsy, visual, or auditory impairment, malnutrition.
4. Specific drug therapy:
 - No drugs has been found to improve intellectual function, except for specific defects as thyroxine for hypothyroidism
 - Treating associated disorders: ADHD (stimulant medication), self-injurious behavior and aggression (neuroleptics).
 - Piracetam may cause some improvement.

Prevention of Intellectual disability

Primary prevention

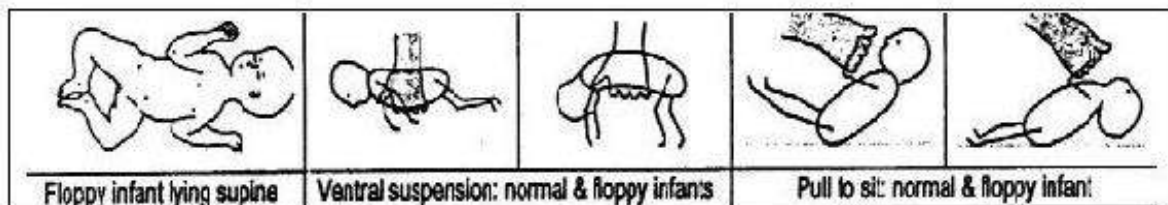
1. Routine childhood immunizations
2. Biochemical neonatal screening for hypothyroidism, galactosemia, and phenylketonuria .
3. Genetic counseling & antenatal diagnosis (amniocentesis) for genetic causes of ID.
4. Rubella vaccination before marriage.
5. Good antenatal & intrapartum care.
6. Adequate management of neonatal problems as hyperbilirubinemia.
7. Adequate management of intrauterine and postnatal infections.
8. Prevention and treatment of PEM.
9. Prevention of accidents.

FLOPPY INFANT SYNDROME

Definition: The term describes the infant who has marked generalized hypotonia

Criteria for diagnosis:

- 1- Lying supine: No spontaneous movements, and Frog-leg position.
- 2- Ventral suspension: head is down and the arms hang helplessly giving inverted U posture



- 3- Vertical suspension: may slip from your hands
- 4- Pull to sit maneuver: marked head lag

Causes:

Central causes:

- 1- Cerebral palsy.
 - Generalised hypotonia
 - Exaggerated deep tendon reflexes
 - Mental retardation
- 2- Chromosomal as Down syndrome.
- 3- Congenital anomalies of the cerebellum.

Spinal cord diseases

Spinal cord diseases cause hypotonia only if the lesion is acute as a result of shock stage e.g. hypoxic ischemic myelopathy and injuries.

The lesion is characterized by:

- Sphincter disturbances are very prominent from the start
- Anesthesia of lower limbs with sensory level on the trunk
- Planter response becomes extensor within few days.

Neuro-muscular causes.

Werdnig – Hoffman disease:

- The commonest cause of floppy infant
- Autosomal recessive
- Characterized by degeneration of anterior horn cells.
- Absent tendon reflexes.
- Bulbar palsy: Weak cough and cry.
- Visible tongue fasciculations.
- Normal mentality.
- Two thirds of infants die by 2 years of age.
- EMG: is diagnostic

Polyneuropathies: e.g Guillain Barre Syndrome

- Post-infectious(demyelination of spinal roots)
- Bilateral and symmetrical weakness
- Absent deep tendon reflexes
- Glove and stocking hypoesthesia

- CSF: protein cell dissociation
- Slow nerve conduction velocity
- EMG: normal

Disorders of neuromuscular transmission:

e.g. infantile botulism caused by toxin of *Clostridium Botulinum* in contaminated food, and congenital myasthenia gravis.

The lesion is characterized by:

- *Acute flaccid paralysis of the limbs and extraocular muscles*
- *Diminished or absent deep tendon reflexes*
- No sensory changes
- EMG is diagnostic

Primary muscle diseases:

E.g., Non progressive congenital myopathy and congenital muscular dystrophy which is a progressive degenerative disease of muscles. Primary muscle diseases are characterized by:

- Bilateral and symmetrical weakness
- Hypotonia and diminished reflexes
- No sensory changes
- No excretory changes
- CPK is elevated in muscular dystrophy
- Muscle biopsy is diagnostic.

Benign congenital hypotonia:

- Non-progressive hypotonia of unknown etiology.
- Normal tendon reflexes

- Mentality is normal.
- Delayed motor development.
- Gradual improvement, sometimes complete.
- CPK, EMG, and nerve conduction velocity are normal.
- Normal muscle biopsy & C.T. Scan of brain

Practice Questions**(Choose one correct answer)**

- 1- Ventral suspension is a test for:
 - a) spastic CP.
 - b) extrapyramidal CP.
 - c) floppy infant.
 - d) all of the above.

- 2- Typical febrile seizures definition includes the following EXCEPT:
 - a) generalized tonic clonic seizures.
 - b) single during the same febrile illness.
 - c) age 9 mo-5 years.
 - d) duration more than 15 minutes.

- 3- Automatism is the manifestation of:
 - a) myoclonic seizures.
 - b) febrile seizures.
 - c) atonic Seizures.
 - d) complex partial seizures.

- 4- Definition of cerebral palsy includes the following EXCEPT:
 - a) non progressive.
 - b) non curable.
 - c) motor Disorder.
 - d) familial disease.

- 5- The drug of choice for treatment of absence seizures is:
 - a) carbamazepine.
 - b) phenytoin.
 - c) phenobarbital.
 - d) ethosuximide.

