Tanta University
Faculty of Medicine
Pediatric Department

PEDIATRICS

Medicine and Surgery Bachelor Program - Credit Points

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By Staff Members of
Tanta Pediatric Depatment

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.***

Index

Chapter 1

Growth and Development

Learning Objectives:

By the end of this chapter, students should be able to:

1. Define infant growth and identify the stages of growth.
2. Know factors affecting growth and development.
3. Demonstrate steps in evaluation of growth.
4. Explain information related to developmental milestones.
5. Define failure to thrive (FTT), discuss its multiple causes, recognize the typical clinical features, and know how to manage an infant or a child presented with it.

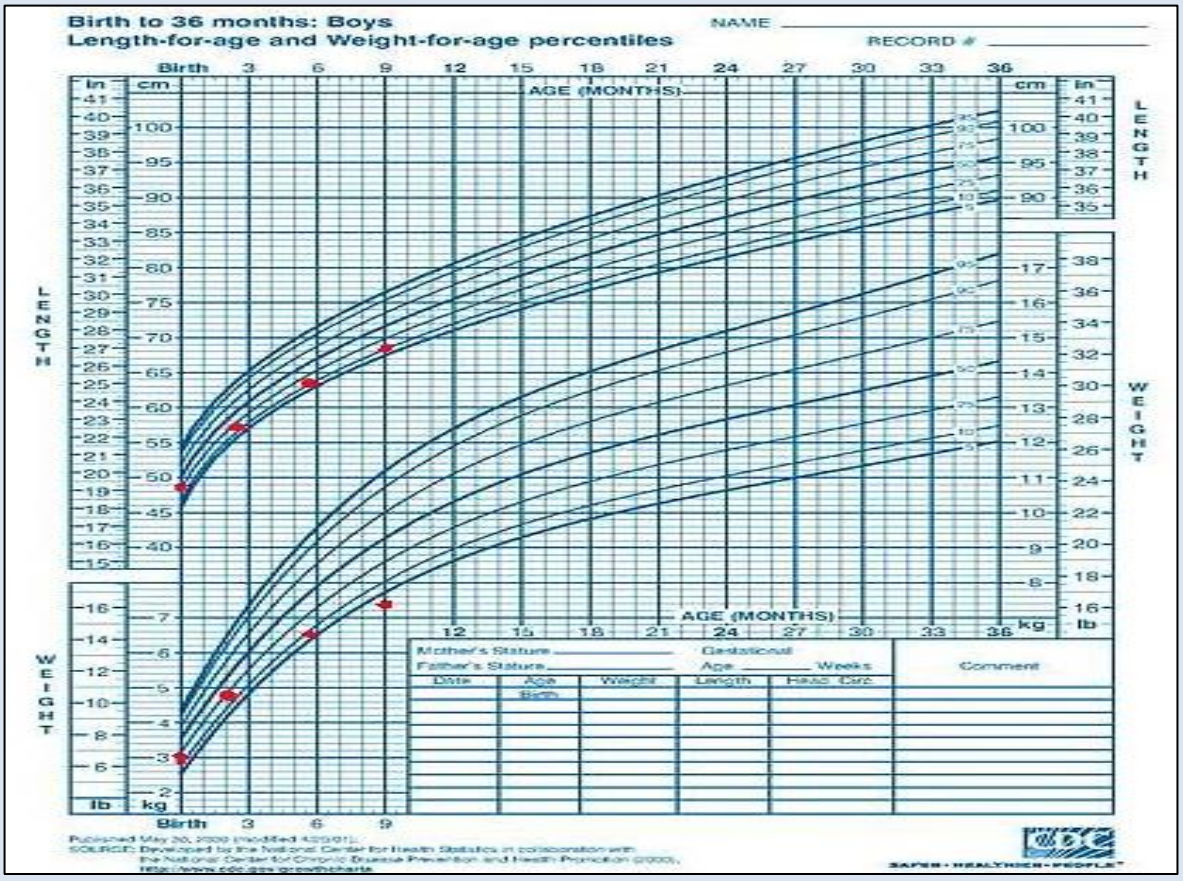
Contents:

1. Factors influencing growth and development.
2. Stages of human growth and development.
3. Assessment of growth.
4. Assessment of development.
5. Failure to thrive.

Growth and Development

Case 1

Osama is a 9-month-old male infant, is seen by his family doctor because of concern that he is not growing fast enough. He is only on the 10th centile for height and below the 5 th centile for weight.



What is the greatest influence on his growth rate at his age?

At his age nutrition has the greatest influence on his growth rate. Along with good health, happiness and thyroid hormones, infant growth (from birth to 12 months of age) is most dependent on good nutrition. Growth in the 1st year of life contributes about 15% to final adult height

What about the other factors; the genes and growth hormone?

Genes are important but without adequate nutrition a child's growth potential will not be achieved. Genetic influences begin to affect growth mostly after the 1st year of life.

Growth hormone is particularly important in determining growth after infancy and continues to exert an effect until growth ceases

What are the points you should look for in your evaluation?

The followings should be looked for in details:

History: medical history, past history, developmental history, dietetic history and family history.

Complete examination: General examination including Anthropometry & systemic examination for detection any signs of vitamins or minerals deficiency or any organic cause.

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

It is the fundamental physiologic process that characterizes childhood, so;

- Nutrition for infants, children, and adolescents should support normal growth and development and,
- Growth should be closely monitored as it is a sensitive indicator of a child nutritional status.

Growth during infancy is:

- Rapid,
- Critical for neurocognitive development,
- Has the highest energy and nutrient requirements relative to body size than any other period of growth?

Factors influencing Growth and Development:

1- Genetic factors

2- Environmental factors and socio-economic status

3- Maternal factors:

- Nutritional deficiencies
- Diabetic mother
- Exposure to radiation
- Infection
- Smoking
- Use of drugs

4- Endocrinal factors: Thyroid and growth hormones.

5- Nutritional factors: child nutrition.

6- Chronic infections: (e.g., tuberculosis) and chronic debilitating diseases (e.g., congenital heart disease (CHD), chronic kidney disease (CKD)

7- Physical activity: bed-ridden children do not grow normally.

Stages of Human Growth & Development:

Growth during early life can be divided into periods:

1. **Intrauterine stage:** (from the time of fertilization to the time of birth)
    1. **Embryonic stage:** (first 8 weeks of gestation)
        - It is the period of organogenesis.
    2. **Fetal stage:** (9-40 weeks of gestation)
        - It is a period of rapid growth and development.
            a. Early fetal period (9-24 weeks of gestation).
            b. Late fetal period (25-40 weeks of gestation).
    3. **Perinatal:** (from 28th week of fetal life to 7th day after delivery)
2. **Extrauterine stage:** (postnatal)
    1. **Neonatal period:** (First 28 days after birth).
    2. **Infancy:** (first 2 years of life)
        - It is the period of most rapid physical growth & mental development.
        - It is the period of weaning.
        - The curious child is exploring what around him.
            a. Early infancy (1-12 months)
            b. Late infancy (12-24 months)
    3. **Toddlerhood:** (from 1-3 years)
    4. **Early childhood:** (preschool age 3-6 years)
        - It is the period of exploring the outside world and starts learning.
    5. **Late Childhood:** (School age 6-12 years)
        - The school child starts studying and having exams.
    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.
            a. Early adolescence: 12-14 years old.
            b. Middle adolescence: 15-16 years old.
            c. Late adolescence: 17-20 years old.

Assessment of Growth:

Physical Growth in pediatrics can be assessed through:

1. **Anthropometry**
2. **Dental age**
3. **Bone age.**

1. Anthropometry

How can you assess anthropometric measures?

- Get an accurate body measurement e.g., weight, height, head circumference, etc. by special scales.
- Compare this measurement with growth standards obtained from normal individuals of same age, sex, and community by plotting this measurement on percentile growth charts.
- The growth chart is the best tool to determine patterns of growth, with separate charts for boys and girls (review the clinical book).
- The charts measure weight for age, height for age, head circumference for age, weight for height, and body mass index (BMI).
- Each chart has multiple curves (either 5–95% or 3–97%).

a. Weight:

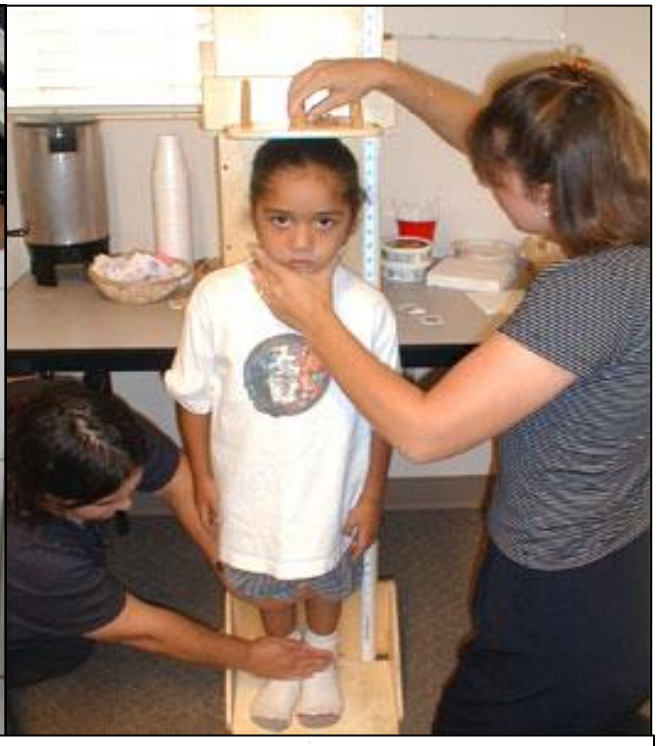
- Average weight at birth is 3 - 3.5 kg.
- There is an initial weight loss of 5-10 % during the first 3 to 4 days of life. The loss is usually regained by the 7th –10th day of life.
- **During infancy, weight increases as follows:**

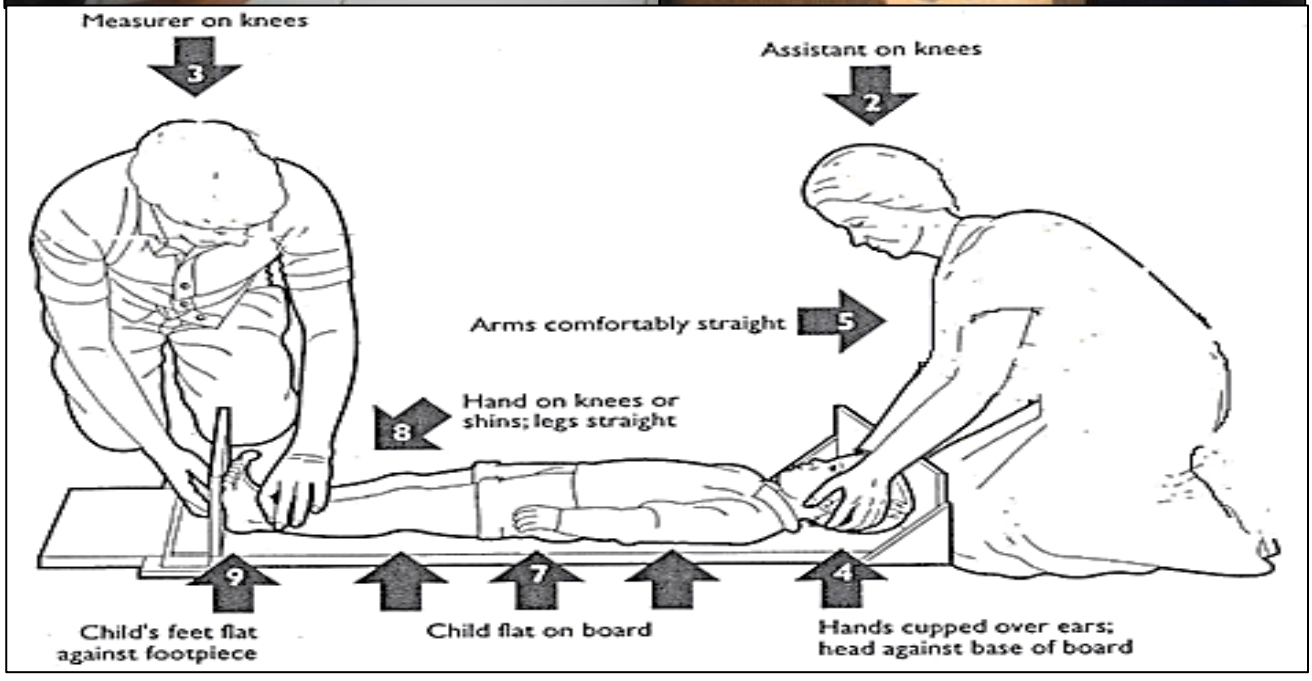
  - 750 g (3/4 kg) / month for the first 4 months (wt = 6 kg at 4 month)
  - 500 g (1/2 kg) / month for the second 4 months (wt = 8 kg at 8 month)
  - 250 g (1/4 kg) / month for the third 4 months (wt = 9 kg at 12 month)

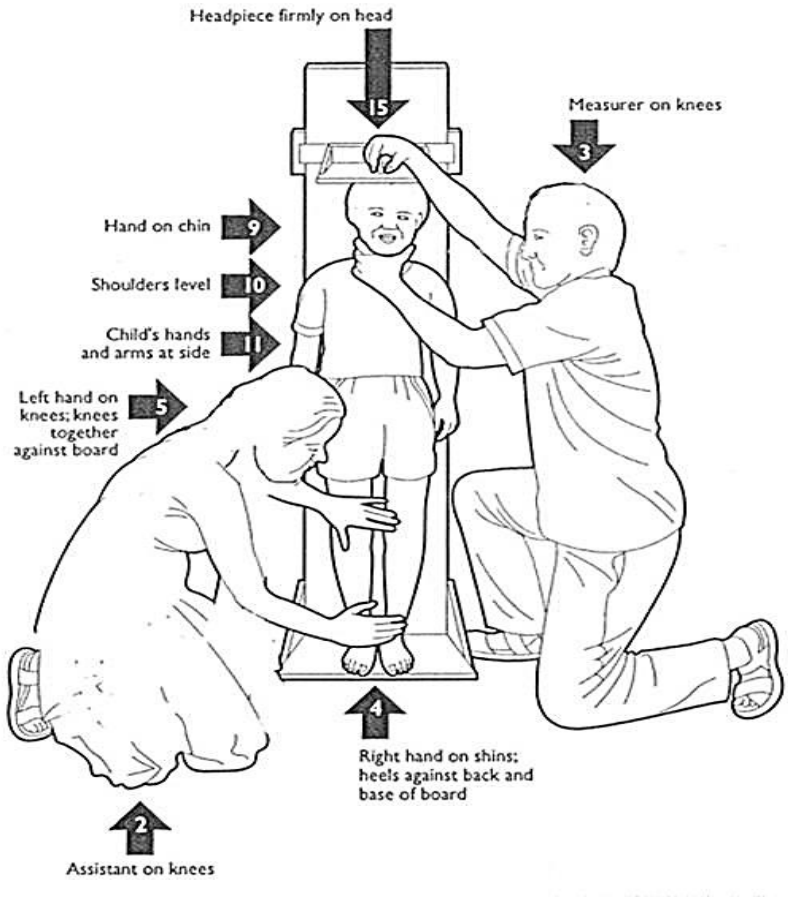
- During early childhood (from 2-6 years):
  - Weight in kg = (Age in years x 2) + 8
- During late childhood (from 7-12 years):
  - Weight in kg = $\frac{(\text{Age in years} \times 7) - 5}{2}$

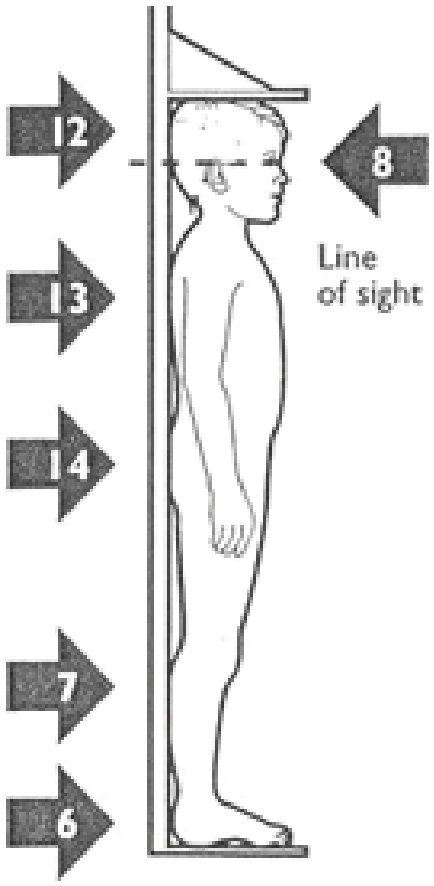
b. Length / Height:

- **Length:** (recumbent supine length) is taken from infants and children less than 2 years old.
- **Height:** (standing) is measured from children more 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).









c. 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**

d. 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
- **From the end of 1st year to adulthood**
  - Head circumference increases only 10 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

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

e. Mid-arm Circumference:

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

- **Normal Mid-arm Circumference:** It is between 13.5 and 14.5 cm in children 1-5 years old.
- **Overtly malnourished** those below 12.5 cm.
- **Border line malnutrition** those between 12.5 and 13.5 cm.

f. Body Mass Index (BMI):

- BMI = Weight (kg) / Height^2 (meter)

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

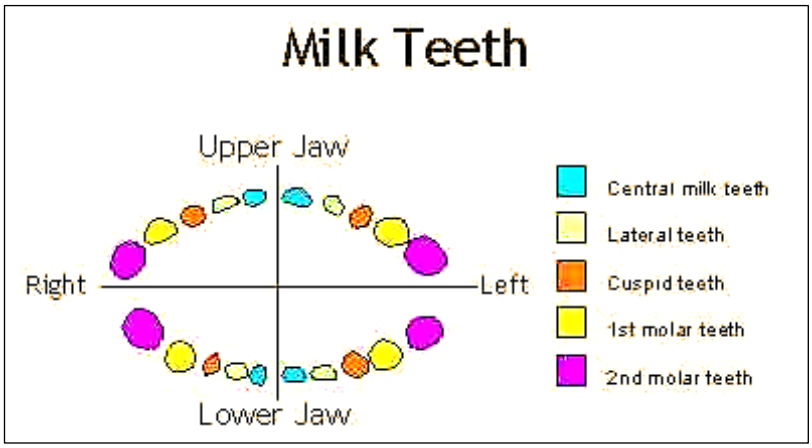
Weight Status Category	Percentile Range of BMI for age
Underweight	< 5th percentile
Normal or Healthy Weight	5th percentile to < 85th percentile
Overweight	85th to < 95th percentile
Obese	95th percentile or greater

2. Teething

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

a. Deciduous teeth (milk) (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	**8-11 months (8 teeth) at 9m**
First molars (4 new teeth)	**12 months (12 teeth at 1 year)**
Canines (4 new teeth)	**18 months (16 teeth at 1.5 years)**
Second molars (4 new teeth)	**24 months (20 teeth at 2 year)**



b. 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)**

3. Skeletal (osseous) maturation

- **Bone age, determined radiographically**, is the best index for assessment of general growth as bone age equals to the chronological age of normal individuals.
- **The following data are usually assessed:**
  1. Number and size of epiphyseal centers.
  2. Size, shape, density, and sharpness of outline of the ends of bones.
  3. Distance separating epiphysis and metaphysis or the degree of fusion between these two elements.
- **Time of ossific centers appearance in the X-ray:**
  1. **At birth:** The ossific centers at the lower ends of femur and the upper end of tibia are usually present at birth
  2. **At age of 3 weeks:** The ossific center appears in the head of humerus.
  3. **At the age of 2 mo-6 yr:** The ossific centers of the carpal bones in the wrist appear successively, approximately one center per year. (Roughly between 2-6 years bone age = number of carpal centers –1)

     e.g; two carpal centers are present at one year of age.
- This can be determined by comparing the radiograph of the child bones with standard atlas of bone maturation radiographs of different ages.
- **Clinical application** *(discrepancy between the chronological age and bone age)*
  1. Retardation of bone age: the bone age is lower than the chronological age in the following conditions: prematurity, undernutrition, rickets, endocrinal hypofunction like hypothyroidism.
  2. Advanced bone age: the bone age exceeds the chronological age in the cases of precocious puberty.

Assessment of Development

Case 2

Omar has just had his first birthday party. During his party he commando crawled with great speed, although he cannot walk. He managed to pick off all the round chocolate sweets from his birthday cake. He can say two words with meaning. After his birthday party, he impressed his guests by waving goodbye.

Which area of Omar's development is delayed?

None – his development is within normal limits. He has achieved normal milestones for 12-month-old.

Explain what are the gross motor, fine motor, social and language developmental milestones does Omar have?

Gross: Omar commando crawls, so is expected to walk later than the median age of 12 months.

Fine: He is able to perform a pincer grip to be able to pick small chocolates off his birthday cake

Social, emotional, and behavioral development: He can wave goodbye.

Speech and hearing: He is able to say two words with meaning.

Case 3

Female infant demonstrates rolling from front to back. When prone she lifted her torso off the couch on her hands. When pulled to a sitting position she has a straight back and good head control. She sits briefly unsupported and bears weight on her legs. She is not crawling and does not attempt to pull to stand.

As regard to her gross motor development what is her developmental age?

6 months old.

Regarding the fine motor development what do you expect her to do?

Reaches to objects & brings them to mouth,

Transfers objects between hands.

If this infant coos and only shows social smile but does not recognize her mother yet, what is the expected age as regards to her social development?

She has 4 months old only as regard to her social and language development.

What is the next step in her plan management?

Regular follow up of neurological and developmental milestones.

If there is a language delay, hearing loss must be excluded firstly.

If there is a lack of development or regression of language skills with impaired social interaction, restricted activities and stereotypic behaviors, autistic spectrum disorder to be considered.

Many factors may affect development as genetic factors, maternal factors, nutritional factors or any chronic disease. So, complete history taking and full clinical examination including (neurologic examination), development testing and anthropometric measurements must be done.

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

- It 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:

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.

- Assessment is based on acquisition of milestones occurring sequentially and at a specific rate: each skill area has a spectrum of normal and abnormal.
- Abnormal development in one area increases likelihood of abnormality in another area, so careful assessment of all skills is needed.
- Developmental diagnosis is a functional description/classification and does not specify an etiology.
- Developmental delay is performance significantly below average, i.e., developmental quotient (developmental age / chronologic age X 100) of <75; may be in ≥ 1 areas; 2 assessments over time are more predictive than a single assessment.

1.Milestones in 1st year of life

Age (mon)	Gross Motor	Fine Motor	Social	Language
1	Prone: Raises up head momentarily	Primitive palmar grasp still present	Spontaneous smile	
2	Prone: raises chin off couch (sustained)			
3	Supports head & chest on forearms	Open hands spontaneously, active palmar grasp	Appropriate social smile	Coos, laugh
4	Prone: raises his chest supported on his wrists			
5	Supine: rolls from supine to prone position	Reaches to objects & brings to mouth		
6	Sits supported (momentarily)	Transfers objects between hands	Recognizes mother, shows like/dislike	Babbles with **M** speech
7	Sits unsupported	Crude radial grasp		
8	Rolls over from prone to supine position			Mono syllable voices (**Ma**)
9	Crawling on his abdomen, pull to stand	Assisted Pincer Grasp	Waves bye bye plays pat a cake	Imitates sounds
10	Creeps on hands & knees, Stands supported	Tries to retrieve dropped objects		Poly syllable (**Mama**) speech
11	Stands unsupported	Unassisted Pincer grasp		
12	Walks supported	Releases objects on command	Comes when called	Two Meaningful words

2. Milestones after the first year

Age (mon)	Gross Motor	Fine Motor	Social	Language
18 mon	Walks upstairs with assistance	Feeds from spoon, drinks with cup	Mimics actions of others	At least 6 words
24 mon	Runs	Builds a tower ofsix blocks	Plays with others	2–3-word sentences
36 mon	Rides a tricycle, stands on one foot briefly	Draws circle	Help in dressing	Counts 3 objects, knows name, age, sex

Major developmental disorders:

1. **Intellectual disability**: IQ < 70–75 plus related limitation in ≥ 2 adaptive skills, e.g., self-care, home living, work, communication
2. **Communication disorders**: (deficits of comprehension, interpretation, production, or use of language)
3. **Learning disabilities:** Deficits (based on standardized tests) in one or more of these activities; reading, listening, speaking, writing, math
4. **Cerebral palsy.**
5. **Attention deficit/hyperactivity disorder**
6. **Autism spectrum disorders.**

Failure to Thrive (FTT)

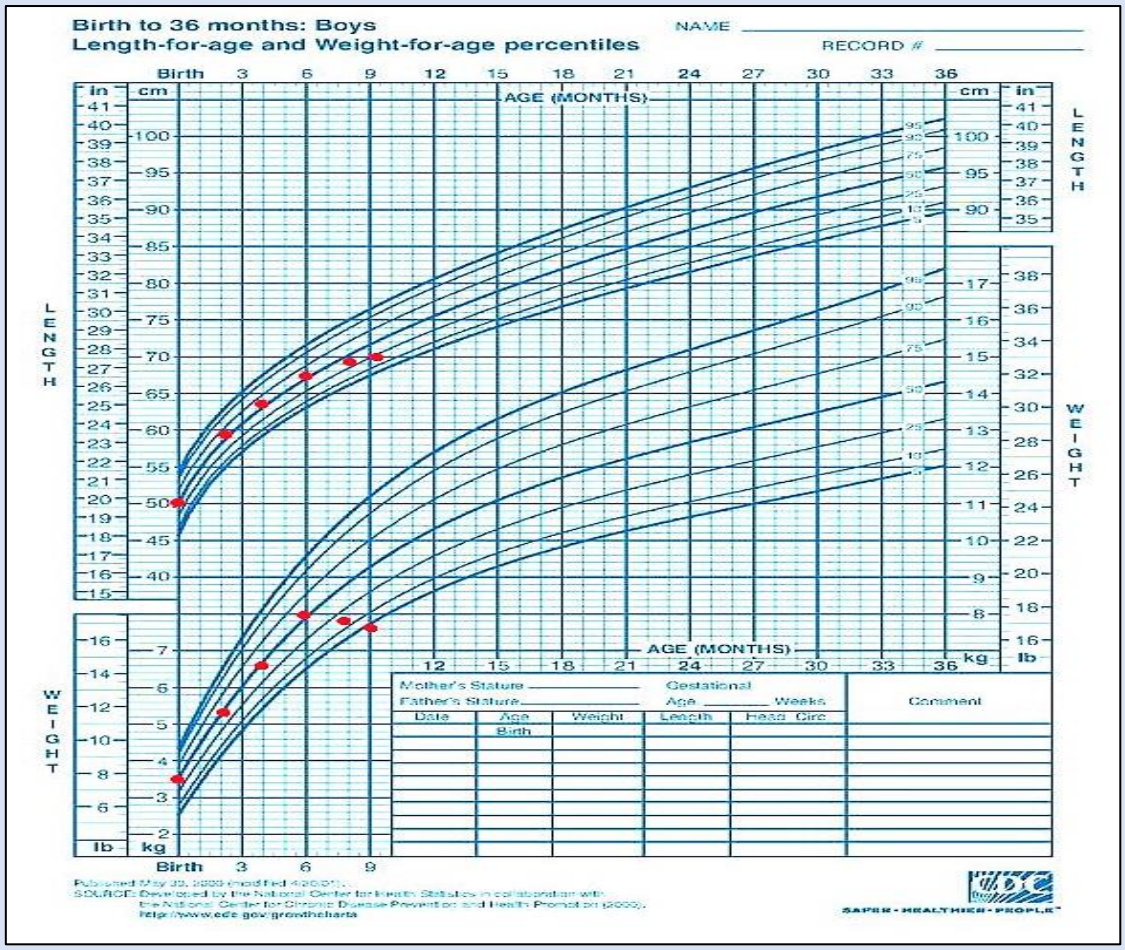
Case 4

History

Rami is a 9-month-old boy who is referred to the outpatient clinic with failure to thrive. His birth weight was 3.5 kg, he gained weight well initially and was weaned at 6 months. His appetite has been poor over the past couple of months and his mother describes him as miserable. He has no vomiting and opens his bowels four times a day. The stool is loose and smelly but contains no blood or mucus. Rami's mother breast-fed him until 4 months of age. His father has Crohn's disease, for which he has required several operations.

Examination

Rami is a thin, pale-looking infant. He is miserable and cries easily, and his abdomen is distended. There are no signs of tenderness, masses or organomegaly. The oral cavity and perianal area appear normal. There are no other signs. His centile chart is shown.



Investigations:

Haemoglobin	82 g/L
Mean cell volume	68 fl.
White cell count	9.8×10^9/L.
Platelets	432×10^9/L.
C-reactive protein 9 mg/L	(N<6 mg/L).

Ferritin	6 ng/ml	
Urea and electrolytes	Normal	
Liver function tests	Normal	
Bone chemistry	Normal	
Immunoglobulins	Normal	
Celiac screen:		
Anti-tissue transglutaminase IgA antibody	>100 U/mL	N (0–8 U/Ml)
Urine dip	Negative	
Stool	no bacterial growth, no ova, cysts or parasites.	

What is meant by failure to thrive?

Failure to thrive is a descriptive term and not a diagnosis. It is often defined as a weight, or a rate of weight gain, that is significantly below what is normal for a child of that age and sex.

Also, it can be defined as a weight that has fallen two centile lines on the standard growth charts. Although this term can refer to height as well as weight, it is usually used in relation to weight in children under 2 years of age.

What are the causes of failure to thrive?

The commonest cause of FTT is poor nutrient intake, So, take a full dietary history.

Poor nutrient intake may be due to feeding mismanagement (as mechanical problem e.g., cleft palate, Malabsorption e.g., coeliac disease, Excessive loss of nutrients e.g., vomiting due to gastro-esophageal reflux Increased nutrient requirement e.g., congestive cardiac failure) or psychosocial problems (as child abuse and neglect). It may also be the result of a combination of many of these factors and in some cases no cause is found.

What is the likely diagnosis and how could it be confirmed?

Rami's likely diagnosis is coeliac disease. Steatorrhea (with pale, greasy, smelly stool) and diarrhea are typical. Rami's abdominal distension is due to distension of intestinal loops with fluid and gas.

The centile chart shows that Rami's weight has crossed two centile lines since he was 6 months, and he has lost weight. This would correspond with weaning at 6 months and the introduction of gluten in wheat and other foods.

Rami's anemia is secondary to his poor nutrient intake and malabsorption. Folate as well as iron deficiency may occur.

Anti-tissue transglutaminase (anti-TTG) is >95 per cent accurate in diagnosing coeliac disease (it is important to simultaneously measure immunoglobulin A (Ig), as anti-TTG is an IgA antibody and IgA deficiency would invalidate the test).

The definitive diagnosis is usually based on an endoscopy with a jejunal biopsy.

Note that Crohn's disease is very rare in this agegroup so, Rami's father illness is coincidental.

What is the appropriate treatment for this condition?

Treatment is with a gluten-free diet.

Failure to Thrive (FTT):

- **Definition:** a term used to describe children who are not growing as expected. Weight is consistently or progressively decreasing below the 3rd to 5th percentile for age and sex, or there is decrease in the percentile rank of 2 major growth parameters in a short period.

- **Etiology:** the cause may be an identified medical condition or may be related to environmental factors. Most cases of FTT are multi-factorial. The physiologic basis for FTT of any etiology is inadequate nutrition and is divided into:

1. Organic FTT
2. Non-Organic FTT
3. Mixed.

1. Organic FTT:

Growth failure is due to an acute or chronic disorder that interferes with nutrient intake, absorption, metabolism, or excretion or that increases energy requirements.

Some Causes of Organic Failure to Thrive	
Mechanism	**Disorder**
Decreased nutrient intake	CNS disorder (cerebral palsy) Cleft lip or palate
Malabsorption	Celiac disease Cystic fibrosis Disaccharidase deficiency (lactase deficiency) Inflammatory bowel disease Short gut
Excessive loss of nutrients	Gastroesophageal reflux disease Pyloric stenosis Protein-losing enteropathy Proteinuria
Impaired metabolism	Chromosomal abnormality (Down syndrome) Classic galactosemia Inborn errors of metabolism

Increased energy requirements	Bronchopulmonary dysplasia Cystic fibrosis Heart failure Hyperthyroidism Infection

2. Non-organic FTT:

Up to 80% of children with growth failure do not have an apparent organic disorder. Growth failure occurs because of environmental neglect (e.g., lack of food), stimulus deprivation, or both.

1. **Lack of food** may be due to:
   - Poverty.
   - Poor understanding of feeding techniques.
   - Improperly prepared formula (e.g., over-diluting formula to stretch it because of financial difficulties).
   - Inadequate supply of breast milk (e.g., the mother is under stress, exhausted, or poorly nourished).

2. **Stimulus deprivation:**

Nonorganic FTT is often due to disordered interaction between a child and caregiver. In some cases, the infant or the child becomes depressed, apathetic, and ultimately anorexic due to stimulus deprivation.

3. Mixed FTT

In mixed FTT, organic and nonorganic causes can overlap; children with organic disorders also have disturbed environments or dysfunctional parental interactions. Likewise, children with severe undernutrition caused by nonorganic FTT can develop organic medical problems.

- Clinical manifestations:

- Children with organic FTT may present at any age depending on the underlying disorder.
- Most children with nonorganic FTT manifest growth failure before age 1 year and many by age 6 months.
- Age should be plotted against weight, height, and head size on growth standards and growth charts
- Weight is the most sensitive indicator of nutritional status. When FTT is due to inadequate caloric intake, weight falls from the baseline percentile before length does.
- Reduced linear growth usually indicates severe, prolonged undernutrition.
- Simultaneous fall of length and weight suggests a primary disorder of growth or a

prolonged inflammatory state.

- Reduced growth in head circumference occurs late and indicates very severe or long-standing undernutrition.
- FTT is associated with physical and social delays, and if occurring in older children, delayed puberty.
- A child who does not gain weight satisfactorily despite outpatient intervention usually is admitted to the hospital so that all necessary observations and diagnostic tests can be made.
- During hospitalization**,** the child's interaction with people in the environment is closely observed.
- Some children with nonorganic FTT have been described as wary of close contact with people, preferring interactions with inanimate objects if they interact at all.
- Hospitalized children who begin gaining weight well with proper feeding techniques, and number of calories are more likely to have nonorganic FTT.

- **Diagnosis:** it can be reached by:

  - Frequent monitoring of the anthropometric measures especially the weight.
  - Thorough medical, family, and social history.
  - Diet history.
  - Laboratory testing.

- **Testing:** if a thorough history or physical examination does not indicate a particular cause, the following screening tests are recommended:

- Complete blood count including differential leucocytic count.
- ESR.
- BUN and serum creatinine and electrolytes levels.
- Urinalysis (including ability to concentrate and acidify) and culture.
- Stool for pH, reducing substances, odor, color, consistency, and fat content.
- Other tests that are sometimes appropriate include:
  - Thyroxine level if growth in height is more severely affected than growth in weight
  - Growth hormone deficiency should be suspected when height and weight fall off simultaneously
  - A sweat test should be done if the child has a history of recurrent upper or lower respiratory tract disease, a ravenous appetite, foul-smelling bulky stools, hepatomegaly, or a family history of cystic fibrosis.

- Newborn screening results should be reviewed for other genetic diseases.
- Investigation for infectious diseases for children with evidence of infection.
- Radiologic investigation if there is anatomic or functional pathology (e.g., pyloric stenosis, gastroesophageal reflux).

- **Prognosis:**

- Prognosis with organic FTT depends on the cause.
- With nonorganic FTT, most of the children ages > 1 year achieve a stable weight above the 3rd percentile.
- Children who develop FTT before 1 year are at high risk of cognitive delay, especially verbal and math skills. If diagnosed before 6 months, where the rate of post-natal brain growth is maximal, are at highest risk.
- General behavioral problems occur in about 50% of children.

- **Treatment:** can be summarized in the following points:

- Sufficient nutrition: a nutritious diet containing adequate calories for catch-up growth (about 150% of normal caloric requirement) and individualized medical and social supports are usually necessary.
- Treatment of underlying disorder.
- Long-term social support providing sufficient health and environmental resources to promote satisfactory growth.

Practice Questions (Choose one correct answer)

1- 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.

2- The average head circumference of an infant at 1 year of age is:

a) 50 cm.
b) 35 cm.
c) 45 cm.
d) 40 cm.

3- The healthy infant shows social smile at the age of:

a) 1st month.
b) 2-3rd month.
c) 3-6th moth.
d) 4-5th month.

4- At one year of age, the number of the carpal ossific centers in the healthy infant is:

a) One center.
b) Two centers.
c) Three centers.
d) Four centers.

5- The normal infant can wave bye-bye by the age of :

a) 6^{th} month.
b) 9^{th} month.
c) 12^{th} month.
d) 15^{th} month.

6- In healthy infants, the active palmar grasp appears at the age of :

a) 1^{st} month.
b) 3^{rd} month.
c) 6^{th} month.
d) 4-8^{th} month

Chapter 2

Behavioral Pediatrics

Learning Objectives:

By the end of this chapter, students should be able to:

1. Describe normal social and behavioral development at different age groups
2. Describe factors affecting normal development
3. Describe the different types, causes and management of common behavioral and developmental disorders.

Contents:

1. Factors Affecting development and behavior
2. Some common developmental and behavioral disorders.

Case 1

A healthy 7-year-old boy presents to your office for concerns of difficulty in school. He was born at full term by a repeat cesarean section after an uneventful pregnancy. He met all developmental milestones on time. He is now repeating the first grade. Teachers complain that he frequently does not turn in his homework assignments and when he does it is full of careless mistakes. He often gets out of his chair during class and disrupts his classmates. Even when he raises his hand to answer a question, he usually ends up speaking out of turn. His family has to help him with his homework at night and he requires constant redirecting. His parents are currently separated, and his grandmother provides much of his care as his mother works full-time. His father never finished high school but no one in the family has been diagnosed with a learning disability.

General Examination: The child is a no dysmorphic 7-yearold boy. He cooperates with the examination but is very fidgety and distractible.

Neurologic Examination: Mental Status: He is alert and cooperative. Language: He has fluent speech without dysarthria. Cranial Nerves: His pupils are equal, round, and reactive to light. His extra ocular muscles are intact and there are no visual field cuts. His face is symmetric. The tongue is midline. Motor: He has normal bulk and tone with 5/5 strength throughout. Coordination: Finger-to-nose is intact bilaterally. Sensory: Normal light-touch, temperature, and vibration. Gait: He has a normal heel, toe, flat, and tandem gait. Reflexes: 2+ throughout with bilateral plantar flexor responses.

What is the most probable diagnosis?

Attention deficit hyperactivity disorder.

How is this condition diagnosed?

– There are no specific laboratory tests for the work-up of ADHD
– This child requires a formal assessment of achievement, intellectual abilities, and education.
– Testing is most often performed through the school system or by an independent psychologist.
– This should confirm or exclude the diagnosis of ADHD and/or a learning disability,
– As well as screen him for other psychiatric disorders.
– If there is a concern for a concomitant psychiatric condition, the child
– Should be referred to a psychiatrist for further management.
– Complex cases may require referral to developmental or behavioral specialists

What is the appropriate treatment for this condition?

– 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

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 exceptional) and heavy metal exposure.
4. ***Mass media effects.***
5. ***Death or Traveling*** of one of parents or both, grandparents and beloved person.
6. ***Stressor and multiple or sustained psychical traumas*** as wars, disasters, exams, excessive competitions, 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

A. Breathe Holding Spells (infantile syncope).

Criteria:

– Involuntary.

– Initiated by a noxious stimulus

– Associated with crying

– Consciousness and posture may be lost

- Occurs from infancy through age of 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.

B. Enuresis and Encopresis

Definitions:

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

Types of enuresis:

- Primary or secondary,
- Nocturnal, diurnal or mixed

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

Types of encopresis:

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

Etiology:

- Maturation or developmental defect.
- Sleep disorders.
- 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.

C. 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”!!

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).

- **<u>Intervention strategy for ADHD:</u>**

➢ ***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:***

a) More fish & tuna and sea foods,

b) No more sugars, sweets, chocolate, junk or fast foods.

➢ ***Behavioral 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.
- 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.

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

- 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.

Children who are diagnosed as autistic show problems in three main areas:

- Social interaction
- Communication
- Stereotyped behavior problem.

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 tests 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.

E. Other Behavioral disorders:

1. ***Sleep Disorders*** **(BEARS):**
   - **B > B**edtime Problems.
   - **E > E**xcessive Daytime Sleepiness.
   - **A > A**wakening During the Night.
   - **R > R**egularity and Duration of Sleep.
   - **S > S**noring
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. Triad of ADHD (Attention-deficit /hyperactivity disorder) is:

a) Inattention, hyperactivity and anxiety

b) Inattention, irritability and anorexia

c) Hyperactivity, impulsivity and inattention

d) Confusion, insomnia and inattention

2. Autistic-spectrum disorders (ASD) are caused by interaction of:

a) Genetic and environmental factors

b) Infectious and developmental factors

c) Idiopathic

d) All of the above.

3. Nocturnal enuresis is caused by:

a) Developmental and organic factors

b) Behavioral disturbances

c) Nightmares and terrors

d) All of the above.

4. 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.

5. 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

6. 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

Nutrition and Infant Feeding

Learning Objectives:

By the end of this chapter, students should be able to:

1. Know the nutritional requirements of infants and children.
2. Recognize and define some of common pediatric nutritional disorders, malnutrition, obesity, and rickets.
3. Identify risk factors, possible causes and complications of each of them.
4. Develop clinical diagnosis and select and interpret appropriate investigations for each of them.
5. Construct management plan and formulate proper lines of treatment for these disorders.

Contents:

1. Infant and child feeding
2. Malnutrition
3. Rickets

Infant and Child Feeding

Case 1

2 weeks old full-term baby and still under his birth weight. The mother's nipples are cracked, scabbed, and painful.

What is the normal weight pattern at this age?

Normally full-term baby loses about 7 to 10% of their birth weight and regain them about at the age of 1week after that the infant gains about 25 to 30 grams daily (about 200gm weekly). This baby is not gaining weight adequately.

What could be the cause of the mother nipple crack?

The most common cause of nipple crack and pain is improper attachment of the baby to the breast. Correction of the position and latch can help the crack to heal and decrease pain. One of the causes also is infant tongue tie so oral assessment is important for any baby with a mother with cracked nipple.

How to manage this case?

Counsel the mother about breast feeding position and latch examine the infant oral structures to exclude tongue tie start to supplement the baby with milk. The best supplement is the mother expressed breast milk so the mother can express and give her baby. The second-choice id donor human milk and the last choice will be infant formula.

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)

7. 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.

Daily requirements of vitamins and minerals for infants and children

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 premature babies)	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 g

Infant Feeding

Adequate nutrition during infancy and early childhood is essential to ensure the growth, health, and development of children to their full potential. Poor nutrition increases the risk of illness. Inappropriate nutrition can also lead to childhood obesity which is an increasing public health problem in many countries. Early nutritional deficits are also linked to long-term impairment in growth and health. There is evidence that adults who were malnourished in early childhood have impaired intellectual performance. They may also have reduced capacity for physical work.

The WHO and UNICEF recommended the following:

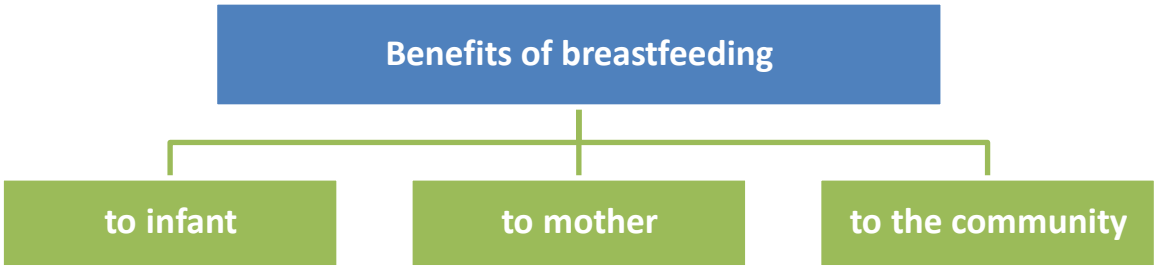
- Exclusive breastfeeding for the 1st 6 months of life.
- Nutritionally adequate and safe complementary feeding starting from the age of 6 months with continued breastfeeding up to 2 years of age or beyond.

Exclusive breastfeeding: means that an infant receives only breast milk from his or her mother or a wet nurse, or expressed breast milk, and no other liquids or solids, not even water, except for oral rehydration solution, drops or syrups consisting of vitamins, minerals supplements or medicine.

Complementary feeding: is defined as the process starting when breast milk is no longer sufficient to meet the nutritional requirements of infants, and therefore other foods and liquids are needed, along with breast milk.

Benefits of breastfeeding:

Breastfeeding confers short-term and long-term benefits on both child and mother.



Benefits to the infant:

1. **provides optimal nutrition for the infant**
    - It contains all the nutrients the baby needs for growth development.
    - It changes in composition overtime as the growing infant's needs.
    - It is easily digested & efficiently used by the baby’s body.

- Breastmilk also provides all the water a baby needs, even in hot climates. There is no need for any additional liquids.

2. Breastmilk promotes optimal growth and development (physically, mentally and psychologically).

a) **Physically**

- Breastfeeding decreases the risk of obesity as infants self-regulate their milk intake. Breastmilk contains hormones regulating hunger and satiety as leptin and ghrelin.
- Breastfeeding also decreases the risk malnutrition.

b) Mentally

It enhances cognitive & intellectual development, as it contains high concentration of long chain polyunsaturated fatty acids (LCPUFA) which have a central role in brain maturation and cognitive development. Breastmilk also contains amino acid taurine that functions as neurotransmitter in the brain.

c) Psychology

It enhances better psychological development as it satisfies the emotional needs of the baby & helps mother & baby to bond (a loving relationship develops between them), So Breastfed babies are psychologically more stable than artificially fed ones. Studies suggest that Breastfeeding for more than 6 months is associated with a lower risk of behavioral disorders as ADHD & Autism.

3. Optimal protection against infections (GIT, Respiratory, Ear infections):

- It is fresh and free of contaminating bacteria.
- It contains secretory IgA antibodies, which prevent microorganisms from adhering to the intestinal mucosa.
- It contains Lysozyme which destroys the cell wall of harmful bacteria and viruses.
- Breast milk is a source of lactoferrin, which is a protein present in breast milk that binds iron to itself thus the harmful intestinal bacteria are deprived of iron which is essential for their growth.
- It contains macrophages that can synthesize complement, lysozyme, and lactoferrin that enhance the immunity of the infant.
- The lower stool pH of the breast-fed infant than that of the infant fed cow's milk helps to inhibit bacterial growth.
- lt contains bile salt-stimulated lipase that digests fats and kills Giardia lamblia and Entamoeba histolytica.

- lt 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.
- Lt 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.

4. **It decreases the risk of allergy, asthma, autoimmune diseases, and malignancies.**
5. **Long term protection against chronic non communicable diseases** (Obesity, hypertension, Diabetes). The protective effect of BF against diabetes may be due to its effect on infant's weight.
6. **Breastfeeding decreases the risk of sudden infant death syndrome.**

Benefits to the mother:

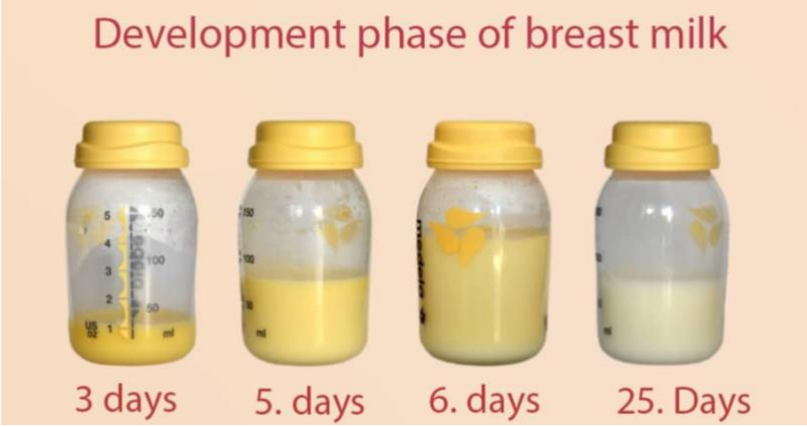
1. Helps involution of the uterus.
2. It helps delay a new pregnancy (lactation amenorrhea)
3. It helps the mother return to her pre-pregnancy weight sooner.
4. It reduces the risk of obesity & metabolic syndrome.
5. It reduces the risk of Hypertension & coronary heart disease.
6. Less effort and needs no time for preparation.
7. A lower incidence of breast, ovarian and uterine has been reported in women who breast-fed their babies.

Benefits to the community:

1. Breastfeeding reduces the financial burden on families (No need to buy formulas, bottles, nor to consume energy for sanitizing the bottles.
2. It decreases medical expenses due to more frequent doctors visit due to decreased rate of infection.
3. It also has environmental benefits. It does not waste resources or create pollution. Breast milk is a naturally renewable resource that requires no packaging, shipping, or disposal.

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 color.
- The total amount of colostrum-secreted daily is small, about 40–50 ml on the first day, but is all that an infant normally needs at this time.
- It contains several times the protein of mature breast milk, more minerals, but less carbohydrate and fat.
- Human colostrum also contains more immunologic factors.



Transitional and mature milk:

Milk starts to be produced in larger amounts between 2 and 4 days after delivery, making the breasts feel full; the milk is then said to have "come in". From day 7 to 14, the milk is called transitional, and after 2 weeks it is called mature milk.

Composition of mature milk:

- **Water**: constitutes 87.5% of human milk.
- **Carbohydrates:** constitute 7% of human milk. Lactose is the main carbohydrate in human milk. Human milk is the highest in lactose among all mammals. Other carbohydrates are present in human milk as oligosaccharides. Oligosaccharides have an important role in defenses against viruses, bacteria and their toxins.
- **Fats "lipids":** constitute 3.8%. It provides 50% of milk calories. Fats are the most variable constituent in human milk. It is directly related to the relative fullness of emptiness of the breast. As a breast empties during a feed, the proportional of fat increases.

- **Proteins:** constitute 0.9% "0.8 – 1.0%". The low protein content is well matched with the still developing renal function of the neonate while providing optimal growth and development. Milk proteins consist of whey and casein. Their levels vary with the stage of lactation from 90:10 in early lactation, 60:40 in mature milk
- **Caloric content:** of human milk is 65 Kcal/dL.
- **Vitamins:** Breast milk normally contains sufficient vitamins for an infant, unless the mother herself is deficient except vitamin D. The infant needs either exposure to sunlight or vitamin D supplement.
- **Minerals:** Iron and zinc are present in relatively low concentration, but their bioavailability and absorption are high. Iron is sufficient for the full-term infant needs till the age of 6months.

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.

After delivery:

1. Breast-feed as soon as possible, in the first hour after birth (golden hour).
2. Breast-feed on demand for 20-30 minutes. If the baby is sleepy, awake him after 3 hours.
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.

The baby is hungry when:

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

Determining adequacy of milk supply:

- 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.

Supplementary feeding:

Some breastfeeding mothers question the adequacy of colostrum feedings and perceive that they have an insufficient milk supply. These women would benefit from reassurance, assistance with breastfeeding technique, and education about the normal physiology of breastfeeding. Inappropriate supplementation may undermine a mother's confidence in her ability to meet her infant's nutritional needs. Inappropriate introduction of infant formula or other supplements may decrease the feeding frequency of the infant, thereby decreasing the amount of breast stimulation a mother receives, which results in a reduction of milk supply.

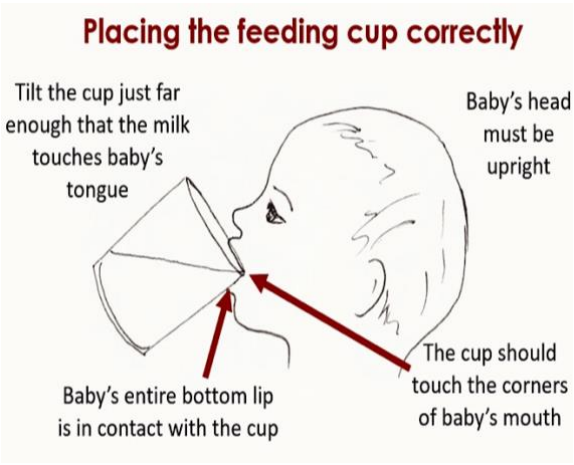
Indications of supplementation:

1. Excess infant weight loss > 10% after the 1st week of life
2. Decreased stool and urine output
3. Signs of dehydration
4. Hypoglycemia and hyperbilirubinemia due to poor infant intake.

Note: All infants must be evaluated for position, latch, and milk transfer before the provision of supplemental feedings.

Choice of supplement:

1. Expressed breast milk from the infant's mother is the first choice for extra feeding for the breastfed infant.
2. If the volume of the mother's milk doesn't meet infant's feeding requirements and supplementation is required, donor human milk is preferable to other supplements.
3. When donor human milk is not available or appropriate, infant formula can be used.
4. There are a number of delivery methods as cup feeding, spoon or dropper feeding, finger-feeding, syringe feeding, or bottle feeding.



Breast feeding and disease transmission:

- Human milk is essentially uncontaminated by pathogenic organisms and contains a lot of anti-infection agents. However, if the mother is infected with human immunodeficiency virus, human T-cell lymphotropic virus type I or type II, 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:** It is safe if there are no lesions on the breast. In cases where a mother has herpetic lesions on her breast, she should discard expressed breast milk from the affected side until the lesions have healed. Mothers can breastfeed directly from the unaffected breast if lesions on the affected breast are covered completely to avoid transmission**.**
- **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.

Contraindications to Breastfeeding:

A. Absolute contraindications:

- ☒ Infants diagnosed with galactosemia. Alternating breastfeeding with special protein-free can be used in feeding infants with other metabolic diseases (such as phenylketonuria).
- ☒ Mothers diagnosed with the human immunodeficiency virus (HIV)1, human T-cell lymphotropic virus type I or type II (HTLV), or Ebola virus.
- ☒ Mothers using an illicit drug, such as cocaine.

B. Temporary contraindications:

- ☒ Mothers infected with untreated brucellosis.
- ☒ Mothers taking certain medications as chemotherapy.
- ☒ Mothers undergoing diagnostic imaging with radioactive materials.
- ☒ Mothers having an active herpes simplex virus (HSV) infection with lesions present on the breast.

C. Temporary contraindications to direct breastfeeding but the mother can give expressed breast milk:

- ☒ Mothers having untreated or active tuberculosis. The mother may resume breastfeeding once she has been treated appropriately for 2 weeks.

Artificial feeding:

Artificial feeding or replacement feeding is the process of feeding a child who is not breastfeeding with a diet that provides all the nutrients the child needs, until the child is fully fed on family food.

Indications:

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

Types of milk used for artificial feeding:

Milk used in formulas

Dried Powdered milks

1. **Dried Humanized Milk (formula 1)**
   - Contains about 1 gm proteins/dl.
   - 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 .
- However, infants on these humanized milks still showed fewer achievements on growth curves than breast fed infants.

2. Dried follow-on formula (formula 2):

- 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/100ml.).
- 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.
- Used after the first year of life.

Fluid milks

Raw animal milks should not be advised for infant feeding before the age of one year.

Cow's milk:

- It forms large curds in the stomach, slowly digested, and easily contaminated with pathogenic organisms.

Goat's milk:

- Used in many countries, including rural Egypt.
- 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.

Milks	Protein (g/dL)	Carbohydrate (g/dL)	Fat (g/dL)	Minerals (g/dL)	Water	Calories (Kcal/ dL)
Human	1.5	7	4	0.2	87%	67
Cow	3.5	4.5	4	0.8	87%	67
Buffalo	3.5	4.5	7.5	0.8	83%	100

Mature human milk compared to cow's milk

Water:

- The relative amount of water is about 87% 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 1g/dL protein (3.3 g/dL in cow's milk).
- Human milk protein consists of approximately 60% whey proteins, 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 of lactose, while cow's milk contains 4.5g/dl.
- Lactose in breast milk helps the absorption of calcium and provides galactose for formation of galactolipids necessary for brain development.

Fat:

- Fat content of milk is about 3.5 g/dl 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
- 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.

Vitamins:

- The vitamin content of human milk varies with the maternal intake.
- 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.

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.

Caloric requirements:

- Full-term infants 100-120 kcal/kg during the first year of age
- The formula should contain about 20 kcal/oz (oz=30ml).

Fluid Requirements

- During the first 6 months of life 150 mL/kg/24 hr and may increase during hot weather.

Number of feedings daily:

- Feedings are given every 3–5 hr during the first year of life.
- Small or weak infants may prefer feedings at 2-3 hr 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 (oz=30ml) of milk at one feeding.

Disadvantages of artificial feeding:

1. Malnutrition due to errors in preparation of milk.
2. Contamination with increased incidence of diarrhea and its related mortality.

3. Bacterial and viral infections are more common in artificially fed infants.
4. Intolerance and allergies.
5. High expenses.
6. Loss of psychologic benefit of mother-infant bonding.

Underfeeding

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

Symptoms:

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

Signs:

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

Diagnosis:

- Test weighing: an average body weight gain of 100 g every 3-4 days during the first months of life is considered adequate.
- 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:

- Increasing the fluid and caloric intake by complementary or supplementary feeds.

- Correcting deficiencies in vitamin and mineral intake.
- Instructing the mother in the art of infant feeding.
- 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:

- Overweight.
- Regurgitation and vomiting.
- Distension and abdominal discomfort.
- Diarrhea.

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:

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

Complementary Feeding (Weaning)

Complementary feeding or weaning is to accustom the infant or child to take food materials other than milk. This starts when breastmilk is no longer sufficient to meet the infant nutritional requirements, so that other foods and drinks are needed along with breastmilk.

WHO recommends that infants should be exclusively breast fed till the age of 6 months and to continue breastfeeding along with complementary feeding till the age of 2 years. It is recommended no solid foods to be given before the age of 4 months in formula-fed babies.

The aim of weaning is to:

1. Supply sufficient nutrients in which the milk is deficient (iron, vitamins B_1 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 principles of weaning:

1. Complementary foods should be introduced at 6 months of age while continuing to breastfeed on demand.
2. It should not be started during illness or early convalescence.
3. Only one type of new food should be given at a time. The same type of new food is given every day until the baby becomes accustomed to it.
4. Responsive feeding should be practiced that means to feed infants directly and assist them when they feed themselves. Encourage infants to eat, guided by the baby's appetite and never do enforced feeding. Minimize distractions during meals if the child loses interest easily.
5. Good hygiene and proper food handling need to be insured.
6. Start with small amounts of food and increase the quantity and as the child gets older.
7. Gradually increase food consistency and variety as the infant grows older, adapting to the infant's requirements and abilities. Beginning at 6 months, an infant can eat pureed, mashed or semi-solid foods. By 8 months most infants can also eat finger foods. By 12 months, most children can eat the same types of foods as consumed by the rest of the family.

A complementary food should be thick enough so that it stays on a spoon and does not drip off.

8. The number of times that the child is fed complementary foods should be increased as the child gets older. breastfed infant 6-8 months old needs 2–3 meals a day, and a breastfed infant 9–23 months needs 3–4 meals a day.
9. A variety of nutrient-rich foods are given to ensure that all nutrient needs are met. Fortified complementary foods or vitamin-mineral supplements for the infant can be used as needed.
10. Iron rich foods are included in early complementary feeding as:
    - Iron fortified cereals.
    - Iron rich vegetables and fruits with adding vitamin C to increase iron absorption.
    - Pureed poultry/meat/fish.
11. It is recommended to give whole cream dairy products as yogurt, cheese & pudding starting after 6 months (good source of protein, calcium & DHA).

Guide to foods to offer children 6–23 months of age

Age (Mon)	Energy needs in addition to breast milk	Texture	Frequency	Amount
6-8	200kcal/day	Thick porridge, well mashed food	2-3 meals/day	2-3 tablespoons
9-11	300kcal/day	Finely chopped or mashed Finger foods	3–4 meals/day	1/2 cup of 250ml
12-23	550kcal/day	Family food	3–4 meals/day	3/4 to full cup of 250ml

العمر	الغذاء
8-6 شهور	• رضاعة طبيعية حسب الطل • يتم اعطاء 2 الي 3 وجبات يوميا 2-3 ملاعق طعام ويتم زيادتها تدريجيا الي نصف كوب 250 مل • نبدأ بالطعام المهروس جيدا بدون إضافة ملح أو سكر وبالتدريج يتم ترك بعض الكتل في الطعام • أمثلة لبعض الأطعمة: - الحبوب المدعمة بالحديد - اللحوم والدجاج والاسماك - الزبادي والجبن - البيض - الخضروات والفواكه المهروسة - البقول
12-9 شهر	• رضاعة طبيعية حسب الطلب • يتم اعطاء3 الي 4 وجبات يوميا تقريبا بحجم نصف كوب 250 مل • زيادة الكتل في الطعام بالتدريج وإعطاء الطفل الطعام بيده (finger food) • يمكن مزج أصناف مختلفة من الطعام وذلك لزيادة القيمة الغذائية للوجبات مع إضافة الزيوت مثل مزيج الأرز بالخضروات واللحوم أو الدجاج والشوفان مع الفواكه
بعد سنة	• الرضاعة الطبيعية • يتم اعطاء3 الي 4 وجبات يوميا بحجم ثلاثة ارباع كوب 250 مل الى كوب كامل • تستطيع الام ان تعطي لطفلها جميع انواع الطعام (طعام الاسرة)

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 ys (2000 kcal/day at 10 years); for example, at 5 years 1000 + 5 X 100 = 1500 kcal/day.
- For males: + 100 kcal for every year 10 - 18 ys (adult male 2800 kcal/day)
- For females: +50 kcal for every year 11- 14 ys (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

Malnutrition

Case 3

Adam is an 18-month-old black African boy from South Africa. He was born weighing 3.2 kg. He was breastfed until 9 months of age when his sibling was born. He now mainly eats the traditional maize-based porridge, which is grown on the family farm. His weight is just below the 5th centile. He looks thin but has a distended abdomen. There is edema around his eyes and the top of his feet. His hair has a red tinge.

What is the most likely diagnosis?

The patient has Kwashiorkor **(**severe protein malnutrition accompanied by edema). Because of the edema, the weight may not be as severely reduced as in marasmus. He has other features of kwashiorkor, the depigmented hair and distended abdomen.

What are the constant features of this condition?

- Growth failure
- Edema
- Muscle wasting with preservation of subcutaneous fat.
- Psychomotor changes: as irritability, apathy, anorexia.

What are the initial investigations you may ask for?

- CBC.
- Blood glucose level.
- Total serum protein and serum albumin,
- Serum electrolytes (Na, K, Mg, P).

What are the major complications of this condition?

- Hypoglycemia.
- Infections especially gastroenteritis.
- Organs' failure.

What are the main lines of treatment?

1. Treatment of acute emergent conditions like shock, dehydration, electrolytes disturbances, hypoglycaemia, infections, Severe vitamin A deficiency.
2. Dietetic management after stabilization (balanced protein- rich diet with adequate calories).
3. Symptomatic treatment for vitamins and mineral deficiencies.

What are the bad prognostic factors for this condition?

Bad prognostic factors:

- Severe weight loss
- Presence of dehydration
- Markedly enlarged liver
- Disturbed consciousness
- Hypothermia
- Skin hemorrhage.

Malnutrition is one of the leading causes of morbidity and mortality in childhood and it may be due to:

1. **Improper or inadequate food intake:**
    - Insufficient food supply.
    - Poor dietary habits.
    - Emotional factors.
2. **Inadequate absorption of food**
3. **Increased requirements:**
    - Stress.
    - Disease.
    - Treatment with antibiotics.
    - Intake of catabolic or anabolic drugs.
    - Certain metabolic abnormalities.

The diagnosis of malnutrition (Assessment of Nutritional status and Growth):

1. **Dietary evaluation:**
    - Dietary evaluation including feeding history and current food intake through 24hr. Recall or 3 days food record.
    - Measuring the quantity and quality of food intake, regarding the major food elements, vitamins, minerals and trace elements and comparison with the individual's requirements.
2. **Anthropometric measurements Including:**
    - Weight,
    - Length/height,
    - Head circumference,
    - Mid upper arm circumference (MUAC),
    - Body mass index (BMI),
    - Skin folds thickness
    - Muscle mass is calculated as follows: **Mid-arm muscle circumference = mid-arm circumference - (skin fold thickness X 3.14).**
    - Past rates of growth.
    - Data plotted on growth charts according to age and compared with a reference population for detection of any growth abnormalities (increase or decrease).

3. Clinical examination:

For detection any signs of macro and/or micronutrient deficiency or excess or detection of Organic cause & assessment of puberty at age of puberty.

4. Investigations to confirm your provisional diagnosis:

- CBC: Iron deficiency anaemia.
- Protein reserves are assessed from serum albumin and total proteins.
- Rapid turnover proteins, such as transthyrenin, prealbumin, and transferrin for evaluation of current status and response to treatment.
- Lean body mass can be estimated from 24-hr creatinine excretion.
- Others according to the condition
  - Serum levels of essential amino acids / nonessential amino acids.
  - Kidney & liver function: for unsuspected renal failure or hepatic affection.
  - Celiac screen & investigations for other malabsorption like pancreatic insufficiency in cases of cystic fibrosis (CF) including endoscopic examination.
  - Thyroid functions to exclude hypothyroidism.
  - ECHO for congenital heart disease (CHD).
  - X-ray for Bone age.

Classification of malnutrition

1. Waterlow classification of malnutrition:

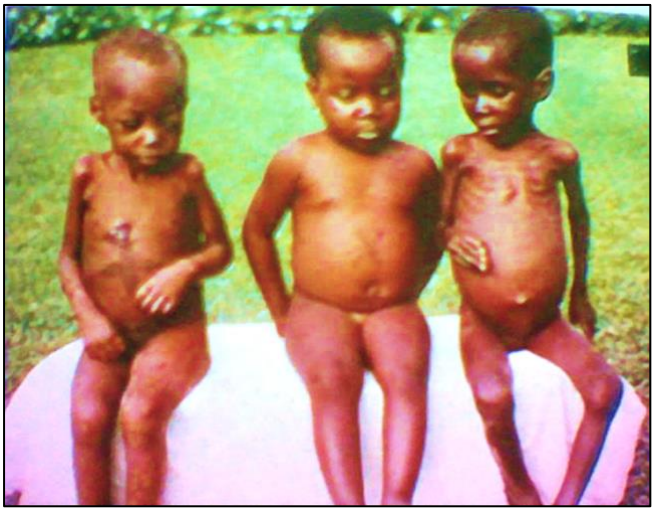
Grade	Acute Malnutrition "Wasting" % Weight-for-height	Chronic malnutrition "Stunting" % Height-for-age*
I (mild)	**< 90**	**< 95**
II (moderate)	**< 80**	**< 90**
III (severe)	**< 70**	**< 85**

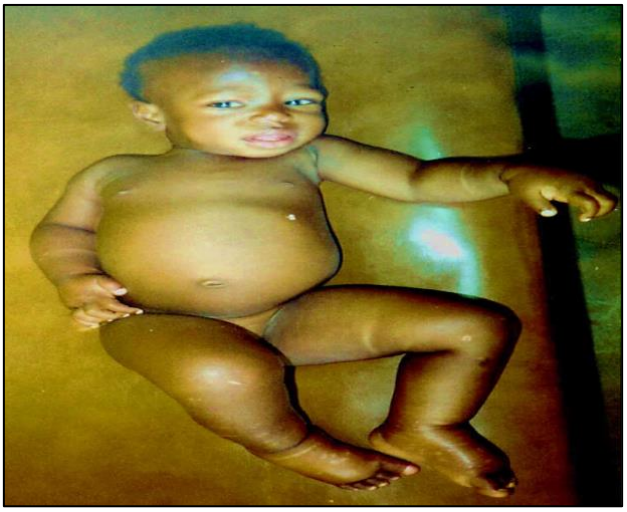
- **% Weight for height:** Child's actual weight divided by 50th percentile of weight for his / her height age, multiplied by 100.
- **% Height for age:** Child's actual height divided by the 50th percentile of height for his / her age, multiplied by 100.

2. Wellcome classification of PEM:

Weight % of normal	Edema	
	Absent	**Present**
60 - 80	Underweight	Kwashiorkor (KWO)
60 or less	Marasmus	Marasmic KWO

Kwashiorkor (KWO)



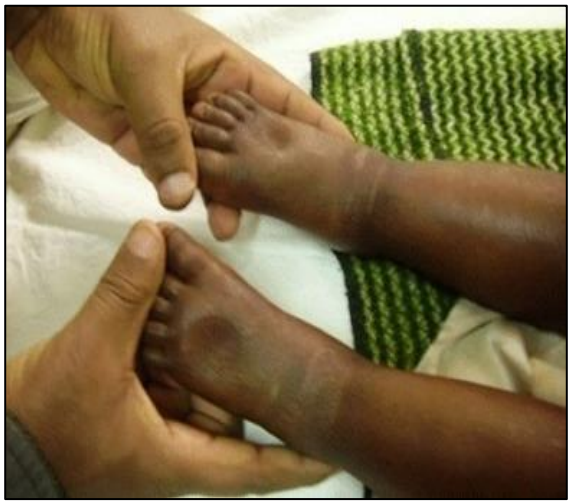


- Kwashiorkor is a clinical syndrome that results from a severe deficiency of protein in addition to an inadequate caloric intake but to a lesser degree.
- The patient depends mainly on carbohydrates in his caloric intake.
- Kwashiorkor means "deposed child," that is, the child no longer suckled.
- It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

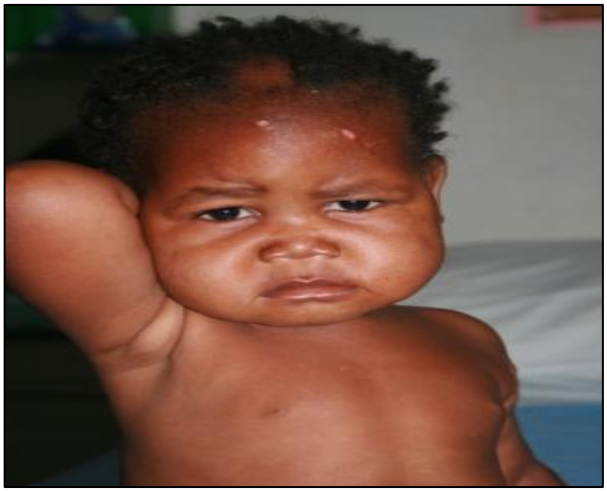
When advanced cases, constant signs are found:



1. **Growth failure:** detected by suitable anthropometric measurements.
2. **Edema**: Edema usually develops early; failure to gain weight may be masked by edema.

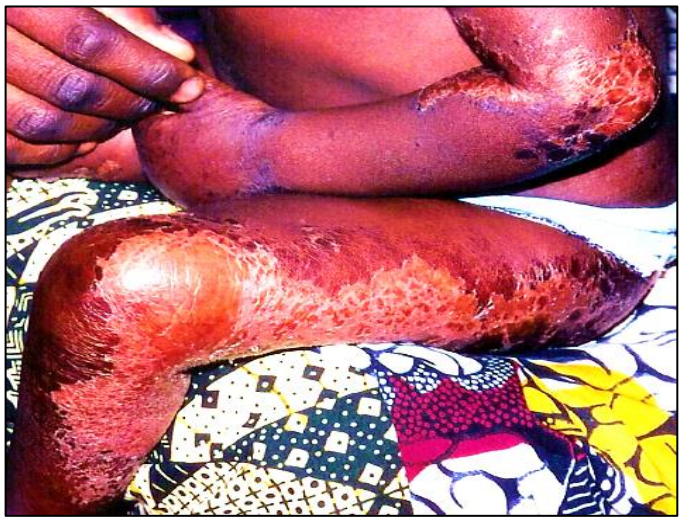
   It is due to decreased plasma proteins, salt retention (due to activation of renin-angiotensin system) and water retention (due to decreased hepatic inactivation of antidiuretic hormone).
3. **Muscle wasting with preservation of some subcutaneous fat:** The muscles are weak, thin, and atrophic, due to 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)

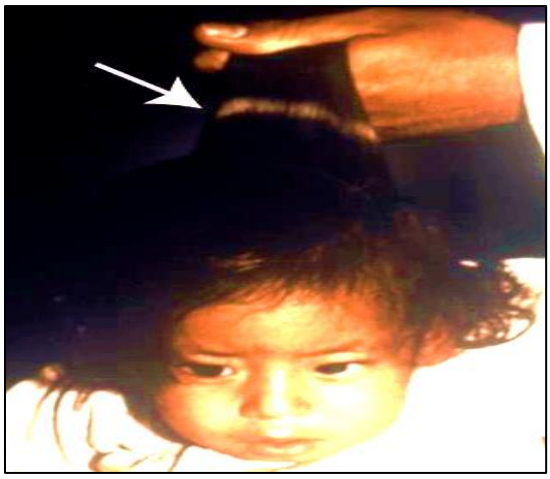


Other signs (usual signs):

- **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. 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/mm^3 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. Anemia 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:

1. 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.

2. 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., uremia.
- CNS disorders e.g., cerebral palsy.

Clinical Manifestations:

1. 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.

2. 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:

- Severe weight loss - Younger age - Presence of infection - 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:

1. Encouragement of breast feeding.
2. Adequate dietary instructions and food distribution.
3. Immunization against infectious diseases.
4. Early detection and treatment of PEM cases.
5. Breaking down bad dietary habits e.g., food withdrawal during diarrhea.

Treatment of PEM:

1. Immediate management of any acute problems:

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

2. 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.

3. Symptomatic treatment:

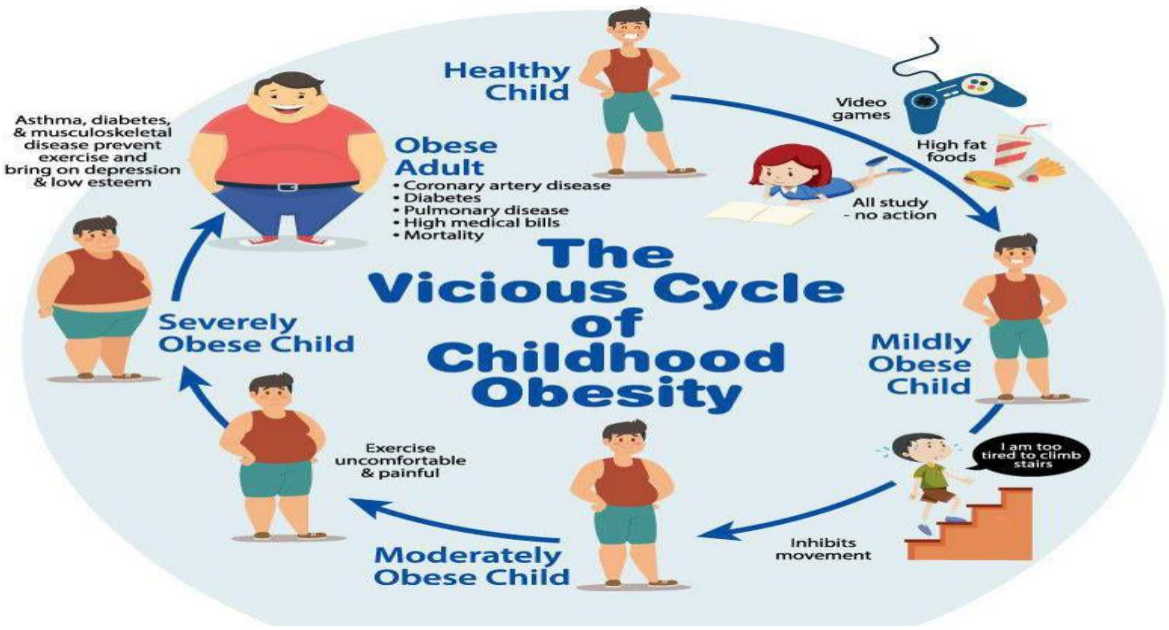
- Bacterial infections and diarrhea must be treated properly. Treatment of parasitic infestations, if they are not severe, may be postponed until recovery is under way.
  - Gentian violet 2%, antibiotic or antifungal creams for dermatosis.
  - Vitamins and minerals, especially vit A, D and B complex,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

4. Signs of improvement:

- Sense of well-being.
- Steady improvement of appetite.
- Disappearance of edema.
- 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 BMI-for age between the 85th and 95th percentiles.



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:**
   - 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.

I. **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. Advice 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 / day

Sources:

– Retinol in animal food: liver, meat, fish, eggs, milk fat.

– Carotenes (provitamin.) in plants: carrots and dark green vegetable.

Deficiency:

– Ocular: 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) Thiamin

Daily requirements: 0.5 mg / day

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

Deficiency: (Beriberi) **- Dry:** polyneuritis **- Wet:** heart failure

Vitamin (B2) Riboflavin

Daily requirements: - 0.5 mg/day (infants) - 1 mg/day (children) **Sources:** As B_1.

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

Vitamin (B3) (niacin)

Daily requirements: 5 mg / day **Sources:** As B_1.

Deficiency: Diarrhea, dementia, and dermatitis.

Excess: Skin flushing, itching and hepatosplenomegaly.

Vitamin (B6) Pyridoxine

Daily requirements: 0.6 mg / day

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

Vitamin (B7) Biotin

Sources: Yeasts, animal products, synthesized in intestine.

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

Vitamin (B9) Folic acid

Daily requirements: 50 µg/day. **Sources:** Green leafy vegetables.

Deficiency: Megaloblastic anemia.

Vitamin (B12) Cyanocobalamin

Daily requirements: 0.5 µg/day **Sources:** Muscles, organ meats, fish, eggs, milk and cheese.

Deficiency: Juvenile pernicious anemia.

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 / day for premature babies.

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

Deficiency: Rickets. **Excess:** Nausea, weight loss, polyuria, nocturia and soft tissue calcifications.

Vitamin (E)

Daily requirements: 5 mg / day

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

Deficiency: Hemolysis in premature babies

Vitamin (K)

Daily requirements: 5 µg / day (infant), 15 µg / day (children)

Sources: Green leafy vegetables and liver.

Deficiency: Hemorrhage. **Excess:** synthetic analogues may produce hyperbilirubinemia in premature Infants.

Rickets

Case 5

Mohammed, a 18-month-old boy, was admitted to the emergency department with a generalized afebrile seizure. This was initially controlled with per rectum diazepam.

Twenty minutes later he had another generalized seizure and needed an intravenous anticonvulsant to control his seizure.

His mother said that he was a healthy child. He was born at term, birth weight 3.1 kg, and was still breastfed. Some weaning foods were started at 7–8 months of age, but he preferred feeding at the breast. He had only recently begun to sit without support, with delayed walking.

His weight on the 10th centile and his head circumference were on the 80th centile. He had marked frontal bossing, widened wrist and other epiphyses, wide anterior fontanelle, and chest rosary beads. He would not take his weight on standing.

What is the most likely diagnosis?

Vitamin D deficiency rickets.

What are the possible risk factors for Mohammed's clinical condition?

It may be due to:

Rachitogenic diet (food poor in Vit. D & Ca):

- Prolonged breastfeeding without appropriate complementary feeding from the 6 months.
- Lack of infant supplementation with vitamin D.
- Poverty or malnutrition.

Inadequate sun exposure (failure of activation of vit. D):

- Dark skin pigmentation and/or restricted sun (UVB) exposure: e.g., predominant indoor living, overclothing, disability, pollution, cloud winter season.

Malabsorption of Vit. D:

- Chronic diarrhea. - Cholestasis.

Generalized malabsorption disorders e.g., inflammatory bowel disease **(**IBD), celiac disease, cystic fibrosis.

What are the investigations indicated to diagnose this case?

Laboratory:

- Serum Ca (decreased) & serum Ph level (decreased).
- Alkaline phosphatase level elevated.

- Vitamin D (25 OH vitamin D) level decreased. **Imaging: -** X-ray on extremities.
What is the appropriate treatment for this condition? - Treatment of hypocalcemic convulsions. - Oral Vitamin D in a dose of 2000-5000 IU/day for 8 weeks. - Shock therapy: Vit D 600,000 IU by I.M. injection single dose. - After 2-4 weeks, if no radiologic or laboratory evidence of complete healing, repeat the dose.

Definition:

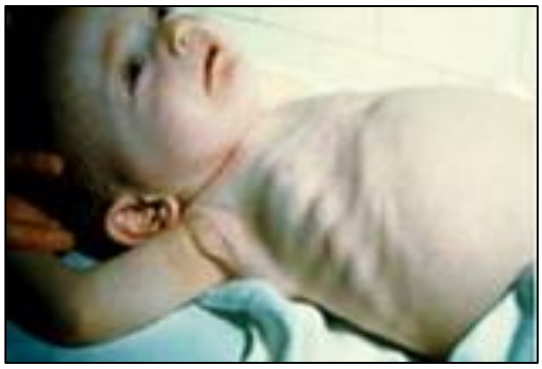
Defective mineralization of growing bones, due to vit D deficiency and/or abnormal metabolism.

Clinical manifestations:

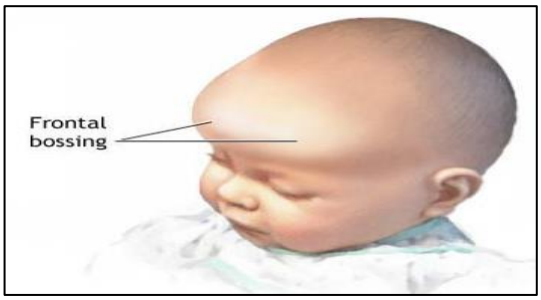
Vitamin D deficiency rickets most commonly occurs at the end of the first year and during the second year of life.

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 month 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:

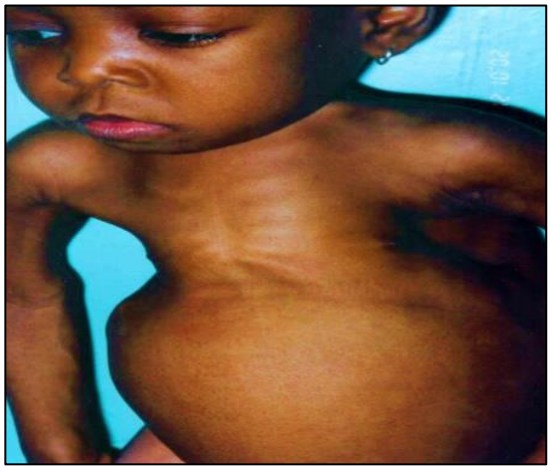
1. Head:

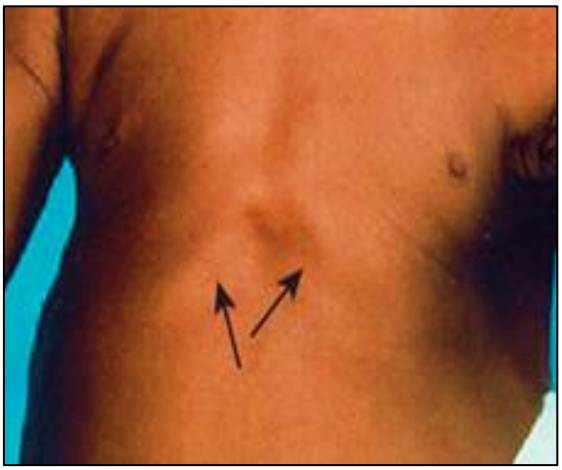
- Bossing of skull: excessive proliferation of cartilage at occipital and parietal eminences makes the skull looks like a box.
- Enlargement of head circumference.

- Delayed closure of anterior fontanels, which remains widely open.
- Delayed eruption of primary dentition with possible enamel hypoplasia.

2. Thorax:

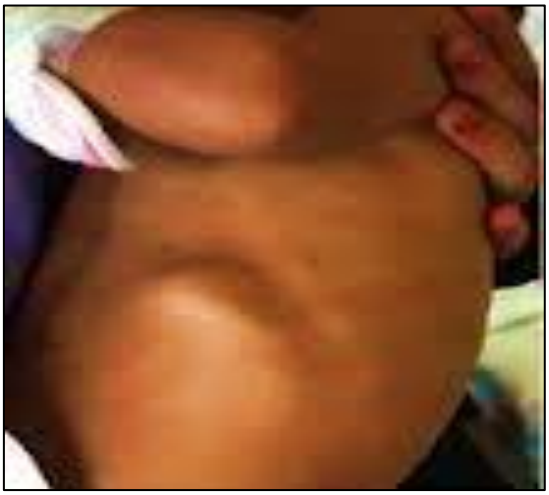
- Rosary beads.
- Longitudinal sulcus: A longitudinal sulcus appears lateral to the rosaries due to compression of rib cage by atmospheric pressure at weakest point.
- Harrison's sulcus: A transverse sulcus along the lower border of the costal margin due to inward traction of the ribs at sites of diaphragmatic insertion.
- Forward protrusion of sternum and adjacent costal cartilage.
- The overall shape of the chest wall is called “pigeon chest”, which is nearly triangular in cross section.

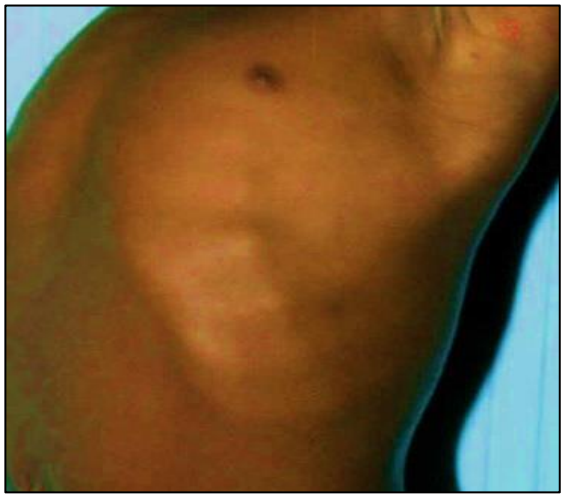




3. Abdomen:

- Liver and spleen become palpable due to deformed chest and weak abdominal muscles and lax ligaments supporting organs. The abdomen appears protruded due to hypotonia of anterior abdominal wall.





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 gross motor milestones.

Complications:

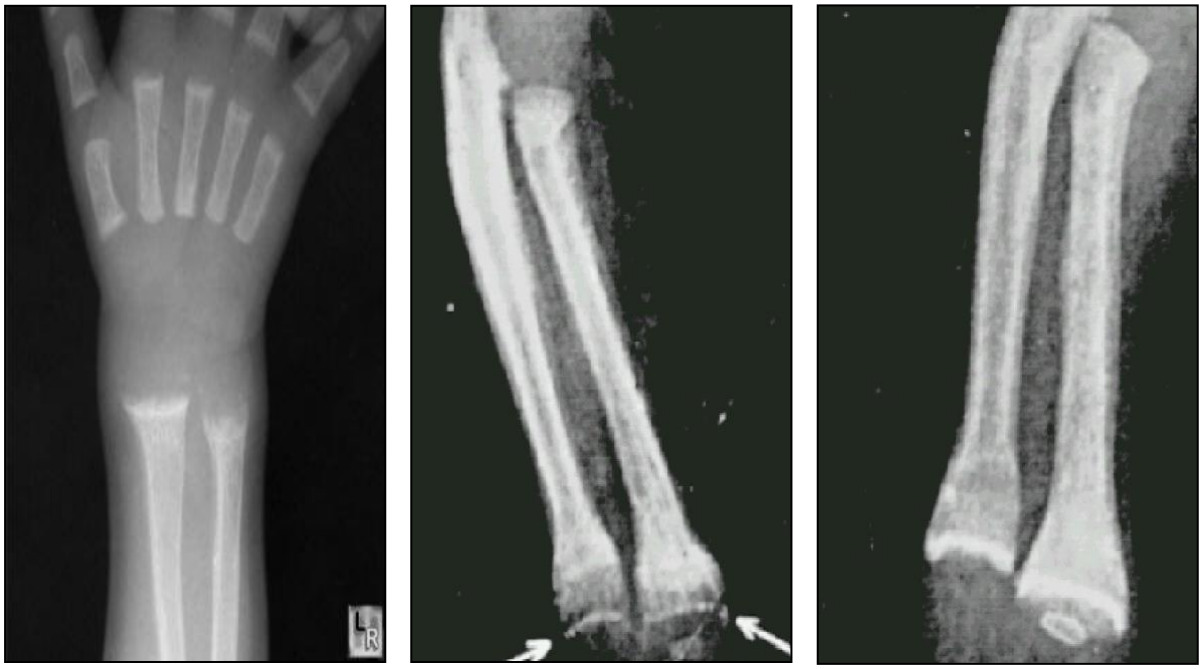
1. Respiratory: infections or atelectasis due to chest deformities.
2. Gastrointestinal tract: diarrhea or constipation.
3. Bony deformities or fractures.
4. Anemia: due to chronic infection or deficiencies.
5. Tetany: due to hypocalcemia in late cases after exhaustion of parathyroids.

Investigations:

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 and decreased after exhaustion of parathyroid function.
- Vitamin D (25 OH vitamin D) level decreased.

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.

Prevention:

- Exposure to ultraviolet rays in sunshine or administration of Vitamin D orally.
- Daily requirements of vitamin D are 400-600 IU/day.
- For low-birth-weight infants, and patients of malnutrition or hypothyroidism receiving their specific treatment, 1000 IU /day are needed for the accelerated rate of growth.

Treatment:

- Oral Vitamin D in a dose of 2000-5000 IU/day for 8 weeks.
- Shock therapy: Vit D 600,000 IU by I.M. injection single dose.
- After 2-4 weeks, if no radiologic or laboratory evidence of complete healing occurs, the dose can be repeated.

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.

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

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.

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:

1. The patient becomes weak, anorexic, and irritable.
2. Vomiting, and loses weight.
3. Hypotonia, constipation.
4. Polydipsia, polyuria, and dehydration.
5. Pallor and macrocytic anemia.
6. Hypercalcemia and hypercalciuria.
7. Aortic valvular stenosis, hypertension.
8. Retinopathy and clouding of the cornea and conjunctiva may occur.
9. Proteinuria and manifestations of renal damage due to progressive nephrocalcinosis and nephrolithiasis.
10. Metastatic calcification may occur in the heart, stomach, lungs, thyroid, and pancreas and blood vessels.
11. 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:

1. Careful evaluation of vitamin D dosage.
2. 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. A breastfeeding mother of 2months old baby. Started to have vesicles on her left breast areola and diagnosed to have herpes simplex. She asks for advice about feeding her baby/ what is your advice?

a) Continue to breastfeed normally as HSV is not transmitted through breastfeeding
b) Stop breastfeeding and separate the mother from her baby
c) Express and discard milk from the affected breast till the lesion heal
d) Express and discard milk from both breast

2. It is found in breast milk and may stimulate the growth and/or the activity of commensal bacteria in the colon :

a) Lysozyme.
b) Lactoferrin.
c) Prebiotic.
d) Secretory IgA

3. The daily requirement of vitamin D for full-term infants is:

a) 100 – 200 Iu.
b) 200 – 400 Iu.
c) 400 – 800 Iu.
d) 800 – 1500 Iu.

4. Which of the following is not a clinical feature of rickets?

a) Craniotabes.
b) Hypertonia.
c) Rosary beads.
d) Harrison's sulcus.

5. The main problems in animal milks don't include:

a) The formation of tough curd due to excessive casein.
b) Higher content of volatile fatty acids.
c) Low mineral content.
d) Lower iron content.

Chapter 4

Diabetes and Endocrine Disorders

Learning Objectives:

By the end of this chapter, students should be able to:

1. How to diagnose and approach to diabetes mellitus and different endocrine disorders.
2. Enumerate findings in investigations in different diseases.
3. Formulate a management plan for diabetes mellitus and different endocrine disorders.

Contents:

1. Hypothyroidism:
   - Congenital hypothyroidism.
   - Acquired hypothyroidism.
2. Diabetes Mellitus:
   - Type 1 DM
3. Short stature.
4. Puberty (normal & delayed).

I. *Hypothyroidism*

Case 1

Before routine neonatal screening was introduced in hospital. Female patient was born as a late preterm AGA with uneventful postnatal period. She was lost for follow up and came back to our outpatient clinic at 6 months of age.

She was noted to have skin mottling, edematous, jaundiced, open mouth, a delay in social smile, support head and sitting, large protruding tongue, protuberant abdomen and difficulty in defecation and umbilical hernia.

Investigations showed a TSH > 150mIu/l. T4 was immediately started at a dose of 15µg/kg/day. TSH & free T4 normalized soon and the dose of T4 was carefully titrated to avoid under or over treatment. Her growth & development was also carefully monitored.

What is the most likely diagnosis?

Congenital hypothyroidism

What are the different causes of the disease?

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:

1- Endemic iodide deficiency causing endemic goiter in the mother.

2- Maternal ingestion of antithyroid drugs or iodine containing drugs during pregnancy.

B- Permanent hypothyroidism (Thyroid dyshormonogenesis):

- 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)

What is the appropriate treatment for this condition?

Sodium L-thyroxine by (ELtroxin ®). Dose is according to the age.

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	

The doses should maintain serum T4 level at 12-15 ug/dL, and TSH below 5 uU/ml, and should give normal bone age.

Congenital Hypothyroidism:

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.

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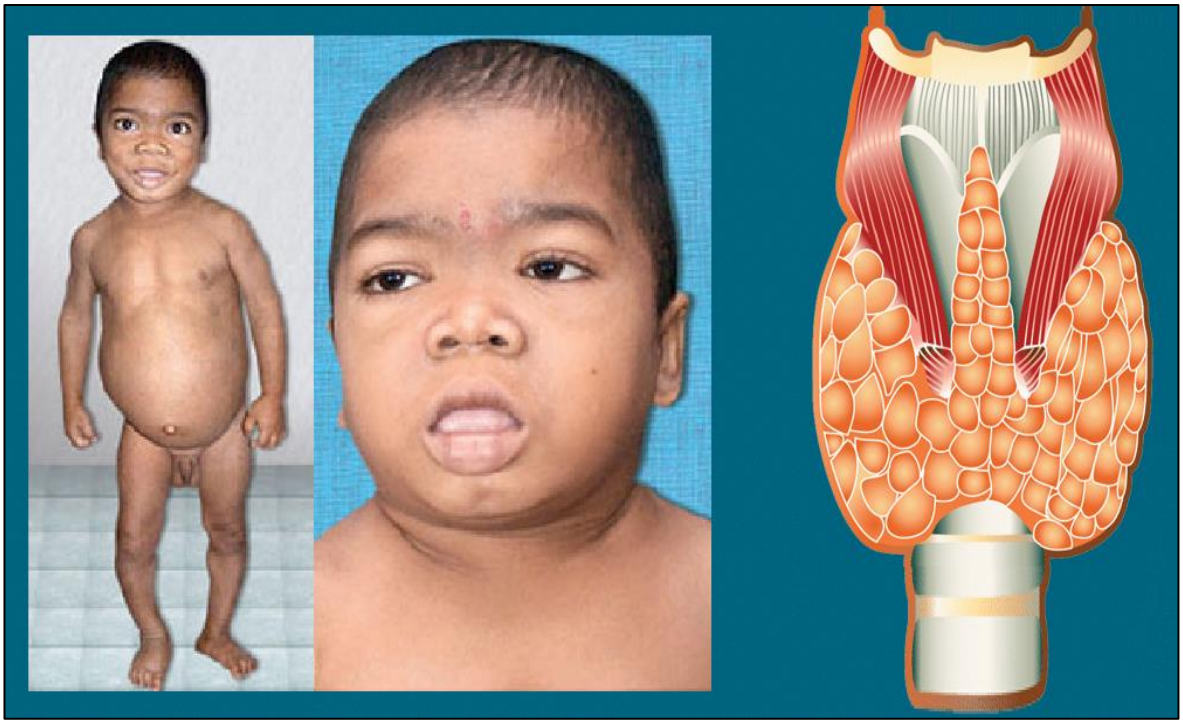
  - Maternal antithyroid or iodine containing drugs during pregnancy.

  b.Permanent ***hypothyroidism*** *(Thyroid dyshormonogenesis):* 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.

II-Secondary Hypothyroidism*:* (Disease in Pituitary gland).

III-Tertiary Hypothyroidism: (Disease in Hypothalamus).



Clinical manifestations:

1. Presentation in neonatal period:

- *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 (T4) deficiency by the transplacental transfer of T4 from mother to fetus.

- *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 glucuronidation.

• The infant sleeps much and cries little.

• Poor appetite and choking spells during nursing.

• Constipation.

• Cold mottled skin 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.*

2. Presentation of untreated hypothyroidism during infancy & childhood:

- 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.

- 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 sub hyoid 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.

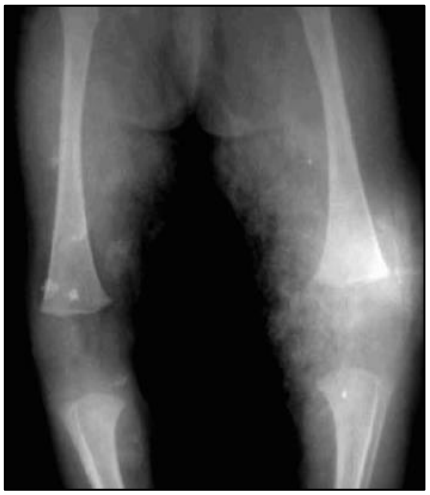
1- Neonatal screening:(Tyroid function)

• This is a major advance in early diagnosis of neonatal hypothyroidism. A drop of blood obtained by heel prick at 3rd -7th day of life is placed on filter paper and sent to a central laboratory. A serum TSH more than 20 micro units I ml (uIU I ml) or T4 less than 6 microgram I dl (ug I 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 *I* dl) and increased TSH (normal up to 6 uIU *I* ml).

3- Radiological examination:



- ***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.
- ***Skull***: large fontanel and wide sutures, Wormian (intra sutural) bones are common.
- ***ECG*** may show low voltage P, QRS and T waves.
- ***Scintigraphic (Isotope) study***: using 1251 or technetium 99Tc can differentiate between aplasia, ectopic thyroid (abnormal location) and defects in thyroid synthesis.

Differential Diagnosis:

1. During the first 2 months of life:

- Causes of prolonged neonatal jaundice.
- Causes of constipation.
- Causes of edema or sclerema.
- Causes of hypothermia.

2. Later:

- 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- 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 (ELtroxin ®)

- ***Dose:***

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	

- The above doses should maintain serum T4 level at reference range according to the age, and TSH below 5 uIU *I* ml, and should give normal bone age.

- ***Transient hypothyroidism:***

- In infants with endemic iodine deficiency or where their mothers ingested antithyroid 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.

- ***The response to treatment can be evaluated by:***

- Clinical assessment:

-GIT: constipation or diarrhea,

-Pulse: Tachycardia or bradycardia

-Appetite,

-Growth rate.

- Investigations:

-Serum T4 level at reference range according to the age,

-TSH below 5 uIU *I* ml,

-Should give normal bone age.

- ***Follow up of the treatment is done by:***

- Clinical assessment:

L –thhroxine overdoses ≥ diahrea ,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

- ***L-thyroxine overdoses:***

Manifests by diarrhea, fever, tachycardia, excessive sweating, irritability, and increased appetite

II. *Diabetes Mellitus*

Case 3

7y old Egyptian boy, presented to the emergency room (ER), with two week history of polyuria, polydipsia & nocturia that waked him up to 6 times per night and weight loss. He also had palpitations, non-bilious vomiting, with generalized abdominal pain. Unfortunately, his family has not brought him till lately, when his symptoms were deteriorating with altered level of consciousness (Glasgow coma scale (GCS) of 13/15) with changes in sensorium and cognitive functions were all present at the time of presentation.

His initial examination revealed severely dehydrated with Kussmaul breathing. Vital signs were the temperature of 36.8°C, heart rate of 124 beats/min, low blood pressure of 70/40, respiratory rate of 30/min with peripheral oxygen saturation of 98%. His weight was 19 kg (10%), and her height was 123 cm (50%-75%).BMI:13(less than 3rd centile).

	Results	References
Urine analysis	Glycosuria and ketonuria and Sp G: 1.030	free
Blood glucose	676	< 200 mg/dl
PH	6.9	7.35-7.45
Co_2	22	35-45 mmHg
Hco^3	2.3	22-26 mEq/l
Corrected Na	134	135-145 mEq/l
K	4.5	3.5-5.5 mEq/l
HbA1c	9.4	< 6.5 %

What is the most likely diagnosis?

A case of diabetes mellitus complicated with diabetic acidosis.

What is cardinal clinical presentation?

Polydipsia, polyuria, polyphagia and weight loss.

What investigations do we need to diagnosis of the condition in previous two weeks before deteriorations?

1- Fasting glycosuria with or without ketonuria.

2- Fasting plasma glucose over 126 mg/dl.

3- Random sugar over 200 mg/dl in the presence of classic symptoms of diabetes.

4- Oral glucose tolerance test: plasma glucose after an oral glucose load is > 200 mg/dl.

5- Serum insulin and peptide C levels are reduced.

6- Glycosylated hemoglobin (HbA1 c) > 6.5 %.

What are the complications of disease?

1. Diabetic ketoacidosis.
2. Hypoglycemic coma.
3. Hyperosmolar hyperglycemic state (HHS).
4. Infections.
5. Stunting of growth and delayed puberty.
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.

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).

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:

Type I diabetes mellitus results from gradual immunologic damage of the B- cells of the pancreatic islets which requires gene predisposition (HLA) and environmental factors (Viral infections, chemicals, diet, seasonality, and geographic locations).

Clinical Manifestations:

1. ***Asymptomatic:*** few cases are detected by routine urine analysis.
2. ***Mild:*** presents with enuresis or failure to gain weight.
3. ***Moderate***: presents with polydipsia, polyuria, polyphagia, and weight loss.
4. ***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: plasma glucose after an oral glucose load is > 200 mg/dL.

5- Serum insulin and peptide C levels are reduced.

6- Glycosylated hemoglobin (HbA1 c) 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 outpatient 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,

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.

Diabetic Ketoacidosis (DKA)

Definition:

- It is a state of academia induced by excess production of ketoacids (acetoacetic acid and beta butyric acids) due to insulin deficiency.

This condition is characterized by:

1- Blood glucose > 200 mg/dl + Glycosuria.

2- Increased Ketones in blood ± ketonuria.

3- Acidosis (Ph<7.3), HC03 < 15 mEq/L.

The pathophysiological mechanisms of Ketoacidosis are due to:

1- Insulin deficiency.

2- Increase counter regulatory hormones (glucagon, cortisol, catecholamines & growth hormone).

3- Precipitating factors:

- Stress (physical or psychological), or Infection.

Clinical features of ketoacidosis:

1- Polyuria, polydipsia, dehydration + polyphagia.

2- Vomiting, abdominal pain (may be severe).

3- Altered consciousness: drowsiness, 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. Glucose (blood & urine) & acetone (urine only).
2. Complete urine analysis.
3. Serum bicarbonate, PH, blood gases.
4. Serum electrolytes, ca, P, creatinine, blood urea.
5. Complete blood picture.
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. 0xygen for cyanotic or shocked patients and/or with Pa02 < 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:

A. Resuscitation fluids:

- For patients who are dehydrated but not in shock, we should begin immediately with 0.9% saline. The volume administered typically is 10 mL/kg infused over 30 to 60 minutes; and a second fluid bolus may be needed to ensure adequate tissue perfusion.
- In the patient with DKA in shock, rapidly restore circulatory volume with isotonic saline in 20 mL/kg boluses infused as quickly as possible through a large bore cannula with reassessment of circulatory status after each bolus.

B. Subsequent fluid management:

- Fluid therapy should begin with deficit replacement plus maintenance fluid requirements over 48 hours.
- Subsequent fluid management can be accomplished with 0.45% to 0.9% saline.
- Shift to glucose 5% + saline (1:1) when blood glucose drops to < 300 mg/dl or If BG falls very rapidly (>90mg/dL/h).
- Potassium is added only when urine flow is satisfactory.
- Oral fluids (carbohydrates & electrolyte mixtures or other liquid diets) can usually be started cautiously within 24 hours.

IV- Insulin therapy:

- Start insulin infusion at least 1 hour after starting fluid replacement therapy; that is, after the patient has received initial volume expansion.
- Correction of insulin deficiency.
- Dose: 0.05 to 0.1 unit/kg/h.
- Route of administration IV.

- An IV bolus should not be used at the start of therapy; it is unnecessary, may increase the risk of cerebral edema, can precipitate shock by rapidly decreasing osmotic pressure, and can exacerbate hypokalaemia.
- In circumstances where continuous IV administration is not possible and in patients with uncomplicated DKA, SC rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion, but, ideally, should not be used in patients whose peripheral circulation is impaired.
- Subcutaneous administration of short-acting insulin (regular) every 4 hours is also a safe and effective alternative to IV insulin infusion in children with pH ≥ 7.1.

V- Bicarbonate therapy:

- Bicarbonate administration may be beneficial in the patient with life-threatening hyperkalemia or unusually severe acidosis (pH <6.9) that has compromised cardiac contractility.
- Dose: 1 to 2 mmol/kg over 60 minutes by IV drip.

VI- Monitoring schedule:

A. 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.

B. Next 12 hours: Laboratory studies as indicated by clinical and biochemical Progress.

VII- Introduction of Oral Fluids and Transition to Sc Insulin Injections:

- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, a dose of basal (long- or intermediate-acting) insulin should be administered in addition to rapid- or short-acting insulin.
- To prevent rebound hyperglycemia the first SC injection should be given 15 to 30 minutes (with rapid-acting insulin) or 1 to 2 hours (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed.
- After transitioning to SC insulin, frequent blood glucose monitoring is required to avoid marked hyperglycemia and hypoglycemia.

III. SHORT STATURE

Case 4

An eight-year, three-month-old girl was referred for slowed growth. Her parents reported three years of growth arrest, during which she continued to wear the same size of clothing and fell well below the third percentile for height. Previous height plotting along the 50th percentile.

Review of systems was negative for headaches, vomiting or vision changes. There was no fatigue, cold intolerance, constipation, or skin or hair changes. Appetite and weight were normal. There were no academic concerns. Breast development began at eight years of age with scant pubic hair that developed shortly thereafter.

Medical history and functional inquiry were noncontributory. She had been born at term weighing 3.7 kg. Parental pubertal timing was within normal limits. Family history was negative for short stature, endocrine, or autoimmune conditions.

Examination revealed a nondysmorphic, proportionate child who appeared much younger than her chronological age. Height was 115 cm below the third percentile, weight was at the third percentile and body mass index at the 25th percentile. Upper: lower segment ratio, arm span, vital signs, optic fundi, and visual fields were normal. There was no thyromegaly, scoliosis.

What is definition of 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).

What are the normal variants of short stature?

		Genetic (familial) Short stature	Constitutional growth delay
Birth length	Birth length	Baby is born small	Baby is born normal in size but grows slowly, so his length is less than 5th percentile over the first 2 years
Maturation	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	Family	Short parents	History of delayed puberty.
Final height	Final height	Becomes a short adult	Normal adult height and sexual development

What are the endocrinal causes of short stature?

Endocrine disease: may be

A- Hyperhormonal:

1- Cortisol excess: Cushing syndrome, and prolonged corticosteroid therapy.

2- 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:

1- Hypopituitarism,

2- Hypothyroidism (congenital or acquired),

3- Type 1 diabetes mellitus.

How do we investigate growth hormone secretion?

Investigation of growth hormone secretion:

- Performed only in short children with slow growth velocity in absence of systemic disease.
- Physiological test: exercise, sleep.
- Pharmacological test: clonidine, glucagon. L dopa, insulin.

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).

1- *Normal variants of short stature:*

- These constitute more than 90 % of cases of short stature.

		Genetic (familial) Short stature	Constitutional growth delay
Birth length	Birth length	Baby is born small	Baby is born normal in size but grows slowly, so his length is less than 5th percentile over the first 2 years
Maturation	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	Family	Short parents	History of delayed puberty.
Final height	Final height	Becomes a short adult	Normal adult height and sexual development

2- Chromosomal anomalies: e.g., Down, Turner, or Laurence-Moon-Biedl syndrome.

3- Intrauterine growth retardation: due to Infections, toxins, or drugs during pregnancy.

4- Under nutrition: PEM, vitamin D deficiency rickets, and mineral deficiencies e.g., zinc, iron.

5- Chronic system disease: Gastrointestinal, congenital heart, renal, pulmonary, chronic infections, collagen disease, liver disease, mental retardation, blood disease.

6- Endocrine disease:

a. Hyperhormonal:

- *Cortisol excess:* Cushing syndrome, and prolonged corticosteroid therapy.
- *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:

- *Hypopituitarism,*
- *Hypothyroidism* (congenital or acquired),
- *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 *I* height, upper /lower segment, span, head circumference mid-arm circumference, subcutaneous fat thickness (skin fold thickness):

A- Proportionate short stature:

• Normal variants.

• Endocrine causes.

• Most causes of growth failure in infancy.

B- Disproportionate short stature:

• With short limbs e.g., Skeletal dysplasia, and osteogenesis imperfecta.

• With short trunk: in Mucopolysaccharidosis, and rickets.

4. *Physical examination:(Examination of all body system)*

- Recognition of special features of specific endocrine diseases (e.g., cretinism), or dysmorphic syndromes (e.g., Down syndrome, Turner syndrome, achondroplasia).
- Measurement of blood pressure (increased in renal disease and decreased in congenital adrenal hyperplasia).
- *Neck*: webbed neck (Turner syndrome), presence of goiter.

- *Heart*: congenital heart disease (e.g., large VSD, Fallot's tetralogy).
- *Chest*: bronchiectasis, asthma.
- *Abdomen*: hepatomegaly (bilharziasis, chronic hepatitis, glycogen storage diseases).
- *CNS*: cerebral palsy, mental retardation.
- 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. *Laboratory investigations:*

- Karyotyping: for the possibility of chromosomal disease; any short female needs karyotyping for exclusion of turner syndrome.
- Thyroid functions (T3, T4, TSH).
- Serum Ca, Ph & alkaline phosphatase: for rickets and hypoparathyroidism.
- Serum albumin, AST & ALT: to exclude malnutrition and hepatic disease.
- Serum creatinine and electrolytes to exclude renal disease.
- ESR: increased in chronic diseases e.g., T.B, chronic inflammatory bowel diseases.
- Sweat chloride test: to exclude cystic fibrosis.
- Serum antigliadin antibodies to exclude celiac disease.

7. 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.

8. Echocardiography: for suspected heart disease.

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.

IV. *Puberty*

Case 5

A 15-year-old girl presented for routine health supervision care. She was doing well overall. She complained of intermittent constipation. When asked about menarche, her mother stated that the patient has not yet had a period and notes that she has had minimal breast development.

There was no known family history of menstrual abnormalities, infertility, polycystic ovary syndrome, premature ovarian failure, thyroid disease, or other autoimmune disease. Her mother reported that both parents had normal pubertal timing, her mother had menarche at age 12 years. On physical examination, she was not dysmorphic. Puberty Tanner stage revealed Breast 1, Pubic hair 2, Axillary hair 1. Other systemic examination was unremarkable. Bone age was of 10 years. Pelvic ultrasound demonstrated infantile uterus with no visible endometrium and small ovaries.

What is the diagnosis?

A case of delayed puberty.

What is the definition of Normal puberty?

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 13 years of age in girls and between 9 and 14 years of age in boys.

What are the Factors 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: obese girls tend to have early menarche. The condition is variable in boys.

6- Genetic factors: familial.

What are 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 (45, XO), and Klinefelter syndroms (47, XXY).

7- Miscellaneous: anorexia nervosa, extreme athletic persons, idiopathic, malnutrition.

Delayed Puberty

Definition

- In girls, delayed puberty is defined as lack of any breast development by 13 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 (45, XO), and Klinefelter syndromes (47, XXY).

7- Miscellaneous: anorexia nervosa, extreme athletic persons, idiopathic, malnutrition.

Practice Questions (Choose one correct answer)

1-Neonatal screening of congenital hypothyroidism depends mainly on:

a) A serum TSH more than 5 uIU / ml
b) A serum TSH more than 10 uIU / ml
c) A serum TSH more than 15 uIU / ml
d) A serum TSH more than 20 uIU / ml

2-Transient hypothyroidism may be due to:

a) Thyroid gland dysgenesis (Aplasia, hypoplasia, or an ectopic gland)
b) Endemic iodide deficiency.
c) Thyroid dyshormonogenesis.
d) Disease in Pituitary gland

3-features of type 1 diabetes mellitus:

a) Onset is usually > 25 Yrs. old
b) Not HLA associated
c) Autoimmune 8 cell destruction
d) Insulin is normal or high

4-For diagnosis DM, plasma glucose after an oral glucose load is.:

a) 100 mg/dL
b) 126 mg/dL
c) 140 mg/dL
d) 200 mg/dL

5-The child is considered short when his or her stature (height or length) is below:

a) The 50^{th} percentile
b) The 25^{th} percentile
c) The 10^{th} percentile
d) The 5^{th} percentile

6- ***Birth length in cases of Familial Short Stature is***:

a) Average
b) Tall
c) Short
d) Unknown

7-Normal puberty begins in boys:

a) Between 7 and 12 years of age
b) Between 8 and 13 years of age
c) Between 9 and 14 years of age
d) Between 10 and 15 years of age.

Chapter 5

Genetics and Dysmorphology

Learning objectives:

At the end of this course the student should

1- Be aware of the basic genetic information

2- Recognize the types of genetic disorders

3-Know the common dysmorphic features and the approach to dysmorphic child

4- Identify teratogens and mutagens

Contents:

1) Introduction
2) Genetic abnormalities:
   a. Single gene disorder
   b. Chromosomal Abnormalities
   c. Multi-factorial inheritance
3) Dysmorphology and congenital malformation
4) Malformation Syndromes: Down syndrome
5) Teratogenesis and mutagenesis
6) Genetic counseling
7) Genetic screening

Introduction

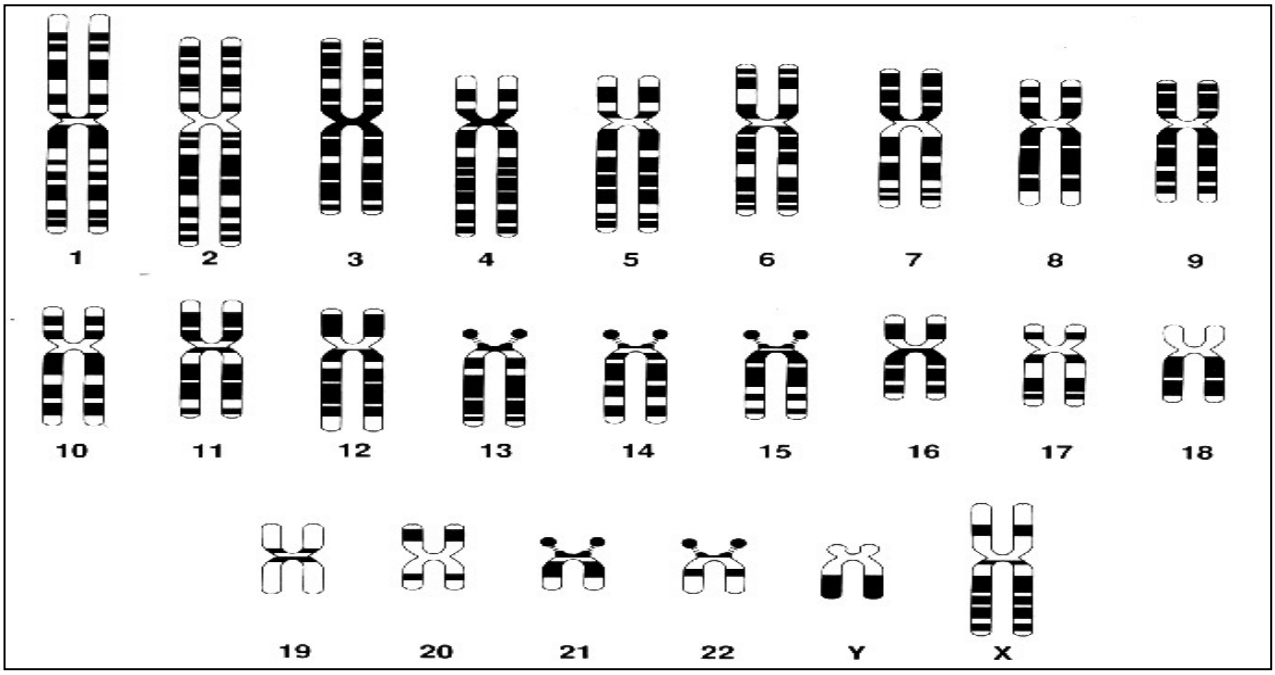
1- Somatic cell: In humans, the normal cell nucleus contains 46 chromosomes or 23 pairs (diploid number). One of each chromosome is paternal in origin (from father) and the other is maternal in origin (from mother). These pairs are divided into:

- 22 pairs called autosomes.
- One pair called sex chromosome.

A male has 44 autosomes and XY sex chromosomes. A female has 44 autosomes and XX sex chromosomes. In female, one X chromosome is an inactive which is called Barr body or sex chromatin.

2- Germ cell (gamete cells): (ova and sperms) contains 23 chromosomes (haploid number). All the ova contain one type of sex chromosome (X), while half of the sperms contains X and the other half contains Y chromosomes.

The normal human karyotype: It consists of 23 pairs of chromosomes: 22 homologous pairs of autosomes and one pair of sex chromosomes XX in the female, XY in the male.



Normal human karyotyping

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).

Chromosome Classification: *Chromosomes are classified according to:*

1. **Length of chromosome:** 7 groups (A-F) according to their length:

   a. Group A: contains chromosome number 1-3 (the longest).

   b. Group D: contains acrocentric chromosomes number 13-15 (medium-sized)

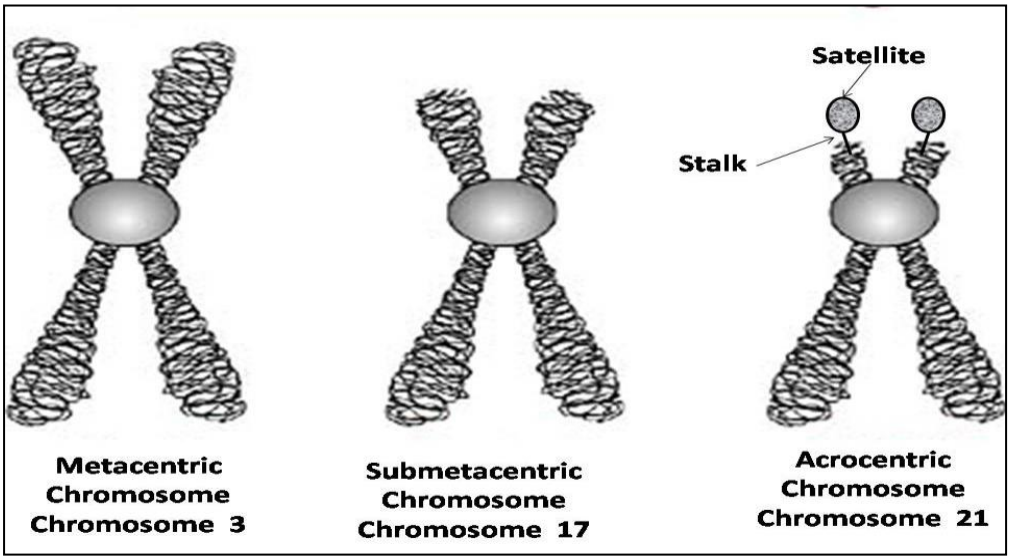
   c. Group G: contains acrocentric chromosomes, (21, 22) and Y chromosome (the shortest).

2. **Position of centromere:** classified into three groups:

   a. Metacentric chromosomes: The centromere lies near the middle of the chromosome where p = q, such as number 1, 3, 16, 19 and 20.

   b. Submetacentric chromosome: The centromere lies closer to one end than the other. P arm is shorter than q arm such as number 2, 4, 12, 17, 18 and X chromosomes.

   c. Acrocentric chromosome: The short arm p is very small, and the centromere lies near one end such as chromosome number 13, 14, 15, 21, 22 and Y chromosome. These chromosomes except the Y have small chromatin masses known as satellites attached to their short arms by narrow stalk and contain genes for rRNA formation.



Chromosome classification according to position of centromere

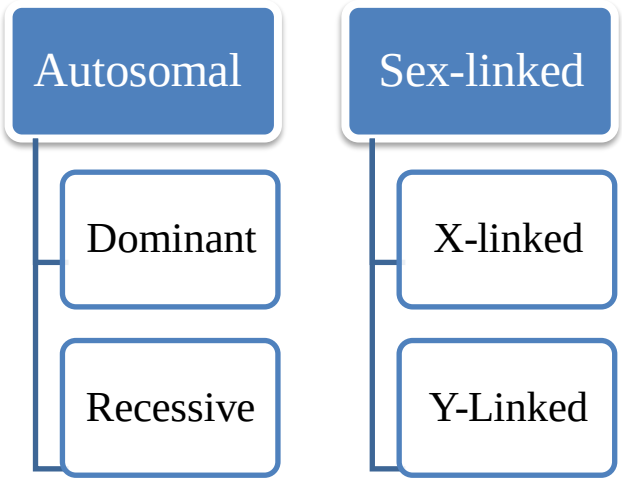
Genetic diseases

Classification of genetic diseases:

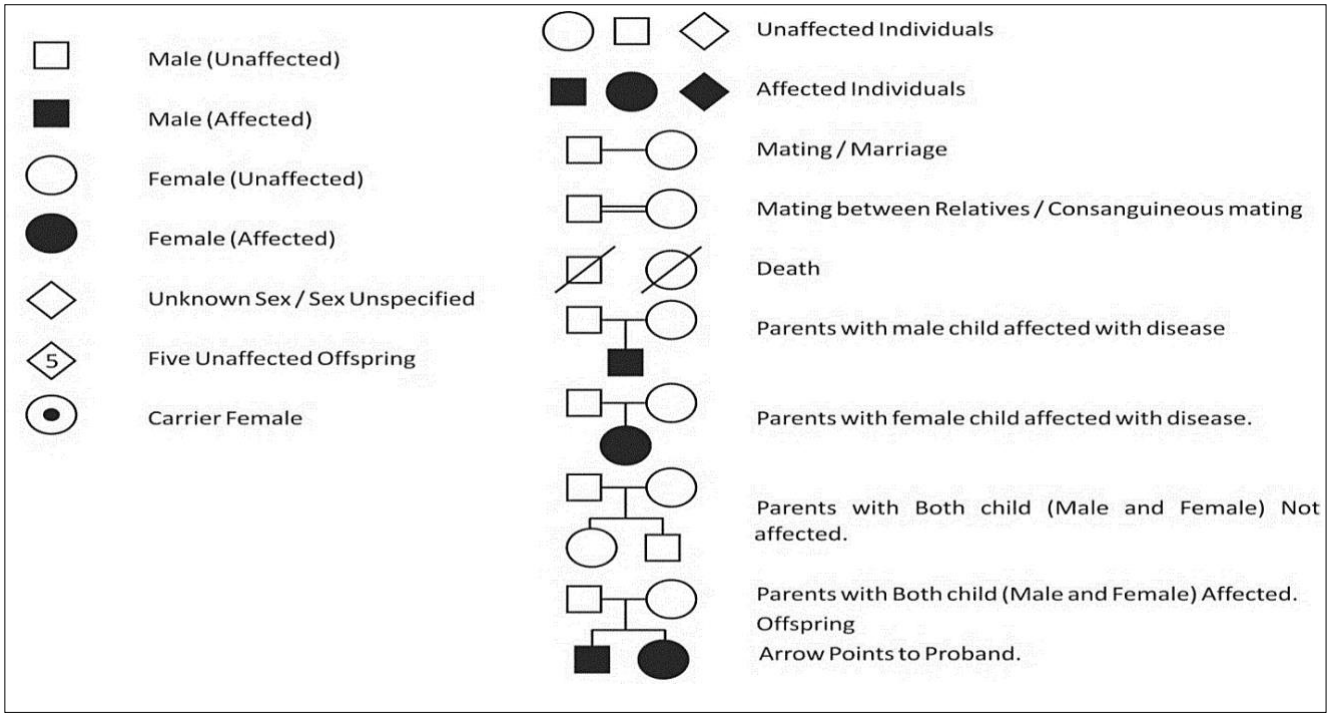
1- Single gene disorders
2- Chromosomal disorders
3- Multifactorial disorders

1-<u>Single gene disorders</u>: Caused by mutations of specific genes in the human genetic material. Disease is said to be autosomal, or sex linked depending on the position of the mutant gene on autosome or sex chromosome.

- ***Autosomal Recessive:*** The disease is said to be recessive when one mutant gene cannot express the *disease.*
- ***Autosomal Dominant:*** The disease is said to be dominant when only one mutant gene can express the disease.



Types of single gene disorders



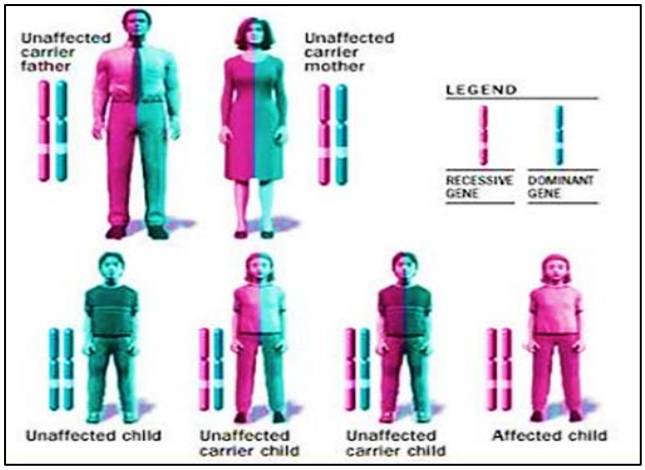
I - Autosomal recessive inheritance: It has the following characteristics:

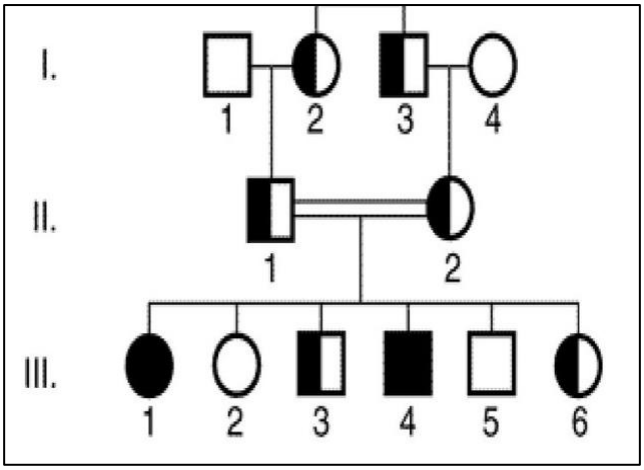
- ***The parents***:

Phenotype: usually normal.

- ***Genotype:***

They are 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:*** Usually "horizontal" i.e., affected individual are in the same generations.
- ***Examples:*** Thalassemia, sickle cell disease, and glycogen storage disease.

Pedigree for autosomal recessive disorder

II-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.

▪ ***Examples:*** Hereditary spherocytosis, Huntington chorea, and achondroplasia.

III- X- linked recessive inheritance: It has the following characteristics:

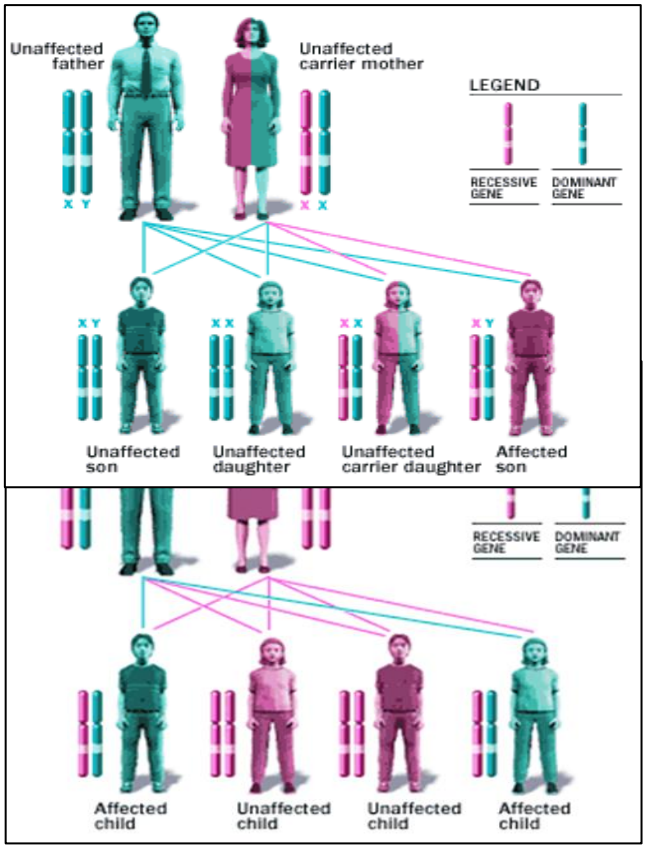
▪ ***The parents:*** The mother is genotypic carrier and phenotypic normal. The father is genotypic and phenotypic normal. There is no relation between consanguinity and this disease.

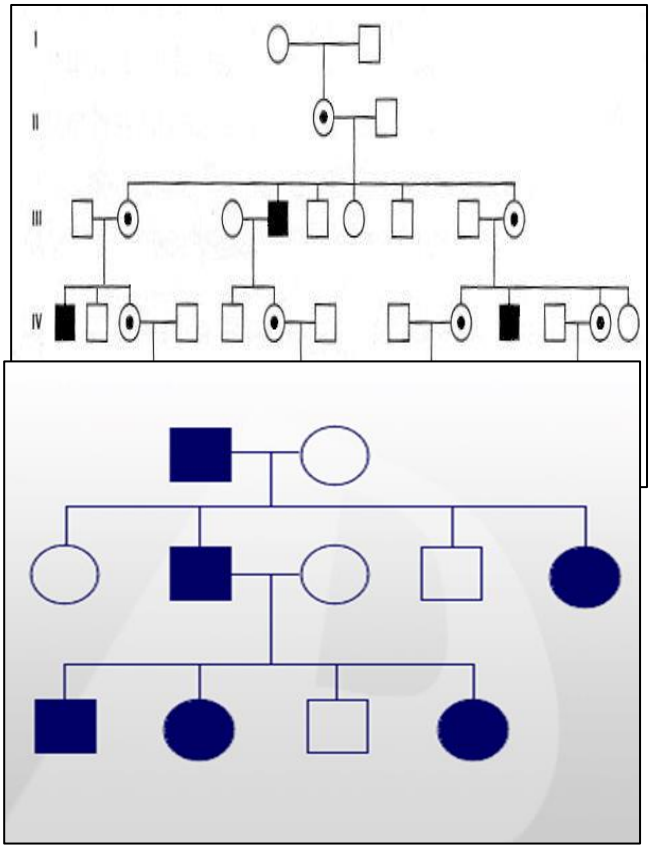
▪ ***The risk of occurrence and recurrence:*** Fifty % of a carrier mother's sons will be diseased and 50% of a carrier mother's daughters will be carriers.

▪ ***The pedigree:*** It tends to be "oblique" i.e., the affected individuals usually are carrier mother's broth

Pedigree for autosomal dominant disorder

▪ ***Examples:*** Glucose - 6 - phosphate dehydrogenase deficiency, hemophilia A and B, and Duchenne muscular dystrophy.





Pedigree for X-linked recessive disorder

IV - Sex -Linked Dominant Inheritance

It is a rare pattern. Its example is vitamin D-resistant rickets.

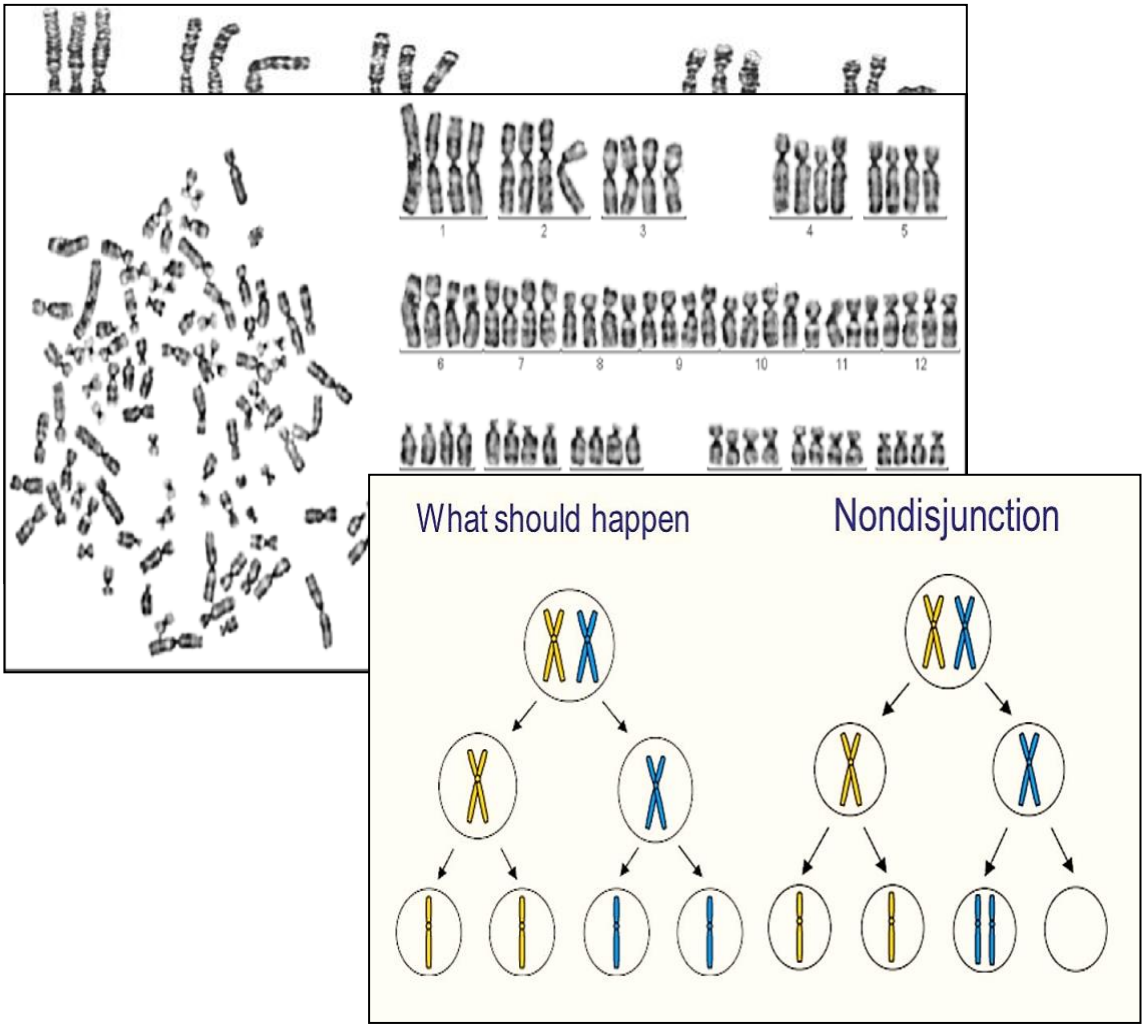
2- Chromosomal abnormalities:

- ***Common causes are:***
  - Late maternal age at the time pregnancy (leads to chromosomal non-disjunction)
  - Exposure to teratogens: e.g., Radiation, Chemicals
- ***Types:***
  - Numerical abnormalities
  - Structural abnormalities

A. Numerical abnormalities

1. Polyploidy: multiple of haploid number (23) of chromosomes, but greater than 2n like:

- ***Triploidy* (3n)** = 69 chromosomes with XXX or XXY sex chromosomes.
- ***Tetraploidy* (4n)** = 92 chromosomes with XXXX or XXYY sex chromosomes.



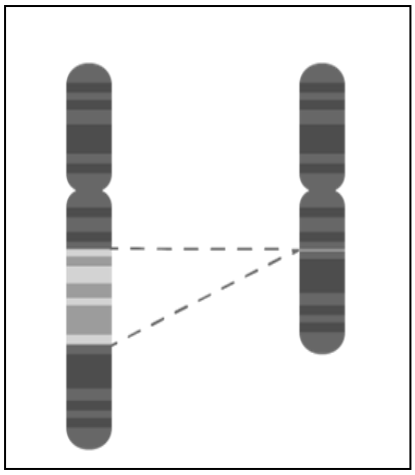
Tetraploidy

2. Aneuploidy: chromosomes number is not the exact multiple of haploid (n) number**,** like

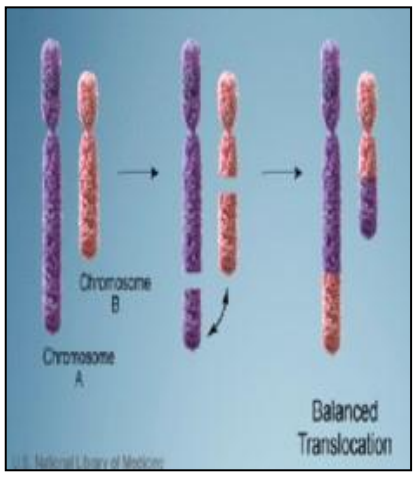
- ***Trisomy 21:*** presence of an extra copy of a single chromosome as in Down syndrome, where there are three copies of chromosome 21 instead of two (47, XY, +21).
- ***Monosomy 45:*** absence of one sex chromosome as in Turner syndrome (45, XO)

B. Structural abnormalities: means abnormality in the structure of the chromosomes.

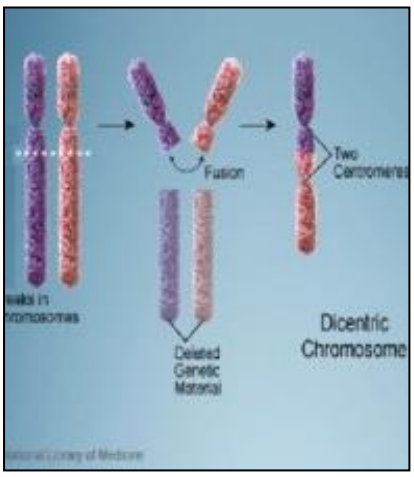
Deletion: portion of chromosome is missing e.g., Cri du chat syndrome {46, (5p-)} which means partial chromosome deletion of chromosome 5.



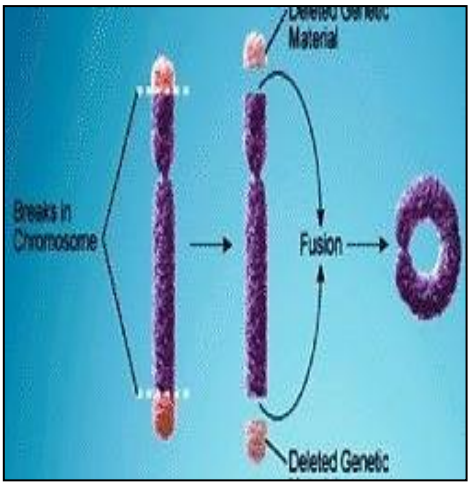
Deletion



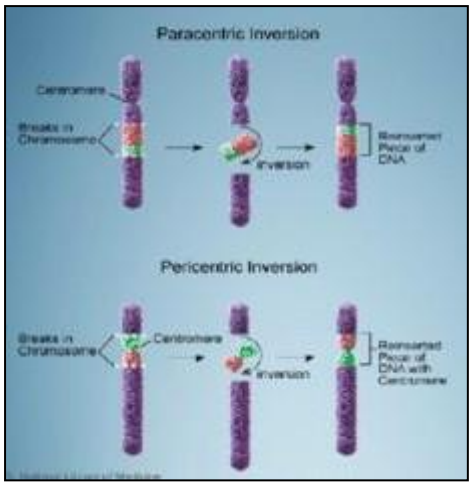
Reciprocal translocation



Robertsonian translocation



Ring Chromosome



Inversion

3- Multifactorial Inheritance:

- Involves the interaction of diverse environmental factors with susceptibility determined by additive effect of many genes e.g., congenital dislocation of hip joint, cleft lip and cleft palate.
- Some disorders have a sex predilection.
- 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.
- The risk of recurrence may be greater when the disorder is more severe.
- ***Examples:*** allergic diseases, pyloric stenosis, and developmental dislocation of the hips.

Dysmorphology and congenital malformations

Definition:

It implies study of human congenital defects and abnormalities of body structure that originate before birth.

The term ***"dysmorphic"*** is used to describe individuals whose physical features are not usually found in other individuals with the same age or ethnic background. "**Dys**" (Greek) = disordered or abnormal and "**Morph**" = shape.

Epidemiology:

Around one in 40 or 2.5 % of all newborns have a malformation at birth.

Etiology:

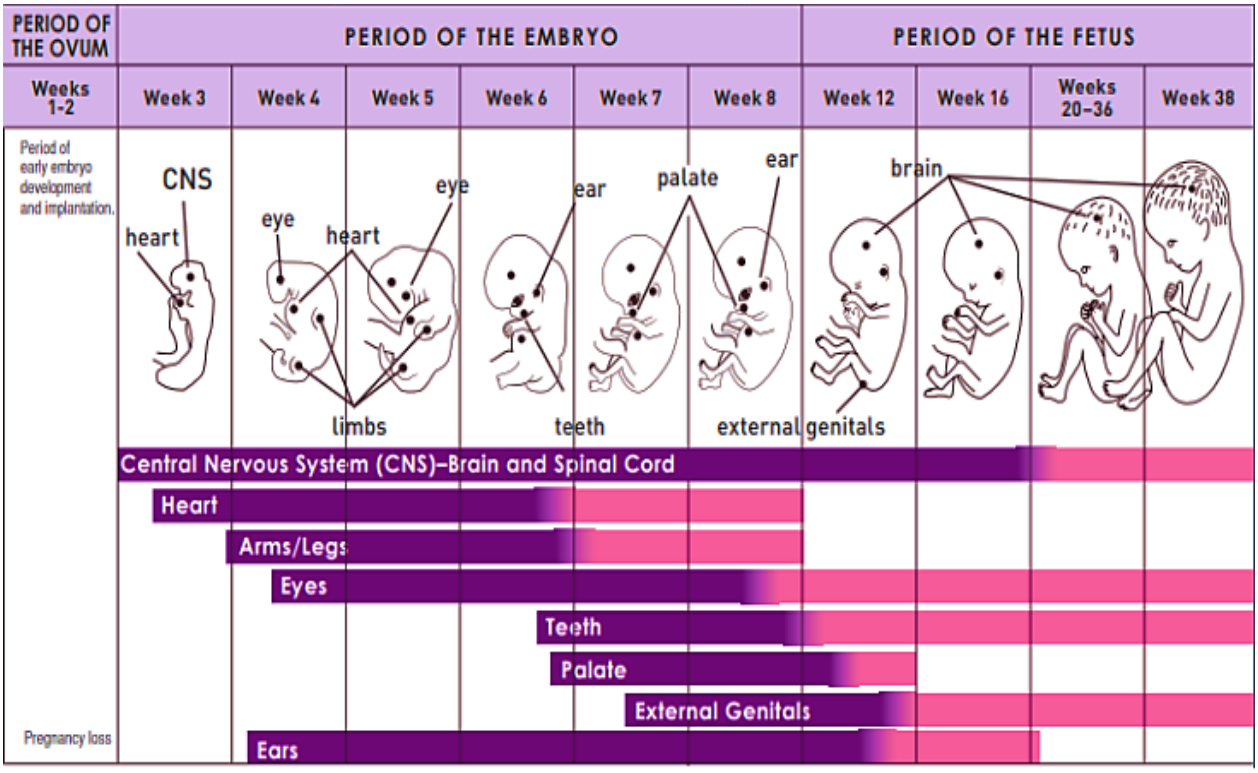
Malformations arise from abnormal embryogenesis due to:

1- <u>Single gene defect.</u>

2- <u>Chromosomal abnormalities.</u>

3- <u>Multifactorial (polygenic):</u> Combination of genetic and environmental factors e.g., diabetes may lead to birth defects such as neural tube defects.

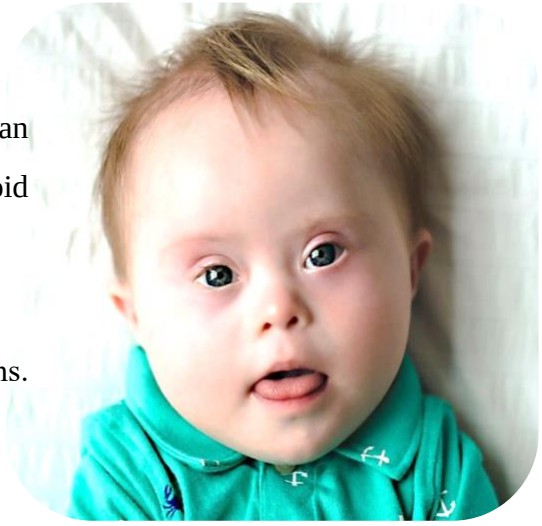
4- <u>Environmental causes (teratogenesis)</u>



Critical periods for birth defects in the human development

Malformation Syndromes

Down Syndrome



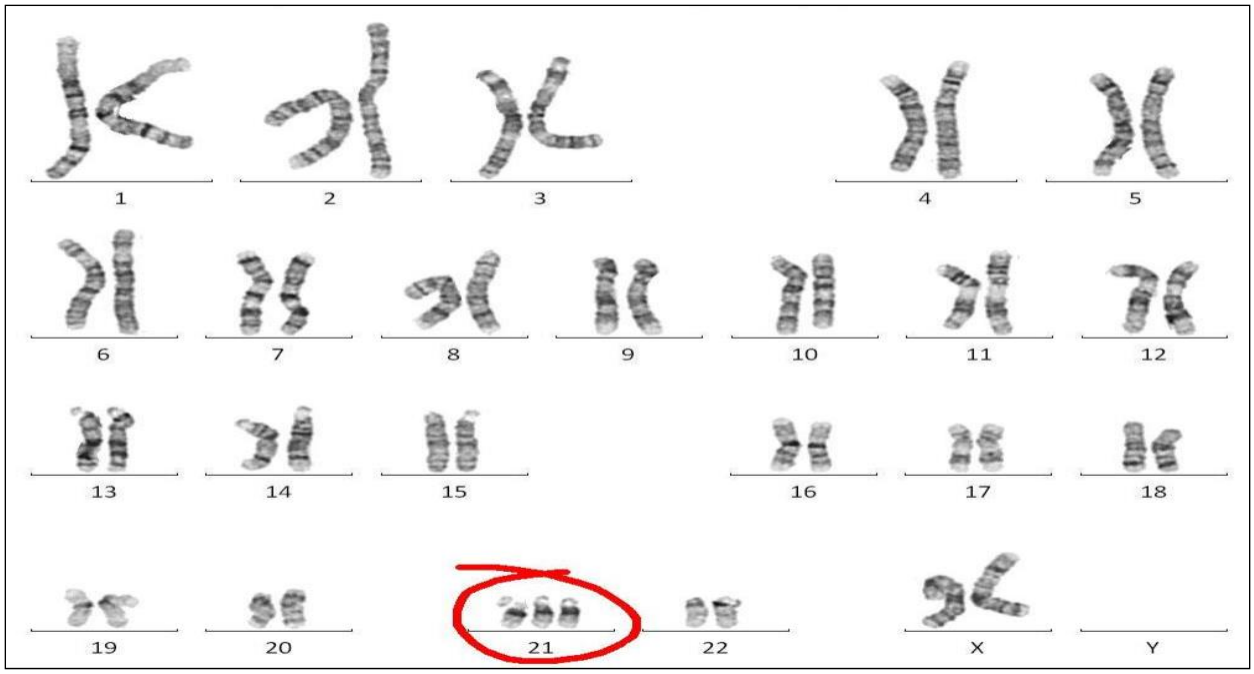
Down syndrome is the most common pattern of human malformation which is characterised by hypotonia, mongoloid facies and intellectual disability.

Incidence:

- Down syndrome occurs in approximately 1 in 600 births.
- Male: female ratio at birth is 1.24: 1.0.

Genetics:

- ***Nondisjunction type (95%)*** All the cells show an additional No. 21 chromosome, i.e., 47, XX, +21. This type is resulting from meiotic non-disjunction. risk of recurrence 1–2% and then increases with advancing maternal age.
- ***Translocation type (4%)*** 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). Most are denovo but may be inherited from balanced translocation carrier parent . Karyotyping of the parents should be obtained.
- ***Mosaic type(1%)*** With mosciacism due to mitotic nondisjunction



Karyotyping of Down syndrome

Clinical Features:

- Upward slanting palpebral fissures; speckling of iris (Brushfield spots); inner epicanthal folds, small low set ears.
- Short stature, mouth open with tongue protrusion; mild microcephaly, short neck, flat occiput, short metacarpals and phalanges; single palmar crease.
- Hypotonia
- Hearing loss (sensorineural, conductive, and mixed)
- Primary gonadal deficiency
- ***Cardiac anomaly*** : endocardial cushion defect > VSD > PDA, ASD; also MVP
- ***GI anomalies:*** duodenal atresia, Hirschprung
- Atlanto-axial instability
- Hypothyroidism
- Acute lymphocytic leukemia (but acute myeloblastic leukemia if in first 3 years of life)
- Intellectual disability

Variable Natural history

- Major cause for early mortality is congenital heart disease
- Muscle tone improves with age
- Rate of development slows with age
- Early onset of Alzheimer disease

Investigations:

1- Cytogenetic study:

- Chromosomal study should be done for confirmation of the diagnosis and detection of the genotype for accurate genetic counseling.

2- Laboratory studies:

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

3- Imaging studies:

- **Echo-Doppler** evaluation is mandatory for all cases even if there are no clinical cardiac abnormalities
- Screening **lateral cervical radiograph** has been recommended at about age 6 years to diagnose unstable atlanto-axial joint.

Genetic counseling:

- **Preconception:**
  - You should tell the mother with advanced maternal age that there is a risk of trisomy and if she got pregnant, she should be followed during pregnancy.
- **Prenatal:**
  - Pregnant women with the risk of having DS (old age, translocation carrier) may get benefit from prenatal diagnosis.
  - Prenatal diagnosis can be achieved by:
    1. ***Screening tests (Triple test)*** >>> Maternal alpha-fetoprotein, unconjugated estriol and human chorionic gonadotropin.
    2. ***Confirmation test:*** amniocentesis or chorionic - villus sampling for chromosomal analysis.
    3. **A**fter definite prenatal diagnosis **medical abortion** may be indicated in some countries
- **Postnatal:**
  - Family with DS must be aware of the nature of the disease and recurrence risk which depends upon cytogenetic analysis of infant and parents.

Recurrence risk:

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

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.

Teratogenesis is concerned with the following:

- The relationship between the anomalies in a child and teratogenic exposure
- The risk of anomalies for a child of a woman who has been exposed to a teratogen
- 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.

1. 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.

2. 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.

3. 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 and fall in several groups:

1. Maternal metabolic imbalance: as children of women with insulin-dependent diabetes mellitus has 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:

• Hyperthermia, regardless of cause, that produces sustained elevation of maternal body temperature to levels substantially above normal (e.g., 40 ºC)

• Lead exposure.

5. *Drugs of abuse*

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

▪ **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.

▪ **Medications:**

– **Thalidomide** exposure in the first trimester of gestation may produce limb reduction defects, facial malformations, and other congenital anomalies.

– **Aminopterin and other cytotoxic drugs** kill rapidly growing cells in the fetus and cause growth deficiency and a variety of other anomalies.

– 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.

- 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.
- Teratogens affect the development of a tissue, organ, or structure. In contrast, a mutation always affects a single cell.

1- If this single cell is a germ cell, the mutation may be transmitted to subsequent generations.

2- 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.

3- 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.

Genetic counseling

Overview:

Genetic counseling is a communication process work with individuals, couples, or families, who have an increased risk of developing or transmitting a genetic disease. An individual who seeks genetic counseling is known as consultand.

Genetic counseling is the process of:

- Checking family medical history and medical records
- Ordering genetic tests
- Evaluating the results of these tests and records
- Helping parents understand:

a. The medical diagnosis and its consequences as prognosis and possible treatment.

b. Modes of inheritance of the disorder and the risk of developing and / or transmitting it.

c. The choices or options available for dealing with the risk.

Indications of Genetic Counseling:

- Advanced maternal age (prenatal diagnosis is offered to pregnant woman over 35 years).
- Known or suspected hereditary condition in the family.
- A fetus with birth defects

- A child with mental retardation.
- Recurrent spontaneous abortions.
- Exposure to known or suspected teratogen.
- Consanguinity.

Information needed by the counselor include:

- ***Pregnancy history***, including current and past pregnancies. *The counselor may ask about:*
  - Births and miscarriages
  - Terminations or abortions
  - Pregnancy complications
- ***Medical and health history:***
  - Major illnesses
  - Chronic conditions such as diabetes or heart disease
  - Early or unexplained deaths.
  - Medications you are taking
- ***The health history of other members of couple's family,*** including:
  - Parents, siblings, aunts, uncles, grandparents, and any relatives with genetic disorders

Steps in Genetic Counseling:

- ***Diagnosis:***
  - The most important step in any genetic counseling is establishing the diagnosis.
  - If this is incorrect, then inappropriate and totally misleading information will be given, which may lead to tragic consequences.
- ***Risk Assessment: The disorder may be:***
  - *Single gene disorder:* based on using the knowledge of applied probability theory.
  - *Chromosomal abnormalities:* e.g., Down syndrome.
  - Multifactorial disorders: These are based on observations derived from family studies rather than theoretical calculations.
  - *Environmental etiology:* No risk of recurrence.
- ***Understanding the options:***
  - When faced a distinct recurrence risk the reproductive options of the couple may include methods of contraception, prenatal diagnosis with or without termination of pregnancy.

- ***Choosing a course of action:***
  - The couple is encouraged to choose the best course for themselves in the light of recurrence risk, the expected burden (psychological, social, economic), the goals of the family and their religions and ethical background.
- ***Long-term contact and support:***
  - Follow–up counseling, by the medical genetics team may be indicated to help the family to deal with the condition effectively.

Genetic screening

Definition:

Genetic screening is a systematic program/testing offered to a specified population of asymptomatic individuals to search for persons that possess genotypes which associated with a disease, predispose to a disease or may lead to a disease in their offspring for the purpose of disease prevention, early treatment, or family planning.

Genetic screening serves several objects:

1. **Management:** Screening can lead to therapy. Newborn screening aims at the earliest possible recognition of disorders in order to intervene.
2. **Genetic counseling***:* Screening can identify those individuals and couples whose pregnancies are at increased risk for producing offspring with serious genetic abnormalities.
3. **Epidemiology***:* Screening can be a source of epidemiological data regarding birth defects.

Criteria for introducing a population-based screening program:

1. **Disease:**
   - High incidence in target population.
   - Serious effect on health.
   - Treatable or preventable.
2. **Test:**
   - Non-invasive and easy to carry out.
   - Accurate and reliable.
   - Inexpensive.
3. **Program:**
   - Widespread with equitable availability.

- Voluntary participation.
- Acceptable to the target population.
- Full information and counseling provided.

Types of genetic screening programs/testing

1. **Preconception screening (before having children):** Involves screening for carriers or identifying couples in which both individuals are asymptomatic carriers of a recessive condition.
   - Cystic fibrosis
   - Fragile X syndrome
   - Blood disorders such as sickle cell disease
   - Spinal muscular atrophy
2. **Prenatal screening (during pregnancy):** identifies whether an unborn fetus has or is at risk of having a congenital condition.

   A- Maternal serum screening: to detect

   - Structural abnormalities: Neural tube defects: α-fetoprotein.
   - Chromosomal anomalies: Down syndrome: Triple test (α-fetoprotein, Estriol, and Beta-hCG).
   - Also discovers problems which primarily affect the health of the mother, like pregnancy-associated plasma protein-A to detect pre-eclampsia or glucose tolerance tests to diagnose gestational diabetes

   B- Ultrasonography: It is now standard practice to offer a detailed (fetal anomaly) scan to all pregnant women at 18 weeks gestation. The presence of chromosome abnormalities can be suspected by detection of an abnormality such as:

   - Cystic hygroma or fetal hydrops: Trisomy 13, 18, 21, Turner's syndrome.
   - Rocker bottom foot: Trisomy 18.

   B- ***Maternal blood screening*** can be done through prenatal cell-free DNA (cfDNA) screening where DNA from the mother and fetus is extracted from a maternal blood sample and screened. It can be used to screen for certain chromosomal disorders, including:

   - Down syndrome (trisomy 21)
   - Trisomy 18
   - Trisomy 13

3. **Neonatal screening (after birth):** Carried out shortly after the baby is born and identifies whether the newborn is at risk of developing a disease in childhood for which prevention or early treatment exists. In Egypt, neonatal screening program for hypothyroidism began in 2000.
   Now it is expanded to include phenylketonuria. (Blood spot screening of a drop of blood from baby's heel on paper card)
4. **Population carrier screening:** Widespread screening for carriers of autosomal recessive disorders in **high incidence populations** was first introduced for the hemoglobinopathies, and has been extended to several other disorders as:
   - Sickle cell anemia in African American populations (1/13)
   - Cystic fibrosis in Caucasian populations (1/25)

   Carrier detection can be supported by **genetic counseling** so that carrier couples will have been forewarned of the 1 in 4 risk that each of their children could be affected.

Advantages and disadvantages of genetic screening:

1. Advantages:

- Enhances informed choice and improved understanding.
- Early treatment when available
- Reduction of birth of affected homozygotes

2. Disadvantages and hazards:

- Stigmatization of carriers (social, insurance and employment)
- Inappropriate anxiety in carrier.

Practice Questions (Choose one correct answer)

1- The normal somatic cell contains:

a) Haploid number of chromosomes
b) Diploid number of chromosomes
c) Aneupoid number of chromosomes:
d) Polyploidy

2- The following chromosome is one of the acrocentric chromosomes:

a) Chromosome 14
b) Chromosome 1
c) Chromosome X
d) Chromosome 4

3-An extra finger in humans is rare but is due to a dominant gene. When one parent is normal and the other parent has an extra finger but is heterozygous for the trait, what is the probability that the first child will be normal?

a) 0%.
b) 25%.
c) 50%.
d) 75%.

4- The most common congenital heart disease in Down syndrome is:

a) VSD
b) ASD
c) Endocardial cushion defect
d) PDA

5- If the mother will be …… at the time of birth, she should consider genetic counseling

a) 35 or older
b) Under 35
c) 30 or older
d) Between 25 and 30

Chapter 6

Infectious and Parasitic Diseases

Learning Objectives:

By the end of this chapter, students should be able to:

1. Classify different causes of fever.
2. Correlate between clinical presentations and the special nature of different infections
3. Formulate a management plan for infectious diseases.

Contents:

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

Fever or Pyrexia

Case 1

History

A 7-year-old girl who presents to the A&E department with a 2-day history of fever, progressively worsening headache, vomiting and neck stiffness. She was admitted to hospital one month ago with pneumonia and developed an empyema, which required drainage. Streptococcus pneumoniae was isolated from blood cultures at that time. Since then she has had several episodes of otitis media treated by her GP.

Examination

A temperature of 38.8_C, heart rate 120 beats/min, her blood pressure is 100/65 mmHg, respiratory rate 20/min and her oxygen saturation is 96 per cent in air. She has multiple enlarged cervical lymph nodes, oral candidiasis, extensive dental caries and suppurative left otitis media.

There are no rash, and cardiovascular, respiratory and abdominal examinations are normal. She is alert but uncomfortable, has marked neck rigidity and prefers the lights to be dimmed. There are no other abnormalities found on neurological examination.

Investigations:

Hb: 11.3gm/dl, WBCs: 23000/L, CRP 207 mg/dl,

CSF analysis: WBCs = 1000/L, proteins = 2200mg/L, glucose = 0.9mmol/L, gram stain: gram positive cocci

What is the most likely diagnosis and appropriate treatment?

This child has acute bacterial meningitis, which is most likely to be due to S. pneumoniae.

This diagnosis is strongly suspected from the acute history and the blood results, and confirmed by the CSF findings. It may have developed secondary to otitis media. She should be commenced on an appropriate antibiotic (most commonly intravenous ceftriaxone) and on intravenous dexamethasone.

Definition:

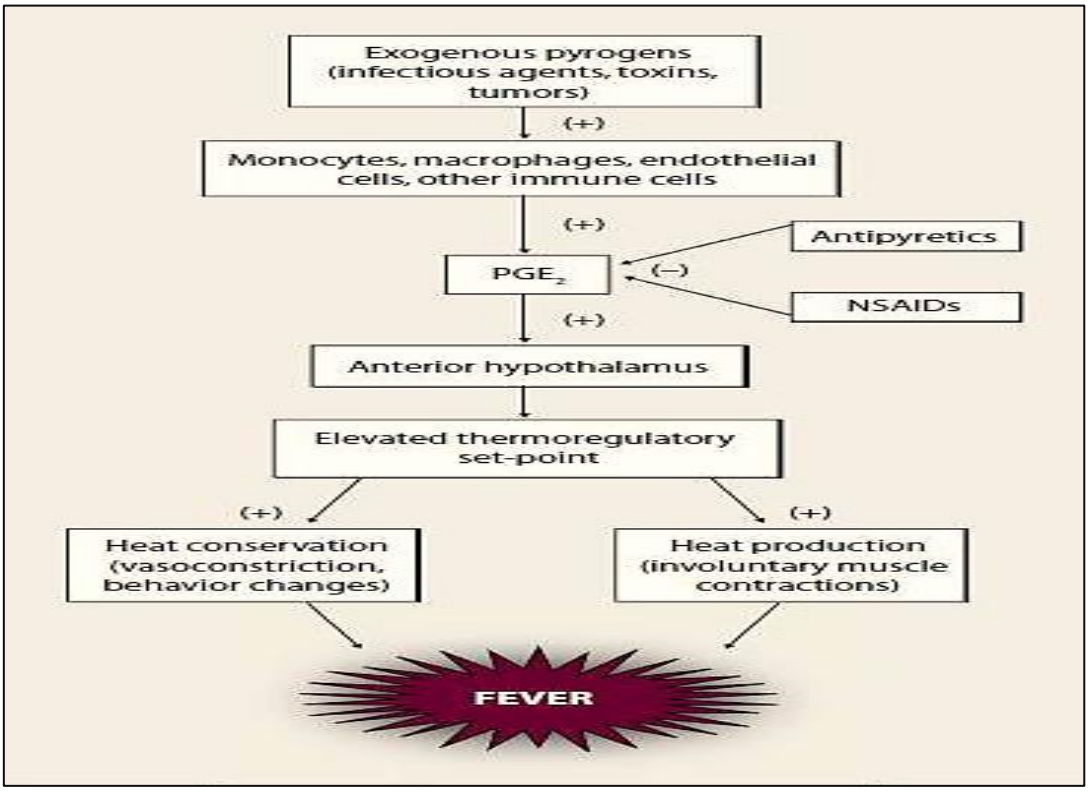
Fever is defined as an elevation of body temperature above the normal daily variation (a rectal temperature >38°C or oral temperature >37.5°C).

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.



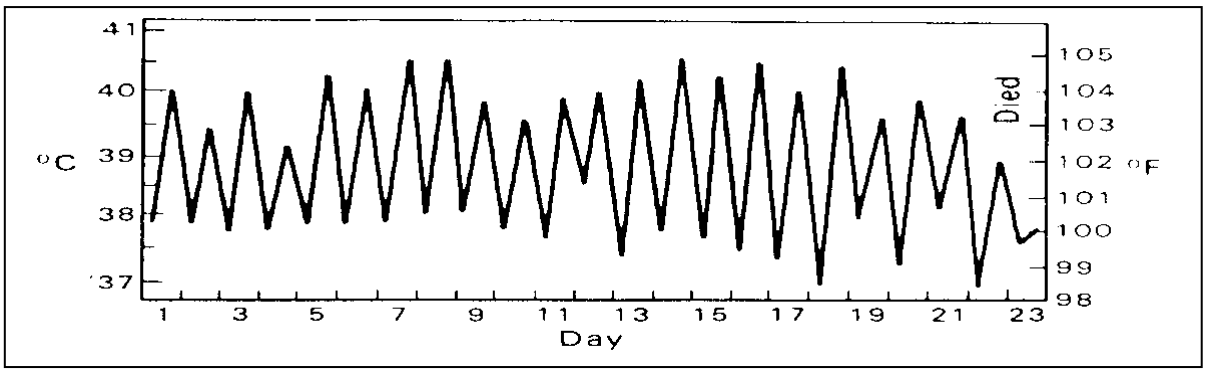
How should temperature be measured?

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

Types of Fever:

1. <u>Continuous Fever:</u> 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^{oC}.

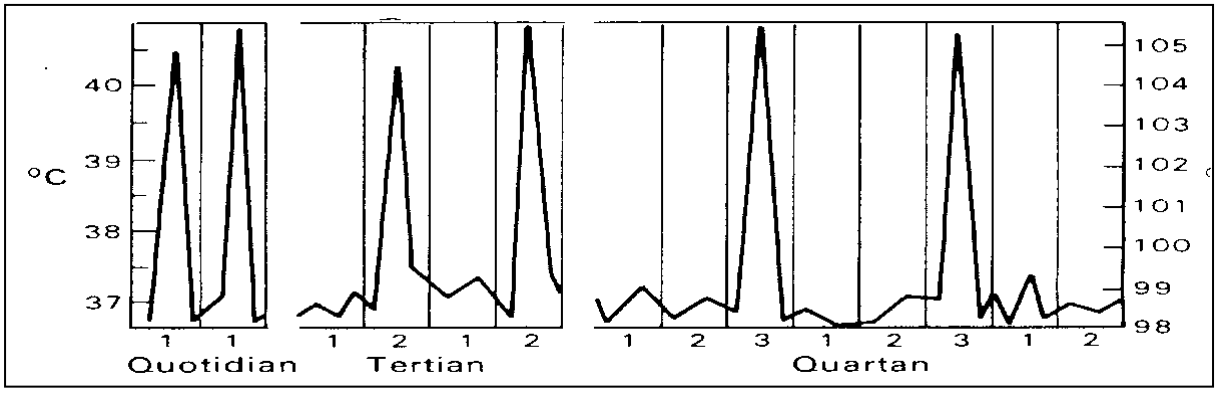
2. <u>Remittent Fever:</u> The temperature doesn't reach base line at any time in the 24 hours, the variation between upper and lower limit exceeds 1^{oC}.



Remittent Fever pattern

3. Intermittent Fever:

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



Intermittent Fever pattern.

4. Undulant Fever:

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

5. Recurrent Fever:

Episodes of fever of more than six month's duration

Etiological classification of fever

- **Infections**
  - ***Systemic infection***: bacteraemia, 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)

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

Treatment:

A. Treatment of the cause.

B. Symptomatic treatment:

- ***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.
- **Environment**
  - Tepid sponge bathing. (Not alcohol, not ice water)
  - A room temperature can be reduced by opening a window or using a fan
  - Clothing should not be underdressed or overwrapped.
  - Hydration: encourage the child to drink cool drinks. Breast feeding should continue.

Fever of Unknown Origin (FUO)

Definition:

Children with fever of 38 ºC or greater (documented by a healthcare provider) for which the cause couldn't be identified (after **3** weeks of evaluation in an outpatient clinic, 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).

A. infections:

1. *Systemic bacterial infections*:

- T.B, Salmonellosis, septicaemia, brucellosis, and meningococcaemia.

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.

B. Rheumatologic Diseases:

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

C. Neoplasms:

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

D. Miscellaneous:

- Drug fever.
- Serum Sickness.
- Familial Mediterranean fever.
- Sickle cell crisis.

- Diabetes Insipidus.
- Inflammatory Bowel disease.
- Thyrotoxicosis.
- CNS dysfunction (Severe brain damage and Epilepsy can cause fevers).
- Immunodeficiency.

E. Undiagnosed Fever

Diagnosis:

- **Careful history**
- **Through physical examination.**
- **Investigations**
  - ***Initial Tests:***
    1. 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.
    2. Blood film may reveal malaria.
    3. Blood Culture
    4. E.S.R:
       - Exceeding 30 mm/hr indicates inflammation.
       - Exceeding 100mm/hr suggests (T.B., malignancy or rheumatologic diseases).
    5. C-reactive protein:
       - (more than 6 mg/dL). It can help to identify children at risk of occult serious bacterial infection.
    6. Liver and Renal functions.
    7. Urine Analysis: UTI is a common source of FUO.
    8. Stool analysis.
    9. Tuberculin Skin Testing.
    10. Common serological tests: typhoid (Widal), brucella, infectious mononucleosis (monospot test).
    11. Radiographic Examination of the chest, sinuses, mastoiditis, or G.I. tract may be indicated by specific history and physical findings

12. 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.

1. Bone marrow examination may reveal leukemic infiltration, metastatic neoplasm, fungal or parasitic diseases and histoplasmosis.
2. Imaging and other evaluations:
   - CT and MRI
   - Abdominal ultrasound.
   - Radioactive scan may be helpful in detecting osteomyelitis and abdominal abscesses.

Fever and Rash

Case 2

Eyad is a 2-year-old boy, is referred to the pediatric unit with a history of fever, cough, blocked runny nose and sticky eyes for 6 days. He received amoxicillin 2 days ago for otitis media, and that evening he started to develop a rash around his ears and hairline. His parents stopped giving the antibiotics, but the rash continued to spread over most of his body. He has been very miserable and lethargic for the last 5 days. They thought the rash may be an allergic reaction to amoxicillin. he has an older brother who has autism. On Examination**,** His temperature 38.5◦ C, his heart rate is 115 beats /min, respiratory rate 20/min, and oxygen saturation is 97 per cent in air. He weighs 14 kg (75th centile) and he is miserable and lethargic. He has a widespread maculopapular erythematous rash, which is coalescing over his face, neck and torso. capillary refill time is 2 s. he is coughing and there are lots of transmitted upper airway noises heard throughout his chest. His abdomen is normal. His nose is streaming with catarrh and he has a purulent discharge from his right ear. His pharynx is red and he has exudative conjunctivitis.

What is the most likely diagnosis?

This is a case of measles. The history is typical, with a catarrhal prodrome phase of fever, conjunctivitis, cough and coryza, preceding development of the rash 3–5 days later, Koplik's spots may be seen as small white spots on the buccal mucosa (usually disappeared within 1 day of the rash starting). The rash is maculopapular and starts around the hairline and behind the ears, spreading downwards across the body.

What complications may arise from this disease?

- Pneumonia - Corneal ulceration -Suppurative otitis media - Gastroenteritis
- Febrile convulsions - Encephalomyelitis (rare) and subacute sclerosing panencephalitis (very rare)

What essential piece of history has been omitted?

Vaccination history, in this case he didn't receive MMR vaccine.

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** like in cases with chickenpox, herpes simplex, herpes zoster and papular urticaria.
- **Pustule:** 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.

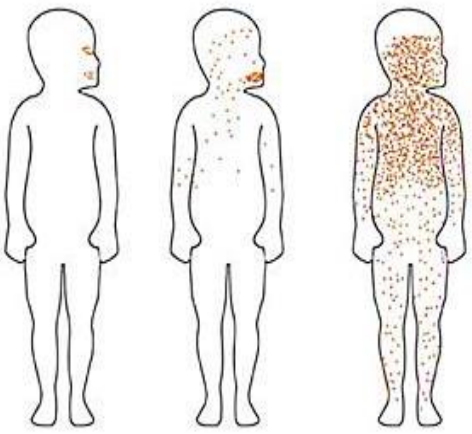
Incubation period: 1 to 2 weeks

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:

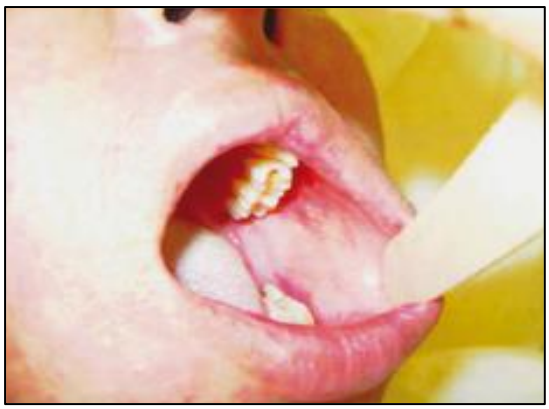


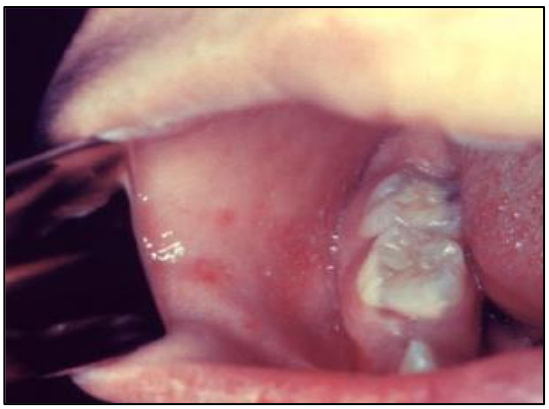
Progression of Measles infection

➢ **Typical illness**

1 – *Prodromal (catarrhal) stage:*

- (**Severe**) It lasts for about 3 days.
- 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, (small bluish-white spots on a red background may be seen on the buccal mucosa 2 days before & 2 days after onset of rash).

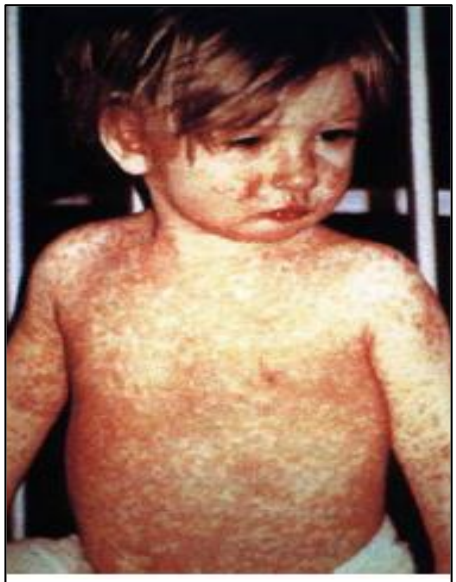




Koplik's spots on the buccal mucosa of a child with measles

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.



Development and distribution of Measles

➢ **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.

➢ **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.

➢ **Measles in the immunocompromised host:**

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

Complications:

I - Respiratory complications:

- Otitis media, it is the most common complication of measles.
- Pneumonia, it is the most common cause of death in measles. It may be caused by:

a) Measles virus itself (Hecht's pneumonia).
b) Secondary bacterial infection, particularly the pneumococcus, streptococcus, staphylococcus, and H. influenza.
c) Exacerbation of an existing tuberculous process.

- Other respiratory complications: sinusitis, laryngitis, bronchitis, and bronchiolitis.

II - Neurologic complications:

- *Encephalitis:*
  - 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 complications: as Guillain-Barre syndrome, and cerebral thrombophlebitis.

III - Hematological complications:

- Black (hemorrhagic) measles
- Thrombocytopenic purpura.
- DIC.
- Purpura fulminans 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: Rubella, roseola, enterovirus, scarlet fever, and drug eruption.

Treatment:

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

II.Symptomatic & supportive lines:

- Antipyretic (avoid aspirin)
- Sedative
- Antitussive.

- Oral vitamin A (400,000 IU).

III.Specific treatment: No specific treatment.

IV.Post exposure vaccination: Nonimmunized people, including infants, may be given the measles vaccination within 72 hours of exposure, to provide protection. If measles still develops, the illness usually has milder symptoms and lasts for a shorter time.

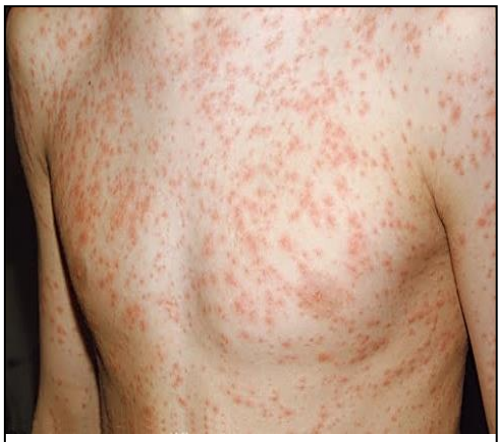
V.Immune serum globulin: Infants, immune-deficient children, pregnant women may receive immune serum globulin with in six days of exposure to the virus.

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

Prevention: Immunization.

German measles

(Rubella) (Three-day measles)



Rubella rash on chest and arms

***Etiology*:** Rubella virus (RNA virus).

Mode of infection: Droplet or Transplacental.

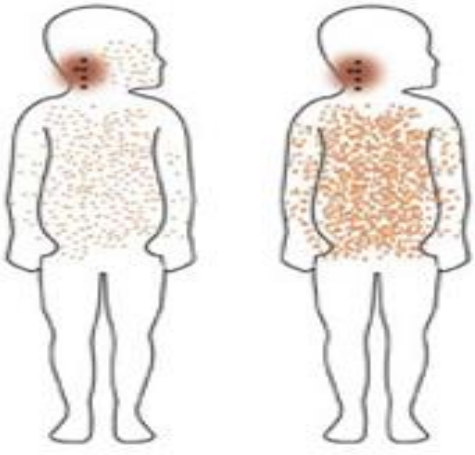
Incubation period: 2 to 3 weeks

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 ºC) or absent.
- Mild catarrhal symptoms are usually present.
- The most characteristic sign is cervical lymphadenopathy.



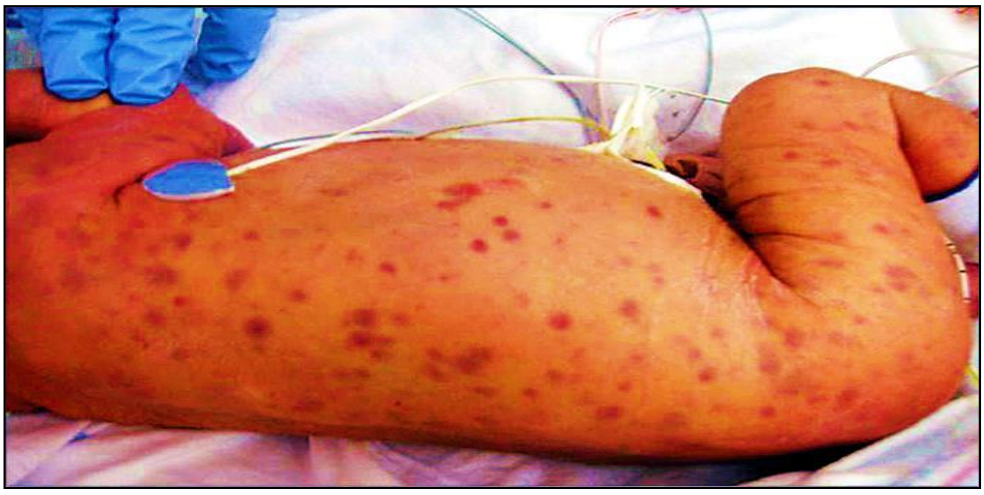
Progression of Rubella infection

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.

III. Congenital rubella syndrome

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



Infant with "Blueberry Muffin" skin lesions of congenital Rubella

Complications:

1.Encephalitis.

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

Investigations

1. Direct viral isolation from nasal or throat specimens.
2. Indirect demonstration of antibodies:
   - Hemagglutinin inhibition (HI) antibody test.
   - 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.

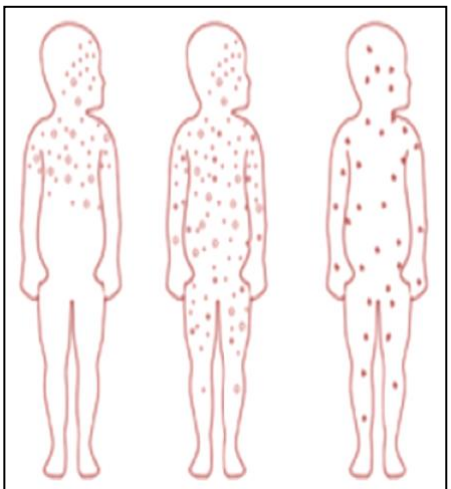
(Chickenpox) Varicella

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

Mode of infection: Droplet or 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).



Progression of Chickenpox infection

Clinical manifestations:

In normal children:

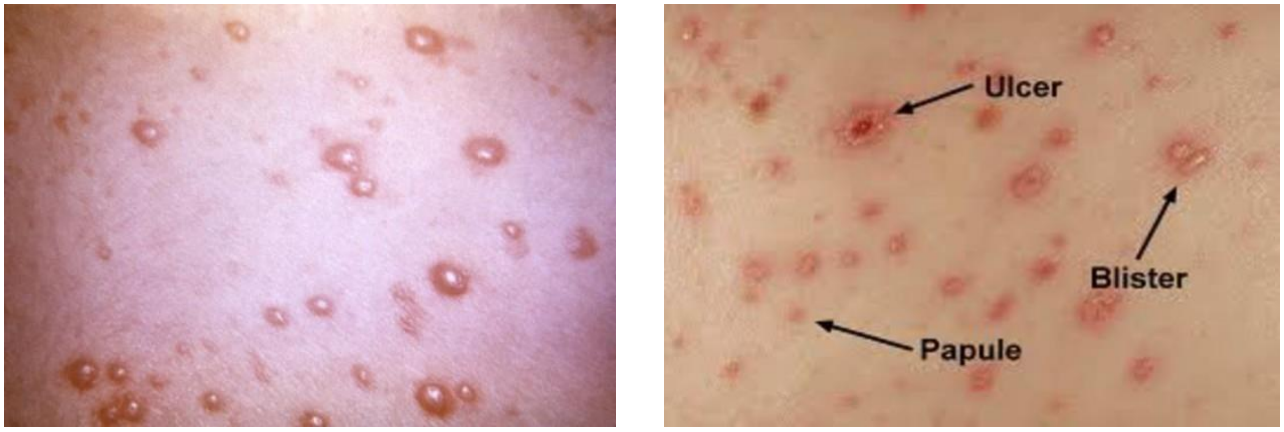
✓ ***Prodromal stage*:** usually short (about 24 hours), with mild symptoms (mild fever, anorexia).

✓ ***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.

In immunocompromised children: A severe, disseminated, and fulminant course.



Characteristic skin rash in chickenpox infection

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 infection is common and may be fatal.

Investigations Rarely required but, isolation of virus from scraping of the lesion may be useful.

Treatment

1. **General lines:** The fingernails should be trimmed. Daily bathing is advised.
2. **Symptomatic treatment:**
   - ✓ Local and systemic antipruritic agents may be required.
   - ✓ Antipyretic other than aspirin may be indicated.
3. **Specific therapy:**
   - ✓ Acyclovir (500 mg/m^2/dose given over 2 hrs. every 8 hrs.) is indicated in immunocompromised children.

4. Treatment of complications

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

Prevention: See immunization and isolation measures.

Prognosis:

- ***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

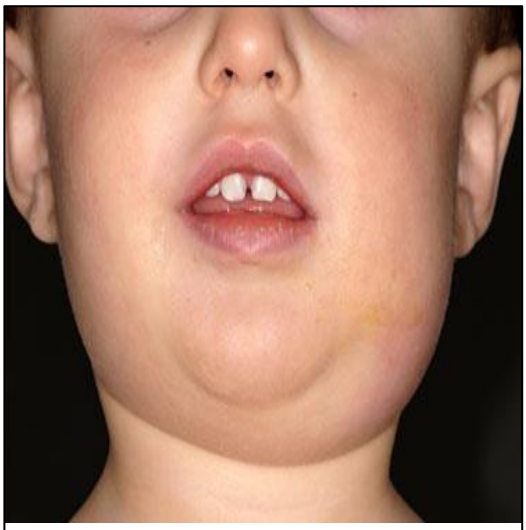
Infectivity period: from 7 days before to 9 days after the onset of parotitis.

Epidemiology:

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

Clinical Manifestations:

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



Parotid swelling caused by Mumps infection

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

Complications:

1. CNS complications:

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

2. **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.
3. **Oophoritis:** fever and abdominal pain
4. **Pancreatitis**: A mild involvement of pancreas may occur producing fever, vomiting, epigastric pain and tenderness.
5. **Deafness**: Mumps is a leading cause of unilateral sensorineural deafness, which may be transient or permanent.
6. **Ocular:** These include dacryoadenitis, papillitis, or uveokeratitis.
7. **Other rare Complications**: Nephritis, thyroiditis, myocarditis, purpura.

Differential Diagnosis:

1. **Other parotid swellings**: Other viral infections, suppurative parotitis, recurrent parotitis, and tumors of parotid.
2. **Other neck swelling**: Cervical lymph nodes enlargement, and osteomyelitis of ramus of mandible.

Investigations:

1. Direct isolation of virus from saliva, urine, nasopharyngeal swab or spinal fluid.
2. Indirect estimation of circulating antibodies.

Treatment: Only symptomatic treatment is indicated

Prevention: See immunization and isolation measures.

Bacterial Infectious Diseases

Scarlet Fever

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

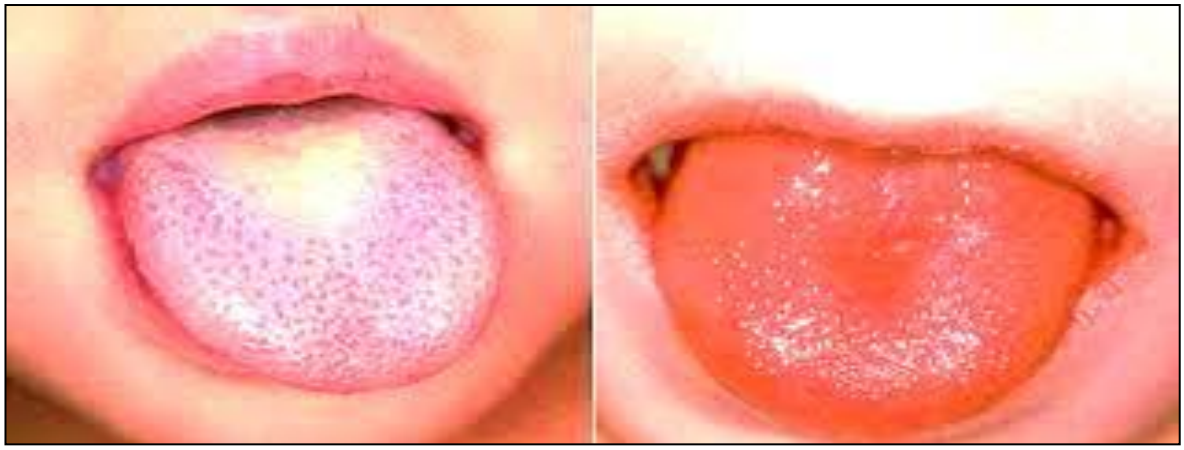
Mode of infection: Droplet infection.

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.

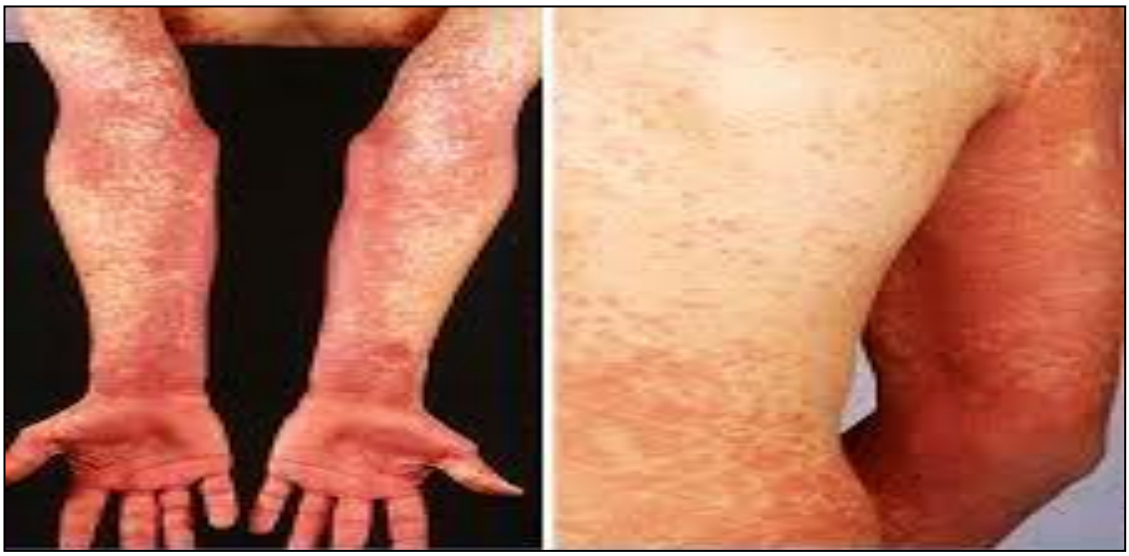
- ***Fever:*** Abrupt rise of temperature and may peak at 39.6-40°C on the second day and gradually returns to normal within 5-7 days in untreated patients.
- ***Sore Throat*:**
  - **The tonsils** are hyperemic and edematous and may be covered with a gray-white membrane.
  - **The pharynx** is inflamed 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**]
  - **The palate and uvula** may be edematous, reddened, and covered with petechiae.



White and Red strawberry tongue

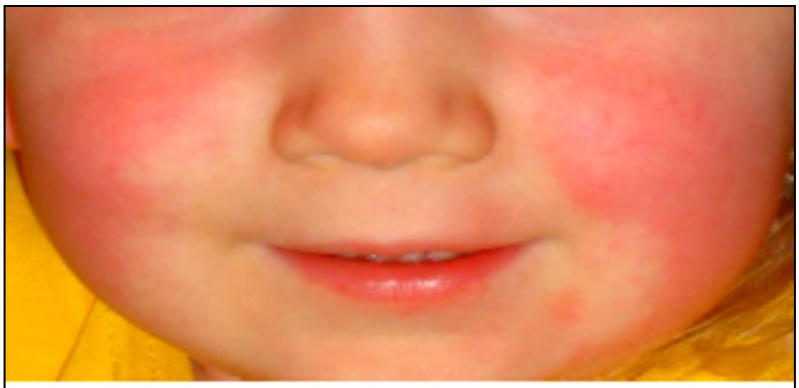
- **Exanthem (rash):**
  - Within 12-24 hrs. of onset of disease, the typical rash appears.

- 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.



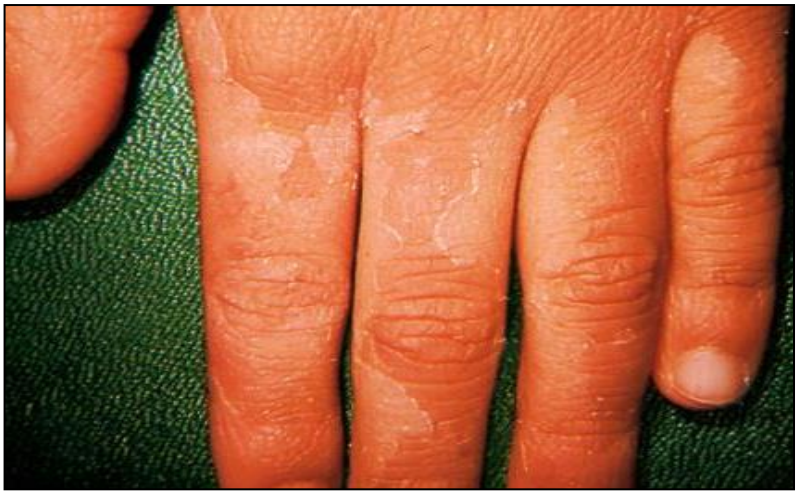
Characteristic skin rash in scarlet fever

- The forehead and cheeks appear flushed, and the area around the mouth is pale [**circumoral pallor**].



Red cheeks and pale area around the mouth in scarlet fever

- **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.



Desquamation in hand of patient with Scarlet ferver

Diagnosis:

1. **Clinical diagnosis:** - as mentioned before.
2. **Laboratory diagnosis:**

- ***Throat culture***: to detect the causative organism [group A 6 -hemolytic streptococci].
- ***Increased Anti - Streptolysin O [ASO] titer:*** Normal value: 170-330 Todd units in school aged children, rises within 2 weeks after acute infection.
- ***Leukocytosis*** may or may **not** be detected.
- ***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** for 10 days.
   - A single intramuscular injection of **a long acting benzathine penicillin G**.
2. **Erythromycin** 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, diagnosis is not usually 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 yawing 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:

(1) Clinical diagnosis: as mentioned before.

(2) Laboratory diagnosis:

- Leukocytosis (20,000-50,000 cells/mm^3 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 culture of nasopharyngeal swabs
- Detection of antibodies against pertussis toxin.

(3) Chest x ray: may show perihilar infiltrates, atelectasis, or emphysema.

Differential Diagnosis:

- **Other causes of paroxysmal cough:** including foreign body, bronchial asthma, 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:

1-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.

2-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:

1- **Active immunization:** DTaP vaccine.

2- **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:

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

Meningitis

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

Etiology:

1- Bacterial Meningitis (septic):

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

2- Viral, fungal meningitis (aseptic meningitis).

3- 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 diplopic veins into the dural sinuses and from there along meningeal veins into the brain.

III. **Iatrogenic:** Introduced during lumbar puncture procedure.

Pathology:

- **Meningeal reactions:**
  - Exudate may be distributed around the brain and spinal cord, may be pus.
  - Vascular arteritis and thrombosis of vessel
- **Brain substances:**
  - Damage of cerebral cortex due to thrombosis, hypoxia, bacterial invasion or toxic encephalopathy
- **Spinal and cranial nerves:**
  - Inflammation of spinal nerves and roots produces meningeal signs.
  - Inflammation of cranial nerves produces cranial neuropathies.

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

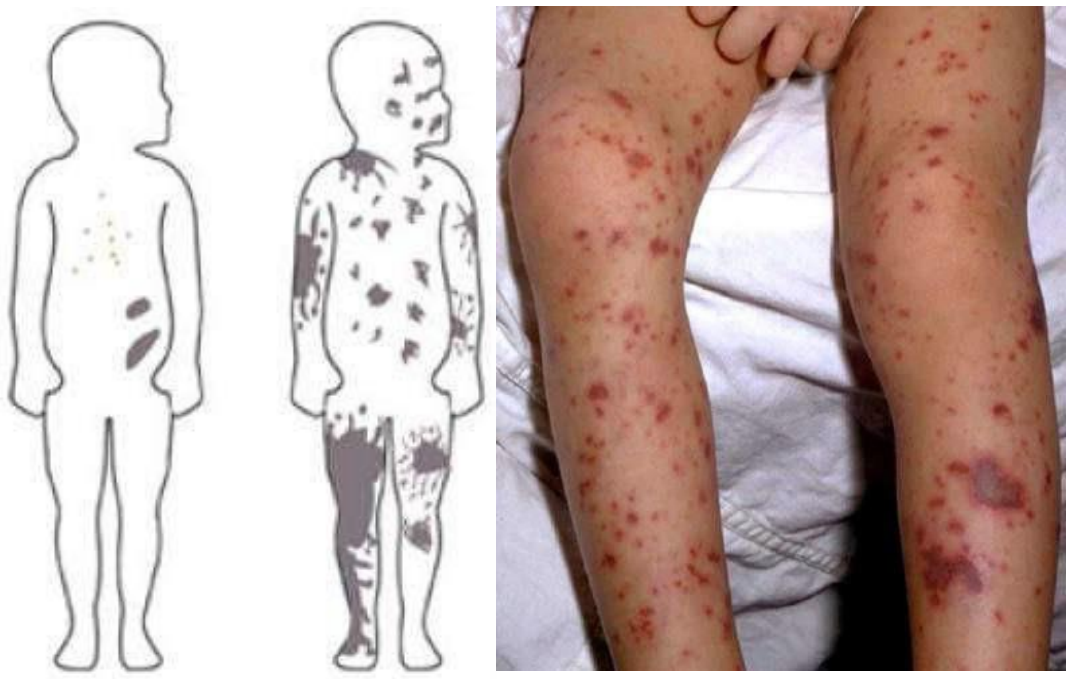
Clinical Manifestations:

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):

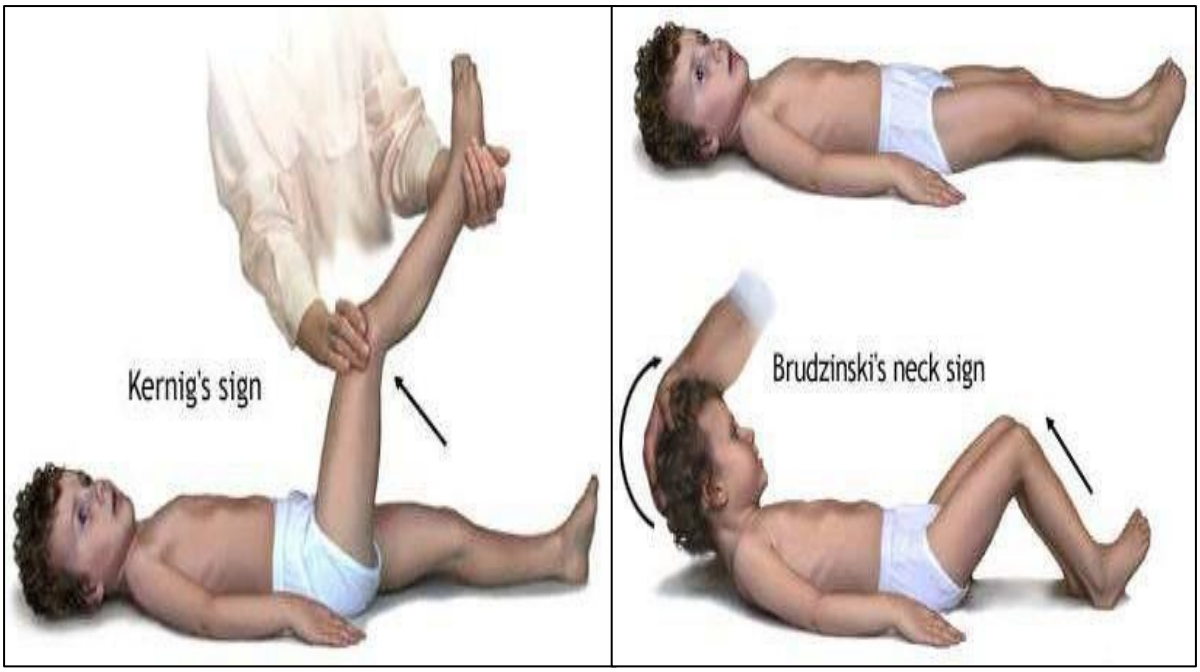
- Due to bacteremia and include fever, anorexia, poor feeding, tachycardia, and hypotension. Meningococcal meningitis is usually associated with characteristic purpuric spots.



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.



signs of meningeal irritation

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 sings: include decerebrate or decorticate posturing, stupor, coma or sings 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:

- ✓ Hospitalization and isolation.
- ✓ Repeated medical & neurologic assessment.
- ✓ Intravenous administration of medications.

II. Symptomatic treatment:

- ✓ ***Seizures:*** see (Convulsion).
- ✓ ***Increased ICP:*** IV Furosemide (1 mg/kg), mannitol (0.5 – 1.5 g/kg) and dexamethasone.
- ✓ ***Anti-inflammatory agents:*** Dexamethasone
  - 0.15 mg / kg / every 6 hr IV for 2:4 day
  - Reduce the inflammatory response and decrease the neurological complications auditory complications.

III. Specific treatment:

- ✓ ***Empiric antibiotic therapy:***
  - Ampicillin (300 mg / kg / 24 hrs. every 6 hrs.)
  - Cefotaxime: 200 mg / kg / 24 hours., every 6 hrs
  - Ceftriaxone: 100 mg / kg / 24 hrs., for 14 days
- ✓ **Specific antibiotic therapy:**
  - *Meningococcal:* Intravenous penicillin-G 300,000 U/kg/24hr for 7 days.
  - *H. Influenza:* Intravenous ampicillin for 10 day is the drug of choice
  - *Pneumococcal:* IV penicillin is the drug of choice for penicillin sensitive organism.
  - Chloramphenicol is the treatment of choice for resistant strains.

Prevention:

- **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.
- **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

Case 3

Sandy is a female child aged 7 years was presented to outpatient clinic of pediatrics with recurrent attacks of diarrhea alternating with constipation, Foul-smelling, greasy stool that can float, Stomach cramps, Upset stomach and nausea, her parents mentioned that she get tired easily , her weight is below the 5th percentile for age and suffers from poor appetite ,on examination heart rate 110 beat per minute, temperature 37.4^{oC}, blood pressure 100/70, stool analysis as done revealed *giardia lamblia trophozoites* and *cysts.*

What are the most common complications?

Acute or chronic diarrheal disease. Failure to thrive, post-infectious functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia giardiasis may cause ocular complications, arthritis, skin allergies or myopathy. Moreover, giardiasis is now a well-established cause diminished cognitive functions, and chronic fatigue.

What is the treatment of choice?

Tinidazole: single oral dose of 50 mg/kg

Nitazoxanide:

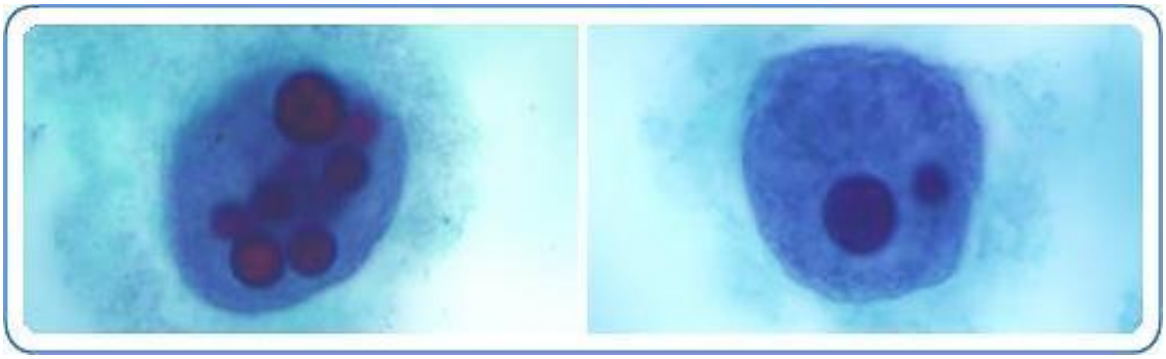
- 1-3 yr: 100 mg (5 mL) bid for 3 days.
- 4-11 yr: 200 mg (10 mL) bid for 3 days.

What is the prognosis?

Most cases with giardiasis fully recover within two months after having mild to moderate digestive symptoms. Some people continue to have gastrointestinal symptoms (such as lactose intolerance or irritable bowel syndrome) long after the infection is gone.

Amebiasis

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



Trophozoites of *E. histolytica* with ingested erythrocytes

- 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:

- Amebiasis is the third leading parasitic cause of death.
- 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: usually asymptomatic, and cysts are found in their feces.

1. 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.

2. 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:
  - **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.
  - **Endoscopy and biopsies:**
    - Performed when stool samples are negative and the index of suspicion for amebic colitis remains high.
  - **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:

- It 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.

- A course of diloxanide furoate is recommended following completion of Metronidazole or Dehydroemetine therapy.

2. Metronidazole:

- A tissue amoebicidal drug used in invasive amebiasis of the intestine, liver, or other organs.
- 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. Dehydroemetine:

- It is the recommended alternative therapeutic agent, if the case is severe or if metronidazole cannot be used.
- 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

4. Chloroquine is also useful in the treatment of amebic hepatic abscess because it is concentrated in the liver.

5. Amebic liver abscesses are treated with:

- specific therapy as outlined earlier.
- Aspiration of large lesions or left lobe abscesses may be necessary if:
  - rupture is imminent
  - If the patient shows a poor clinical response 4-6 days after administration of amoebicidal drugs.

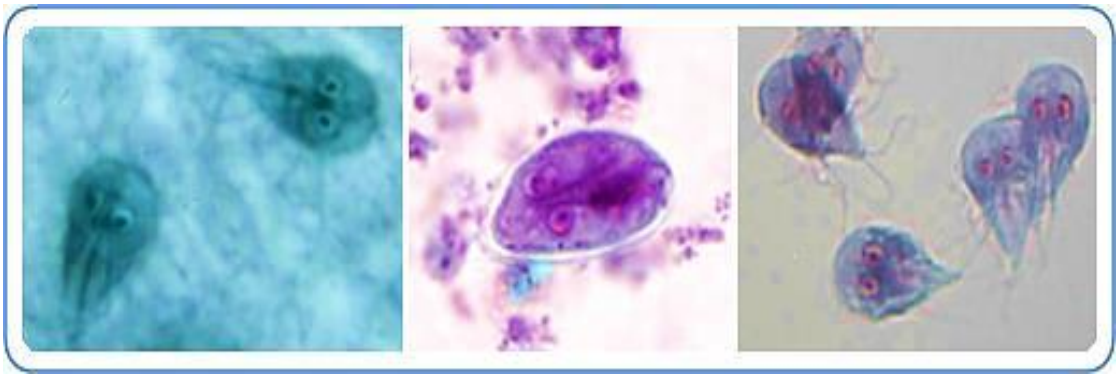
6. Stool examination should be repeated 2 weeks following completion of anti-amoebic therapy as a test of cure.

Control of Amebiasis: There is no prophylactic drug for 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.

Giardia Lamblia Infection (Giardiasis)

Giardia lamblia is a microscopic parasite that causes the diarrheal illness known as giardiasis.



Giardia intestinalis trophozoites and cyst

- While the parasite can be spread in different ways, drinking infected water is the most common method of transmission.
- The infection is more prevalent in children.

Epidemiology and Risk factors:

- 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 Giardia infection and may mimic relapse or reinfection.

Diagnosis:

- **Stool analysis:** G. lamblia trophozoites or cysts may be found.
- **Duodenal aspirate or biopsy**
- **Antigen detection tests:** highly sensitive and specific.

Treatment: When Giardia is symptomatic, it should be treated because of the potential for chronic or intermittent symptoms.

1. **Treatment of choice:**
   - ***Tinidazole***: single oral dose of 50 mg/kg
   - ***Nitazoxanide***:
     - ✓ 1-3 yr: 100 mg (5 mL) bid for 3 days.
     - ✓ 4-11 yr: 200 mg (10 mL) bid for 3 days.
2. **Alternative:** ***Metronidazole*** (15 mg/kg/day three times a day for 7 days).
3. **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.

Adult female A. lumbricoides and fertilized eggs

Clinical Findings:

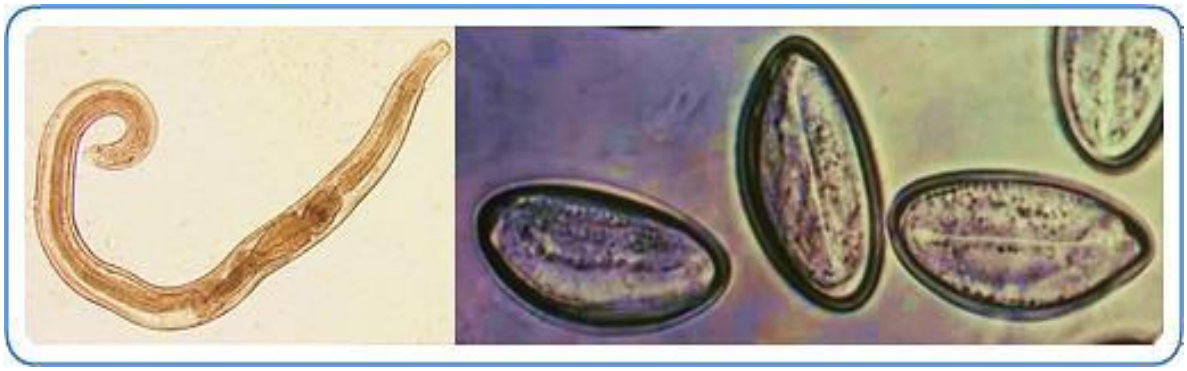
- It may be asymptomatic.
- Presenting by abdominal pain, weight loss, anorexia or hyperphagia, diarrhoea or vomiting.
- Heavy infections can cause intestinal obstruction.
- Cough due to migration of the worms through the body.

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**.



Adult male of E. vermicularis and eggs of human E. vermicularis

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

- **Direct visualization** of the worms in the perianal region 2 to 3 hours after the infected person is asleep.
- **Analyzing samples from under fingernails** under a microscope.
- **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.

Practice Questions (Choose one correct answer)

1. ***Regarding Enterobius Vermicularis infection in children, all the followings are true EXCEPT:***
    a) Itching around the anus usually at night is the common complaint.
    b) Occasionally eggs or adult worms are seen in stool examination or swabbing of skin around the anus.
    c) Treatment of all members of the family is not routine.
    d) Can be treated by Flubendazole 100 mg as a single dose.

2. ***The main causes of FUO in children are the following EXCEPT***
    a) Infections.
    b) Rheumatic diseases.
    c) Neoplasms.
    d) Metabolic diseases.

3. ***A 15-month-old infant presents with a day history of blanching confluent rash which started on his face and now covers his entire body. He is miserable with conjunctivitis and fever of 38.5 0 C. The illness started with runny nose and cough 5 days previously. What is the most likely diagnosis?***
    a) Scarlet fever
    b) Sweat rash.
    c) Chickenpox.
    d) Measles.

4. ***A 4-year-old child presents to the emergency department with a 2-day history of high fever and sore throat. She suffers self- limiting convulsions and is admitted for observation. The next day pinpoint red papular rash develops allover her body with circum-oral pallor. What is the most likely diagnosis?***
    a) Measles.
    b) Rubella.
    c) Scarlet fever.
    d) Chickenpox.

5. ***An 8-year-old girl present with low grade fever and a diffuse maculopapular rash. On examination her physician notes mild tenderness and marked swelling of her posterior cervical and occipital lymph nodes. Three days after the onset of illness, the rash has vanished. What is the most likely diagnosis?***

    a) Measles.

    b) German Measles.

    c) Roseola Infantum.

    d) Infectious Mononucleosis.

6. ***An 8 years old male child is brought to clinic by his mother because he developed a rash on his trunk. The rash began as red papules and then became vesicular. The boy had low grade fever before the rash and the rash seems spreading to other areas. What is the most likely diagnosis?***

    a) Herpes Simplex.

    b) Chickenpox.

    c) Impetigo.

    d) Meningococcemia.

Chapter 7

Preventive and Social Pediatrics

Learning Objectives:

By the end of this chapter, students should be able to:

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.

Classification of prevention:

I. <u>Primary prevention:</u> 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. <u>Secondary prevention:</u> aims at early detection of the disease and stopping or reversing its progress.

a) Neonatal screening for hypothyroidism.

b) Long-acting penicillin for rheumatic fever.

III. <u>Tertiary prevention:</u> 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 psychological and emotional disorders.

6- Prevention of infectious diseases through 4 steps:

7- Isolation of infected person from those at risk.

8- Eradication of vectors that transmit the infection.

9- Elimination of infective organisms.

10- 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. antibotulinum.

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

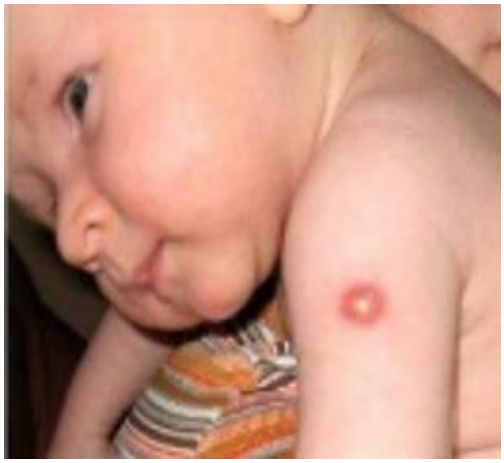
1. BCG

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:

- Cutaneous ulceration,
- Localized lymphadenopathy, and
- Less commonly, subcutaneous abscess formation, osteomyelitis, dissemination, and death
- A major theoretical disadvantage of BCG is the production of sensitivity to tuberculin.

Contraindications:

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

POLIOVIRUS VACCINES

Types:

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

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

Comparison of OPV and IPV

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

Preparation:

➢ The viruses are grown in tissue cultures of monkey kidney cells. The viruses are formalin-inactivated in IPV.

➢ 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.

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 multiplicating 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.

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 5^{th} 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 **Crying**	**< 40.5 $^{0}_{c}$** **Transient**	**>40.5 $^{0}_{c}$** **Persistent > 4 hr**
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.

Hepatitis B vaccine

Preparation:

- It's a recombinant vaccine composed of a subtype of HbsAg.
- Prepared by inserting a plasmid containing HbsAg gene 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:

- It is now obligatory in Egypt for all infants.
- Newborns to hepatitis B mother should receive the vaccine along with hepatitis B immunoglobulin immediately at birth.
- Staff and patients of hemodialysis.
- Patients receiving frequent blood or blood component transfusion.
- 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.

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.

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.

Recommended Immunization Schedule

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

Age	Vacccine	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

- ***0ne 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 10 ys.

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's a live attenuated vaccine.
- It's given as MMR subcutaneously.
- It's recommended after the first year.
- It's 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:

a. Standard human immune serum globulin (HISG) e.g. ISG for prevention of Rubella during pregnancy.

b. Special human immune serum globulins with a known antibody content for specific illness e.g. hepatitis B immune globulin (HBIG).

c. Animal serums and antitoxins as Diphtheria antitoxin, tetanus antiserum.

Peparations 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.	Given within 5 days after exposure
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).	0.06 ml/kg.	Given immediately after exposure
2. Varicella-zoster immune-globulin (VZIG).	2-4 ml.	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.

Period of recommended isolation

Disease	Recommended Isolation
*** Measles rash**	From onset of catarrhal stage through 4th 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 0.05 ml 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 8

Gastro-Intestinal Diseases

Learning Objectives:

By the end of this chapter, students should be able to:

1. Recognize and define some of common pediatric gastro-intestinal disorders; vomiting, constipation and diarrheas.
2. Identify risk factors, possible causes and complications of each of them
3. Develop clinical diagnosis and select and interpret appropriate investigations for each of them.
4. Construct management plan and formulate proper lines of treatment of these disorders.

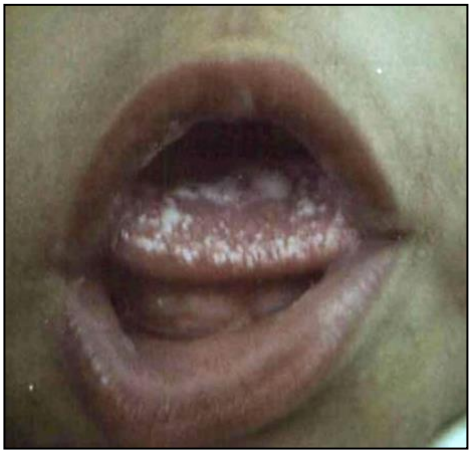
Contents:

1. Vomiting.
    a. Gastro-esophageal reflux.
    b. Hypertrophic pyloric stenosis.
2. Constipation.
3. Pediatric diarrheal disorders.
    a. Acute diarrhea.
    b. Persistent Diarrhea.

Some Disorders of Gastro-intestinal Tract

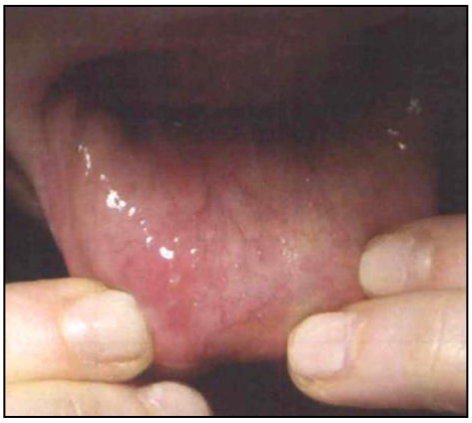
A-Stomatitis:

Oropharyngeal Candidiasis



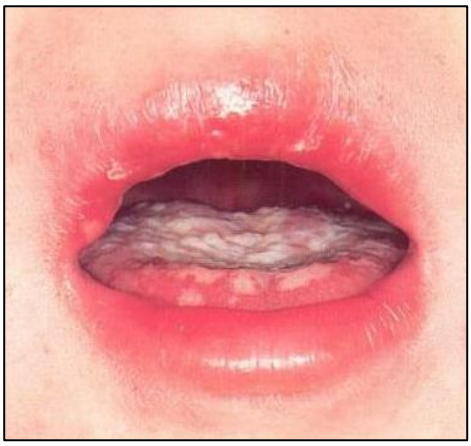
- Oropharyngeal infection with ***Candida albicans*** (thrush, moniliasis).
- Common in neonates from contact with the organism in the birth canal.
- Infants and children following myelosuppressive or prolonged antibiotic therapy.
- The lesions appear as white plaques on the oropharyngeal mucosa, which can be removed leaving inflamed surface that may bleed.
- 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.

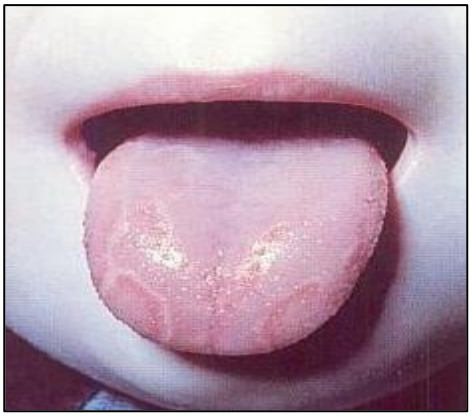
Herpetic Gingivostomatitis



- Incubation period is 1 wk.
- Starts with fever and malaise, then the gingiva becomes erythematous with clusters of small vesicles erupting throughout the mouth.

- 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 anotherwise normally roughened tongue.

B. Gastro-esophageal reflux

It is the most common esophageal disorder in children of all ages.

***Definition*:** Gastro-esophageal reflux is the return of gastric contents into the esophagus. Physiologically, gastro-esophageal reflux episodes do occur in all people but only occasionally and for short durations, without pathological changes in esophageal mucosa or respiratory tract.

***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.

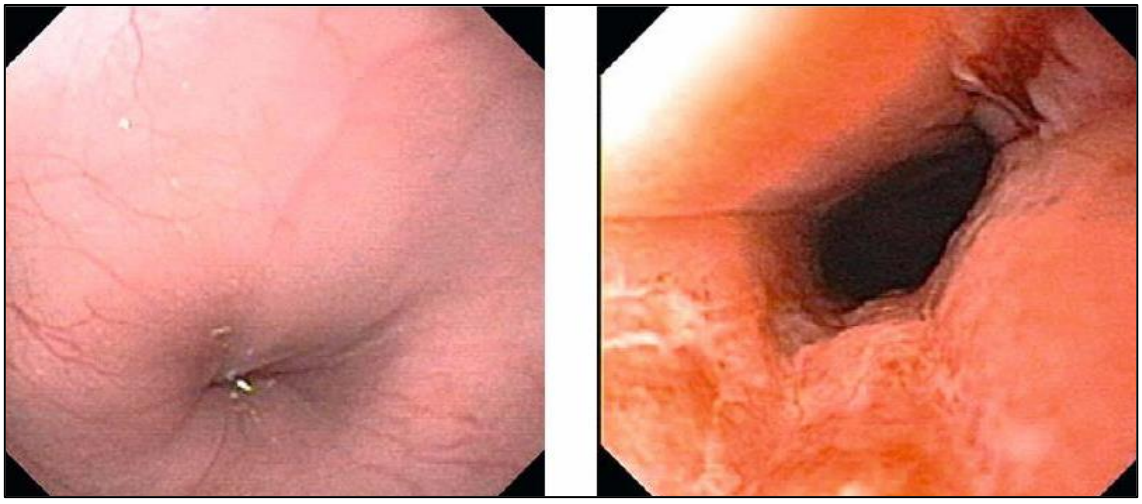
***Clinical picture*:**

In infants:

- Regurgitation (especially post-prandially).
- Signs of esophagitis (irritability, arching, choking, gagging, food refusal).
- Failure to thrive.
- Respiratory (extra-esophageal) 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 vomiting.

***Treatment*:**

1. **Conservative anti-reflux 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. **Mucosal protective agent** as sucralfate may be added in severe cases.
5. **Surgical management** (Nissen fundoplication) for serious unresponsive manifestations persisting beyond 18 to 24 mo of age.

C. Hypertrophic Pyloric Stenosis

Case 1

Ali is a 7-week-old infant who presents to the emergency department (ED) with a 1-week history of non-bilious vomiting. His mother describes the vomit as ‘shooting out’. He has a good appetite but has lost 300 g since he was last weighed a week earlier. He has mild constipation. There is no vomiting in any other members of the family. His sister suffers from vesico-ureteric reflux (VUR) and urinary tract infections.

Examination

He is apyrexial and mildly dehydrated. His pulse is 170 beats/min, blood pressure 82/43 mmHg, and peripheral capillary refill time <2 s. There is no organomegaly, masses or tenderness on abdominal examination. There are no signs in the other systems.

Investigations

Hemoglobin 11.7 g/dl, WBC 10.0 × 10^6/dl, Platelets 332 × 10^6/dl.

Sodium 130 mmol/L, Potassium 3.1 mmol/L, Chloride 81 mmol/L.

Urea 9.0 mmol/L 1.8–6.4 mmol/L, Creatinine 60 µmol/L 18–35 µmol/L

Capillary gas : pH 7.56, PCO_2 6.0 kPa, HCO3 38 mmol/L, Base excess +10

Urine dipstick No abnormality detected

What is the most likely diagnosis?

In an infant of this age with non-bilious projectile vomiting, **pyloric stenosis** is the most likely diagnosis. This condition presents between 2 weeks and 4 months of age (median 6 weeks) and projectile vomiting is typical. The vomitus is never bile-stained as the obstruction is proximal to the duodenum. As with Ali, infants may also be constipated. The hyperchloremic alkalosis is

characteristic and is due to vomiting hydrochloric acid (HCl). The low potassium is due to the kidneys retaining hydrogen ions in favor of potassium ions. The raised urea and creatinine suggest that there is also mild dehydration. The male-to-female ratio is 4:1 and occasionally there is a family history (multifactorial inheritance).

What is the differential diagnosis?

- **Gastro-oesophageal reflux** → usually presents from or shortly after birth
- **Gastritis** → usually occurs with an enteritis and diarrhea.
- **Urinary tract infection** → at this age may present in a very non-specific way and it is therefore mandatory to test the urine. The absence of nitrites and leucocytes in the urine dipstick makes a urinary infection very unlikely.
- **Overfeeding** → can be elucidated from a careful history.

How would you confirm the diagnosis?

The diagnosis could be clinically confirmed by carrying out a test feed. A feed leads to peristalsis, which occurs from left to right. The abdominal wall is usually relaxed during a feed, making palpation easier. A pyloric mass, which is the size of a 2 cm olive, may be felt in the right hypochondrium by careful palpation. An ultrasound is also usually done for further confirmation.

What is the treatment?

Ali is slightly tachycardia (normal pulse rate <1 year, 110–160 beats/min) with a normal blood pressure and capillary refill time. His urea is slightly elevated. Initial treatment consists of treating the dehydration, acid–base and electrolyte abnormalities with intravenous fluids (0.9 per cent saline with 5 per cent dextrose and added KCl would be the appropriate starting fluid in this infant with low sodium and potassium levels). Feeds should be stopped, a nasogastric tube inserted and the stomach emptied. The definitive surgical operation is Ramstedt's pyloromyotomy.

Incidence:

- 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:

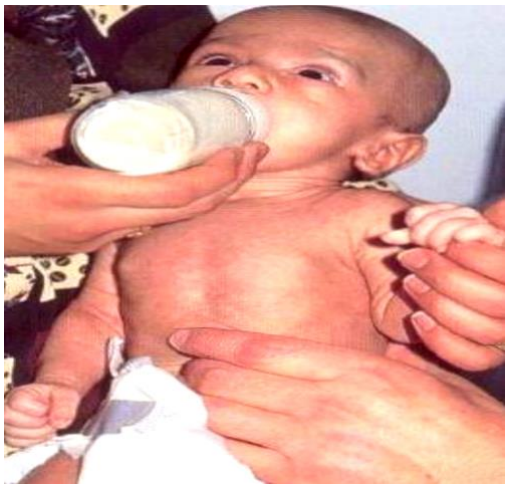
- The cause of pyloric stenosis is unknown.
- Pyloric stenosis is usually not present at birth.
- May be due to abnormal muscle innervation or, elevated serum prostaglandins.

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.

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.

II. Constipation

Case 2

Sara is a 4-year-old girl who presents to outpatients with a 2-year history of constipation. She opens her bowels about once every 5 days and strains. She soils her knickers on most days. She has intermittent abdominal pain, which is relieved by opening her bowels. Recently, there has been fresh blood on the toilet tissue. Sara passes good volume, normal diameter stool. Movicol has been used, with little success.

Sara's mother states that she did not have a dirty nappy until 40 hours of age. She has recently had a urine infection diagnosed by her general practitioner (GP). The illness was mild and responded well to antibiotics. She was delivered by emergency caesarean section because of fetal distress and meconium staining.

Examination

A fecal mass is palpable in the left iliac fossa. Tanya's back and anus appear normal. There are no signs in the lower limbs. Rectal examination reveals palpable hard stool. Her blood pressure is 101/62 mmHg and there are no other signs. Sara's weight is on the 50th centile and her height is on the 25th centile.

What is the most likely diagnosis?

The most likely diagnosis is functional constipation. This condition is associated with fecal masses in the lower abdomen. Severe constipation can lead to an anal fissure (and vice versa).

This is the likely cause of Sara's bleeding. It may be high up in the anus and therefore not visible on inspection. The soiling is involuntary and due to liquid stool leaking from above the hard stool mass in the rectum.

Hirschsprung's disease should be suspected if meconium has not been passed in the first 48 hours of life. However, in this case, the passage of meconium *in utero*, the lack of symptoms in the first 2 years of life and the normal weight make that diagnosis unlikely. Furthermore, in Hirschsprung's disease, the rectum is usually empty. The normal diameter stool makes the rare condition of anal stenosis very unlikely.

Would you carry out any investigations?

No investigations are necessary. Usually, clinical assessment suffices to make the diagnosis.

In children who refuse a rectal examination, or if there is doubt about the diagnosis, then an abdominal X-ray can be useful to assess the degree of faecal loading. Children with constipation are more likely to get urinary tract infections. In a 4-year-old with a history of one, non-severe urinary

tract infection, no investigations are required. Dietary advice needs to be given, encouraging a good fluid intake, a daily high-fiber cereal and fruit and vegetables. Star charts may also help.

What is the treatment?

Initial drug treatment consists of an osmotic laxative such as Movicol. If that is ineffective, a stimulant laxative such as senna should be added. The doses of these medications can be titrated to the frequency of bowel actions, with the aim being for the child to open their bowels daily in a pain-free manner without soiling.

If the child has pain secondary to an anal fissure, lidocaine ointment should help. Whenever possible, treatment is administered orally. However, in some cases sodium citrate or phosphate enemas are required to help dis-impact hard stool in the rectum.

In very severe cases, a bowel cleansing solution such may be needed, and in extreme cases a manual evacuation may need to be performed in theatre. Constipation often starts at the age of 2 years when the child is being toilet trained. Toilet training may lead to 'power struggles' between the child and the family, and thus to constipation. In some cases, psychological intervention is helpful.

***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:**
  - **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.

Red flags in childhood constipation:

- Failure to thrive, weight loss, poor growth.
- Vomiting
- Abdominal distension
- Persistent anal fissures, perianal disease.
- Persistent blood in stool.
- Delayed passage of meconium.
- Weak urinary stream, diurnal enuresis.

Diagnostic studies:

1. **For growth failure, failure to thrive, short stature:**
   - ✓ Thyroid function tests
   - ✓ Celiac panel
   - ✓ Sweat test
   - ✓ Hirschsprung disease
2. **For delayed passage of meconium:**
   - ✓ Anorectal manometry
   - ✓ Rectal suction biopsy
   - ✓ Unprepared contrast enema
   - ✓ Sweat test
3. **For Spinal cord lesions:** Consider imaging the lumbosacral spinal cord (ultrasound, magnetic resonance imaging).
4. **For refractory constipation:**
   - ✓ Thyroid function tests
   - ✓ Serum calcium, Potassium.
   - ✓ Celiac panel
   - ✓ Sweat test

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 softeners 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.

III. Pediatric Diarrheas

Case 3

Ahmed is a 24-month-old boy with Down syndrome, brought to the emergency department (ED) by his mother. He has had diarrhea and vomiting for 1 day. In the last 8 hours, he has drunk 200 mL milk, vomited five times and passed six liquid stools. The vomit is not bilious and there is no blood or mucus in the stools. It has been hard to tell if he is passing urine because every nappy has been soiled.

He has no cardiac problems and no other medical problems except ***glue ear.*** There is no history of foreign travel. He is fully vaccinated for his age. His two elder siblings have recently had diarrhea and vomiting.

Examination

He is miserable and lethargic. His heart rate is 120 beats/ min, respiratory rate is 25 breaths/ min, and his temperature is 37.7°C. He has dry mucous membranes, slightly sunken eyes, normal skin turgor and a capillary refill time of <2 s. His abdomen is soft with no palpable masses. His weight is 11 kg (50^{th} centile on the Down syndrome growth chart).

An oral fluid challenge is commenced in the ED. He drinks 60 mL of oral rehydration solution over 2 hours and vomits once on the floor. He does not pass urine into a urine bag during this period.

What is the most likely diagnosis?

The most likely diagnosis is viral gastroenteritis. Previously rotavirus would have accounted for a large proportion of cases with this type of presentation, but routine vaccination against rotavirus has substantially reduced the burden of this infection. Other viruses causing gastroenteritis include norovirus and adenovirus.

How dehydrated is Ahmed?

Ahmed is clinically dehydrated, but not shocked.

Clinical signs of dehydration and hypovolemic shock in children are as the followings:

Clinical dehydration

• Altered responsiveness (e.g., irritable or lethargic)

• Decreased urine output

• Sunken eyes

• Dry mucous membranes (except for ‘mouth breather’)

• Tachycardia and Tachypnoea

• Reduced skin turgor

Hypovolemic shock • Decreased level of consciousness • Pale or mottled skin • Cold extremities • Weak peripheral pulses • Prolonged capillary refill time • Hypotension (decompensated shock, a late sign) Clinical assessment of dehydration is a relatively crude estimate, and if acute weight loss can be accurately calculated, it is a better measure of the degree of dehydration.
How would you manage Ahmed now? Management of clinical dehydration should involve enteral rehydration (by the oral or nasogastric route) whenever possible. This can be done with an appropriate oral rehydration solution (ORS). After an initial 4-hour period of rehydration (when the fluid deficit is replaced), normal feeds can be resumed, although breast-feeding can be continued throughout. Intravenous rehydration may be associated with a slower recovery and a longer hospital stay, but is necessary if a child needs acute volume replacement for shock, or is unable to tolerate enteral fluids. Ahmed should be admitted for a trial of nasogastric fluid therapy. If he does not tolerate this, he will probably need intravenous rehydration.
How would you calculate the fluid requirements for Ahmed over the next 24 hours? Fluid requirement for 24 hours = Maintenance + Correction of deficit + Replacement of losses

***Definitions*:** 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: diarrheas due to secretory neoplasm (neuroblastoma), malabsorption (cystic fibrosis, celiac disease), endocrinopathy (thyrotoxicosis), anatomical defect (Hirschsprung's disease), immunodeficiency syndrome, or it may be chronic non-specific (Toddler's diarrhea) in a healthy thriving child.
- **Gastroenteritis** is diarrhea due to intestinal infectious agent.

ACUTE DIARRHEA

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. **Infectious diarrhea:**
    a. **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 Entamoeba histolytica, Giardia lamblia, Cryptosporidium.
        ✓ **Helminths:** as Ascaris and ancylostoma.
        ✓ **Fungi:** as Candida albicans.
    b. **Extraintestinal infections (parenteral diarrhea): t**his includes otitis media, pneumonia, and urinary tract infections. Diarrhea may be due to toxic effect or associated enteral infection.
2. **Non-infectious diarrhea:**
    a. **Dietetic factors:** such as overfeeding, underfeeding, food allergy, food intolerance or over concentrated formula.

b. **Malnutrition:** may be due to associated alteration of intestinal mucosa and motility in addition to changes in intestinal flora.
c. **Drugs:** direct villus damage e.g. streptomycin and neomycin, alteration of intestinal flora e.g. ampicillin or osmotic load e.g. Mg containing purgatives.
d. **Environmental factors:** such as hot weather and high humidity.
e. **Psychologic factors:** such as anxiety.

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, 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.

Complications of acute diarrhea:

1. **Dehydration**
2. **Metabolic acidosis**
3. **Shock**.
4. **Electrolyte disturbances:** Hypokalemia, hypernatremia, hyponatremia, and hypocalcemia.
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 (DIC)** due to severe dehydration, shock, acidosis, and toxemia.
10. **Failure to thrive and malnutrition**.

Treatment of acute diarrhea

- *Prevention*
- *Specific treatment of infectious diarrhea by proper antimicrobial or antiparasitic.*
- *Rapid determining and managing the fluid losses, dehydration, and electrolyte abnormalities.*
- *Proper feeding.*

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 avoid contaminated 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 (Rota virus and measles.)

Specific treatment of infectious diarrhea by proper antimicrobials or antiparasitic

a. Role of antibiotics and antiparasitic agents:

- Most diarrheal cases are due to viruses.
- Even great number of bacterial diarrheas is self-limited.
- Antimicrobial and anti-parasitic arn't needed as a routine in the management of acute diarrhea.

b. Indications of antibiotics and antiparasitic drugs 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.

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.

Assessment of diarrheal dehydration

Clinical aspect	No dehydration	Some dehydration	Severe dehydration
General condition	Well, alert	*Restless, irritable*	*Lethargic, unconscious, floppy*
Thirst	Drinks	*Drinks eagerly*	*Drinks poorly or unable to do*
Skin pinch	Returns quickly	*Returns slowly*	*Returns very slowly*
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mouth & tongue	Moist	Dry	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*			

Types of dehydration:

Dehydration may be hypertonic, hypotonic, or isotonic according to relative net losses of water and electrolytes (particularly sodium) from the body.

Isotonic (Isonatremic)	**Hypertonic (Hypernatremic)**	**Hypotonic (Hyponatremic)**
Serum Na 135– 145 mEq/L	Serum Na > 150 mEq/L	Serum Na < 130 mEq/L
Most common type > 2/3 of cases	5-15% of cases especially young infants due to their renal immaturity & decreased renal ability to conserve water.	5-15% of cases
Equivalent losses of water and electrolytes balanced with intake and helped by renal compensation.	There is more loss of water than electrolytes or more intakes of electrolytes than water.	There is more loss of electrolytes than water or more intake of water than electrolytes.
No major water shifts between extracellular and intracellular compartments of body fluid.	Water shifts from inside the cell to the extracellular fluid where sodium concentration and hence osmolarity is high.	In attempt to compensate, water shifts from extracellular to intracellular compartment due to osmotic gradient with resulting cellular edema.
Different signs of dehydration are present **without discrepancy.**	**Cellular dehydration** occurs and this accounts for most of clinical manifestations. The child becomes very thirsty, irritable or drowsy, and may proceed to convulsions, with very **dry tongue**	**Cellular edema** accounts for clinical manifestations of this type of dehydration. The child appears weak, hypotonic with drowsiness or delirium and the **tongue** (representing intracellular compartment status) remains **moist**.
	skin elasticity is relatively preserved giving the texture known as doughy skin	There is severe **loss of skin turgor** (representing extracellular component).

	- 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 - It is **most serious type** with mortality 5-10 times more than other types	In severe cases brain edema with convulsions and coma may occur

Treatment of dehydration:

➢ 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:

1. Giving the patient more fluids than usual.
2. Giving the patient plenty of foods (more than usual).
3. Identifying warning signs of dehydration 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.

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

- A maximum of 200 ml/kg/day of this solution should not be exceeded.
- *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.

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 (proper feeding):**
   - Continue breast-feeding frequently.
   - If the child is not breastfed, give the usual milk in the same full concentration.
   - 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. Other well-tolerated foods can be given according to situation.

- Give 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 2 weeks.
- Lactose free milks are not needed routinely in acute diarrhea as the incidence of significant lactose malabsorption is quite small (1.3%). These milks are frequently refused by the infant due to its bad smell and taste leading to inadequate feeding.
- **Inadequate feeding during acute diarrhea,** particularly in malnourished babies may increase the potential risk for the diarrhea becoming persistent, due to slower regeneration of the brush border.

3. **Taking the child back to the doctor:**
   - The mother should return to rehydration center once any of the warning signs appears.

Warning signs of dehydration
1. The baby did not become well within 3 days.
2. Developed any of the followings: ▪ Marked thirst ▪ Fever ▪ Repeated vomiting ▪ Eating or drinking poorly ▪ Many watery stools ▪ Lethargy ▪ Blood in the stool

➢ 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 within 4 hours.
- 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 20 - 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.

Associated acid-base and electrolyte disturbances:

1. Metabolic acidosis.
2. Hypokalemia (serum potassium less than 3.5 mEq/L).
3. Hyperkalemia (serum potassium more than 5.5 mEq/L).
4. Tetany.

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.

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:

  a. Intolerance to food stuffs:

  - Lactose and monosaccharide intolerance.
  - Fat malabsorption (50%).
  - Mild protein malabsorption.

  b. Cow milk protein allergy (due to passage of macromolecules through damaged intestinal barriers) that perpetuates chronic intestinal injury

  c. Persistent infection: some cases may suffer from intestinal infection with Shigella or Salmonella with continuous intestinal invasion and inflammation.

  d. Bile acid deconjugation occurs by bacterial overgrowth. These deconjugated bile acids are intestinal secretagogues and cause direct mucosal intestinal injury contributing to persistent diarrhea.

Practice Questions (Choose one correct answer)

1- ***Which of the following is not suggestive of pyloric stenosis?***
   a) Constant hunger even after vomiting.
   b) Visible gastric peristalsis.
   c) Hypochloraemia metabolic alkalosis with low plasma potassium.
   d) Bile-stained vomiting**.**

2- ***Bile-stained vomiting would prompt investigation for:***
   a) Gastroenteritis.
   b) Small bowel obstruction.
   c) Gastroesophageal reflux.
   d) Pyloric stenosis.

3- ***When might gastroesophageal reflux be particularly problematic:***
   a) In children with cerebral palsy.
   b) In preterm infants who develop bronchopulmonary dysplasia.
   c) Following surgery for esophageal atresia.
   d) All of the above.

4- ***Manifestations of severe dehydration do not include:***
   a) Polyuria.
   b) Sunken eyes.
   c) Skin tenting.
   d) Tachycardia.

5- ***Which of the following is an organic cause of constipation?***
   a) Hypothyroidism.
   b) Hypercalcemia.
   c) Hirschsprung disease.
   d) All of the above.

6- ***The absence of ganglion cells from the mesenteric and submucosal plexus of part of the large bowel is the cause of:***
   a) Celiac disease.
   b) Hirschsprung disease.
   c) Crohn`s disease.
   d) Cystic fibrosis.

7- ***What type of dehydration which may lead to multiple small cerebral hemorrhages and convulsions?***
   a) Isonatremic dehydration.
   b) Hyponatremic dehydration.
   c) Hypernatremic dehydration.
   d) Mild dehydration.

Chapter 9

Hepatology

Learning Objectives:

By the end of this chapter, students should be able to know:

1. Causes, diagnosis, and treatment of viral hepatitis in children.
2. Different types of infantile cholestasis, causes, diagnosis and treatment.
3. Causes, diagnosis, and treatment of portal hypertension in children.
4. Differential diagnosis and investigations of hepatomegaly in children.

Contents:

1. Viral hepatitis (A, B, C)
2. Infantile Cholestasis
3. Chronic Liver Disease in Children (liver cirrhosis-portal hypertension- ascites)
4. Hepatomegaly in Children

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)

Case 1

A previously healthy male child aged 6 years old presented with acute onset of fever, anorexia, vomiting, right upper quadrant abdominal pain and yellowish discoloration of eyes with dark urine & pale stool. There was no past history of similar condition, and the patient received no drugs in the last few months, but there was positive family history of a similar condition in the last few wks. By examination, there was jaundice and mild tender hepatomegaly. The initial investigations revealed that: total bilirubin 6 mg/dl, direct bilirubin 4 mg/dl, ALT 450 u/l, AST 270 u/l and normal CBC. Abdominal sonar revealed only mild diffuse hepatomegaly.

What is the most likely diagnosis of this case?

The most likely diagnosis of this case is HAV infection because the described clinical features and initial investigations are compatible with the diagnosis of acute infectious hepatitis and HAV infection is the most common type in children.

What are the further investigations needed to confirm the diagnosis of this case?

Biochemical:

Prothrombin time (PT), activity and INR to assess the extent of liver injury.

Serological:

IgM anti-HAV antibodies that appear in serum at onset of symptoms & disappear after 2m.

IgG anti-HAV antibodies that appear during convalescence & persists for many years.

What are the complications of this case?

- Fulminant hepatic failure (FHF) -Aplastic anemia
- Cholestassis - Relapsing (biphasic) hepatitis.

What are the lines of management of such case?

- There is no specific therapy for acute HAV infection.
- Most children are managed at home except if liver cell failure is suspected.
- Balanced diet with low fat intake should be given.

Etiology & 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 onset of hepatitis.

Clinical picture

Incubation period: from 20-40 days.

- Most children have an ***asymptomatic*** subclinical infection.
- ***Symptomatic infection has 2 phases:***
  - **Pre-icteric phases:** Fever, anorexia, headache, and malaise (FAHM) + nausea, vomiting, abdominal discomfort, diarrhea.
  - ***Icteric phases:***
    - Jaundice, dark urine & pale stool.
    - 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.**
   - ***Biochemical:***
     - Serum biphasic bilirubin level rises.

- ALT & AST levels are elevated several folds the normal values.
- Prothrombin time (PT), to assess the extent of liver injury.

– ***Serological:***

- IgM anti-HAV antibodies appear in serum at onset of symptoms & disappear after 2 m.
- IgG anti-HAV antibodies appear during convalescence & persists 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:

– Rapid progression of symptoms.
– Deepening of jaundice.
– Reduction of liver size.
– Development of ascites.
– Neuro-psychiatric changes (Aggressive behavior, encephalopathy).

Laboratory findings:

– Prolongation of prothrombin time (not responding to Vit. K).
– Falling of serum albumin.
– Raised serum ammonia.

B- Aplastic anemia:

- Is a very rare complication it is transient but may be fatal.
- It is due to bone marrow depression.
- Death is usually due to serous infection due to depressed immunity.

C-Cholestassis:

- 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. There is no specific therapy for acute viral hepatitis,
2. Most children are managed at home except if liver cell failure is suspected
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	***Perinatal transmission:*** 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. ***Parenteral:*** In patient receiving transfusion of contaminated blood or blood products, renal dialysis, dental care and through contaminated syringes and needles.

	Child to child transmission: 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 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 wks, followed by antisurface antibodies (HBs Ab).

Complications:

1- Fulminant hepatitis: It occurs more frequently with HBV than other viruses (1%). Risk increases with 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-∝-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 l and 6 months.

Prognosis:

- Recovery may be complete.
- The child may remain as an asymptomatic carrier.
- 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	• Intravenous drug use 40%. • Transfusion of blood and blood products 10%. • Occupational and sexual exposure 10%. • Perinatal transmission is uncommon. ***N.B.*** *Breast-feeding does not transmit HCV.*

Clinical picture:

1. ***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.
2. ***Preicteric phase:*** (FAHM) + nausea, vomiting and abdominal pain.
3. ***Icteric phase:*** Jaundice and dark urine.

Laboratory investigations:

1. ***Transaminases:*** SGPT and SGOT are moderately elevated and fluctuate for long time.
2. ***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.
3. ***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 glomerulo- nephritis.

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 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 nowadaya due development of oral new treatment options that include several potent oral directly-acting antiviral drugs (DAAs).
- Recently, ***Sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni)*** are used to treat HCV in children and adolescents aged 12 years and older or weighing at least 35 kilograms with the same adult fixed dose.

Infantile Cholestasis

Case 2

An infant aged 6 weeks, delivered at full-term, presented by persistent jaundice since few days of early life, hepatomegaly, clay-colored stool and dark urine. The infant was doing well. There was no a past history of incubation. There was no family history of similar condition.

On examination: vital and physical measurements were within normal. Greenish yellow jaundice was present with no pallor, no lymphadenopathy, no splenomegaly and no ascites. Liver was palpable about 5 cm below the right costal margin with firm consistency. Examinations of other body systems were normal. Investigations revealed that total serum bilirubin is 8 mg /dl with direct component is 6.5 mg /dl,. Liver enzymes showed that ALT and AST were mildly elevated but with great elevations in ALP and GGT. CBC was normal.

What is the differential diagnosis of this case?

A. Extrahepatic biliary obstruction (EHBO):

B. Intrahepatic biliary hypoplasia (PIBD):

C. Hepatocellular disease:

What are the investigations of this case?

A-Laboratory procedures:

- Complete liver functions
- TORSCH screening, Sepsis work-up, Hepatitis markers and thyroid functions
- Urine/serum bile acids and amino acids.
- α1-antitrypsin phenotype, Sweat chloride/mutation analysis,

B-Imaging procedures:

-Abdominal Ultrasonography -MRI of liver & biliary ducts (**MRCP**).

C-Ophthalmological consultation.

D- Hepatobiliary scintigraphy (HIDA scan) and Liver biopsy.

F- Intraoperative cholangiography for suspected cases of EHBO only.

What are the complications of this case?

Malabsorption, growth retardation, secondary biliary cirrhosis, portal hypertension and end-stage liver cell failure.

What are the lines of management of such case?

A-Surgical Correction for EHBO:

- *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).
- *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:

- Adequate nutrition.
- Retention of biliary constituents such as bile acids and cholesterol (itch/xanthomata): Administer choleretics such as ursodeoxycholic acid (5-10 mg/kg/day) or bile acid binders (cholestyramine).

C-Liver transplantation: if end-stage liver failure occurs.

Definition: Reduction in bile flow with retention of substances normally excreted in bile (e.g., bilirubin, bile acids & cholesterol) with histopathologic features reflecting nature & degree of disturbances.

Types:

A- Hepatocellular cholestasis: Where an impairment of bile formation occurs.

B- Obstructive cholestasis: Where impedance to bile flow occurs after it is formed.

Causes:

A- Extrahepatic biliary obstruction (EHBO)

- Extrahepatic biliary atresia (EHBA).
- Choledochal cyst.
- Spontaneous rupture of the bile duct.
- Extrinsic compression.

B- Intrahepatic biliary hypoplasia

- Alagille's syndrome.
- Non syndromic ductal paucity.

C- Hepatocellular disease

- Neonatal hepatitis.
- Alpha 1antitrypsin deficiency.
- Inborn errors of bile acid synthesis.

- Drug induced cholestasis.
- Total parenteral nutrition.
- Progressive familial intrahepatic cholestasis.

n.b. *Approximately 75% of neonatal cholestasis cases are due to EHBA or neonatal hepatitis.*

Clinical picture: clinical consequences of cholestasis are due to:

A- Early cholestasis: (symptoms - signs)

I. Retention / Regurgitation of the different components of the bile:

- **Bilirubin (conjugated):** Jaundice with changes in color of urine (dark) and or stool (pale).
- **Bile acid:** Pruritus, bradycardia, and *progressive liver damage (cirrhosis).*
- **Cholesterol:** Xanthomatosis and *progressive liver damage (cirrhosis)*
- **Trace elements (copper, etc.):** *Progressive liver damage (cirrhosis)*

II. Decreased bile salts in intestine:

- **Malabsorption of long-chain triglycerides:** Growth retardation, diarrhea/ steatorrhea
- **Vit. D Malabsorption:** Metabolic bone disease (Osteoporosis, rickets).
- **Vit. K Malabsorption:** Bleeding tendency resulting from deficiencies of Vit. K-dependent coagulation factors.
- **Vit. A Malabsorption:** Thick skin, Night blindness
- **Vit. E Malabsorption:** Hemolytic anemia, neuromuscular degeneration, areflexia, truncal ataxia, ophthalmoplegia, peripheral neuropathy).

B- Late or complicated cholestasis:

I- Biliary liver cirrhosis

II- Portal hypertension [PH] with development of esophagogastric varices

III- End-stage liver failure [ESLF].

C- Other signs:

1.Liver: Early is enlarged, in cirrhosis the liver shows nodular surface and sharp border whereas the size is variable.

2.Spleen: enlarged.

3.Urine: dark, frothy.

4.Bleeding tendency due to Vit. K-dependent coagulation factors deficiencies esophageal varices due to PH or gastritis and peptic ulcer due to defective catabolism of gastrin hormone.

Diagnosis

a. The initial step in identification of cholestasis is the finding that the conjugated bilirubin is more than 20% of the significantly elevated level of total bilirubin.

b. The next step: Is the early recognition of the treatable medical or surgical causes of cholestasis.

- ***Medical causes*** (sepsis, endocrinopathy e.g., hypothyroidism or panhypopituitarism, or galactosemia).
- ***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 biliary cirrhosis).

A- 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,

-Thyroxine and TSH.

-Urine/serum bile acids, amino acids and urine reducing substances measurement

-α1-antitrypsin phenotype, Sweat chloride/mutation analysis,

B-Imaging procedures:

- Abdominal Ultrasonography
- MRI of liver & biliary ducts (MRCP).

C-Ophthalmological consultation.

D- Hepatobiliary scintigraphy (HIDA scan).

E- Liver biopsy.

F- Intraoperative cholangiography for suspected cases of EHBO only.

Treatment

A- Surgical:

- *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).
- *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:

- Adequate calories for maintenance of good nutrition.

- Malnutrition due to malabsorption of dietary long-chain triglyceride: Replace with dietary formula or supplements containing readily absorbed medium-chain triglycerides.
- Large doses of fat-soluble vitamins (A, D, E and K) to correct malabsorption of these vitamins.
- Retention of biliary constituents such as bile acids and cholesterol (itch/xanthomata): Administer choleretics such as ursodeoxycholic acid (5-10 mg/kg/day) or bile acid binders (cholestyramine).

C- Liver transplantation: if end-stage liver failure occurs.

PORTAL HYPERTENSION (PH)

Case 3

A child aged 6 years old presented by mild hematemesis and melena since few hours to the emergency department. There was past history of incubation and umbilical catheterization during the incubation period. He was receiving no medications.

On examination: Physical growth was normal. There was mild pallor, mild tachycardia, hemodynamic stability, and moderate firm splenomegaly with no hepatomegaly, no ascites, no lymphadenopathy, and no skin rash. Examinations of other body systems were normal.

CBC, liver function tests, bleeding and coagulation profiles were within normal limits. Liver size and echogenicity were normal by hepatic ultrasound. Resuscitation of the patient was performed in the emergency department during initial evaluation and obtaining the suitable blood samples.

What is the most likely diagnosis of this case? Explain why?

The most likely diagnosis is **prehepatic portal hypertension** with **bleeding varices** duo to: presence of past history of incubation and umbilical catheterization, presence of isolated splenomegaly, hematemesis and melena, normal liver size, echogenicity and functions together with no evidence generalized bleeding tendency.

Enumerate the most 2 appropriate diagnostic investigations to confirm the diagnosis ?

The most 2 appropriate diagnostic investigations to confirm this diagnosis are **abdominal ultrasound with Doppler** examination of the portal venous system to confirm prehepatic portal hypertension (PV Cavernoma) followed by **upper GIT endoscopy** to confirm bleeding varices .

Enumerate the most 2 appropriate therapeutic procedures for this case?

The most 2 appropriate therapeutic procedures for such condition are repeated sessions of **endoscopic sclerotherapy** or **endoscopic band ligation** to eradicate varices according to the available expertise and endoscopic equipments.

What are the common causes of upper gastrointestinal bleeding in children?

Common causes of upper gastrointestinal bleeding in children include:

Esophagitis, Gastritis, Esophageal varices, Peptic ulcer diseases, Mallory-Weis tear. Pill ulcer, swallowed blood. Foreign boy ingestion, Coagulopathy.

Definition: PH exists when pressure in portal vinous system rises above 10-12 mmHg.

Etiology (classification): *classified according to the anatomic location of the disease:*

A. Pre-hepatic obstruction (most common type in children):

- ***Portal vein occlusion:***
  - Thrombosis (umbilical sepsis, umbilical venous catheterization in the neonate).
  - Extrinsic compression.
- ***Splenic vein thrombosis:*** This might be a congenital anomaly or acquired.

B. Hepatic obstruction:

- ***Cirrhosis:*** post-necrotic, biliary, cardiac, autoimmune, drug-induced,cryptogenic.
- ***Schistosomiasis.***
- ***Chronic active hepatitis.***
- ***Congenital hepatic fibrosis.***

C. Post-hepatic obstruction:

- ***Veno-occlusive disease, Budd-chiari syndrome.***
- ***Right ventricular failure, constrictive pericarditis.***

Clinical picture:

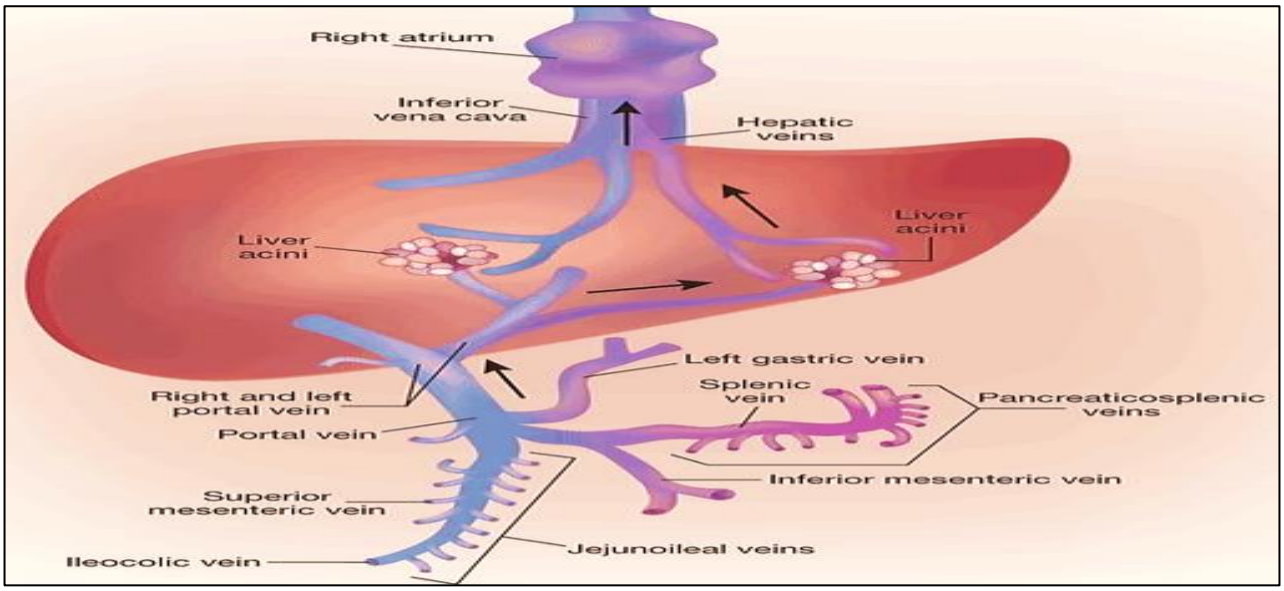
- Features of the underlying hepatic disease.
- GIT bleeding: hematemesis or melena.
- Splenomegaly with features of hypersplenism (low Hb concentration, low total white count and thrombocytopenia).
- Dilated cutaneous collateral vessels.
- Ascites.
- Failure to thrive due to malabsorption and porto-systemic shunt.
- Hepatic encephalopathy due to due to porto-systemic shunts.

Diagnosis:

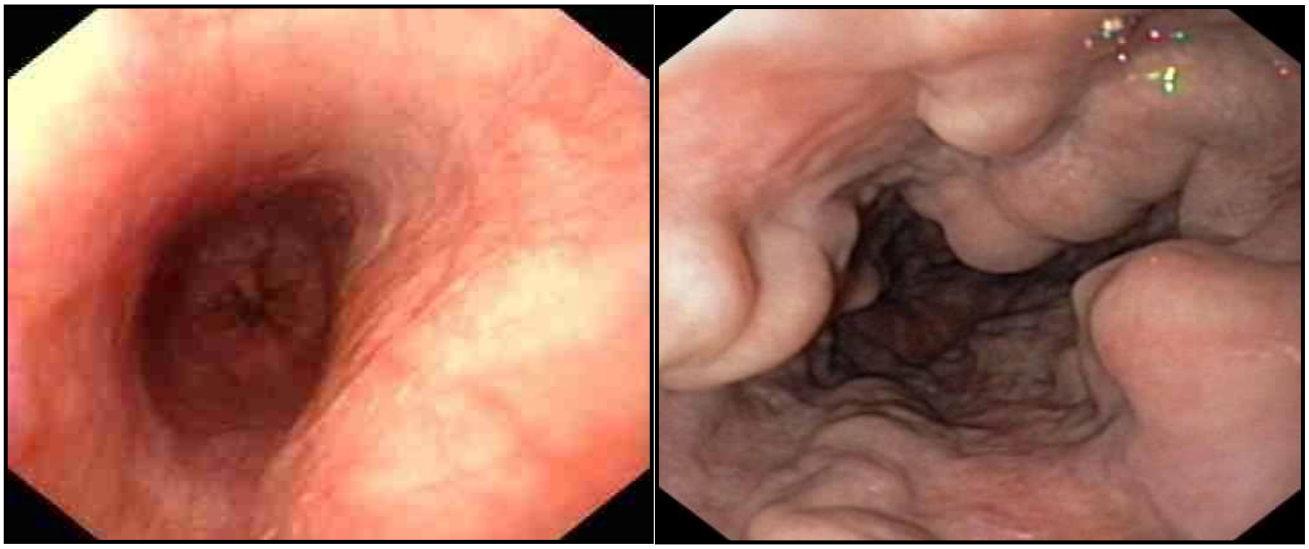
A- Non-Invasive Investigations of portal hypertension:

- ***Initial Lab Investigations:*** full blood count, liver and renal function tests.
- ***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.

- Liver stiffness measurement ***by ultrasound-based elastography (FibroScan) or by MRI- based elastography*** to predict liver fibrosis stages and the presence of varices.



B- <u>Endoscopy of upper GIT:</u> to detect esophageal varices, gastric varices, peptic ulcers, PH gastropathy.



(Normal esophagus compared to one with esophageal varices by GIT endoscope)

C- <u>Invasive Measurements of portal hypertension</u> <u>(not-routinely done)</u>

- ***Operative portal vein (PV) measurement.***
- ***Percutaneous transhepatic measurement.***
- ***Transjugular measurement.***
- ***Hepatic vein catheterization.***
- ***Intrasplenic measurement.***

Treatment:

i) **Gastrointestinal bleeding:** it requires emergency treatment (Resuscitation of the patient followed by urgent endoscopic variceal sclerotherapy or endoscopic variceal band ligation).

ii) **Hepatic encephalopathy:** Nasogastric administration of neomycin or lactulose, I.V vitamin K & fresh frozen plasma (FFP), Repeated enema with lactulose, Restriction of protein intake for short periods.

iii) Surgical procedures in portal hypertension:

- Porto-systemic shunts.
- Transjugular intrahepatic portosystemic shunting (TIPS).

IV) Liver transplantation: if ESLF occurs.

Hepatomegaly in children

Causes and Mechanisms

Mechanism	Causes of Hepatomegaly
Inflammation/ Infections	– **Infections:** • Viral (hepatitis A, B, C, D, E, Cytomegalovirus, Ebstein-Barr virus, etc.) • Bacterial (sepsis, pyogenic liver abscess, military TB, Brucellosis, typhoid fever) • Parasitic (Schistosomiasis, malaria, hepatic amebiasis, hydatid cyst, Visceral larva migans, Fasciola hepatica, etc.) – **Toxins or Drugs** – **Idiopathic neonatal hepatitis** – **Autoimmune liver disease** – **Kupffer cell hyperplasiaå**
Inappropriate Storage	– **Glycogen**: Glycogen storage disease, diabetes mellitus, parenteral nutrition – **Lipids**: Neimann-Pick disease, Gaucher disease, Wolman disease – **Fat:** Obesity, DM, parenteral nutrition, mucopolysaccharidoses types I through IV, Fatty acid oxidation defect, NAFLD/NASH. – **Metals**: Wilson disease (Copper), hemochromatosis (Iron) – **Abnormal proteins**: Alpha-1-antitrypsin deficiency
Infiltration	– **Primary neoplastic tumors**: Hepatoblastoma/Hepatocellular carcinoma – **Primary non-neoplastic tumors**: Hemangioma, hemangioendothelioma, teratoma, focal nodular hyperplasia – **Metastatic or disseminated tumors**: Leukemia, lymphoma, neuroblastoma, histiocytosis – **Cysts**: Parasitic cyst, choledochal cyst, polycystic liver disease – **Hemophagocytic syndromes** – **Extramedullary hematopoiesis**
Vascular/ Congestion	– **Suprahepatic**: Congestive heart failure, Restrictive pericarditis, Suprahepatic web, and Hepatic vein thrombosis (Budd-Chiari syndrome) – **Intrahepatic**: Veno-occlusive disease

Biliary Obstruction	– **Cholelithiasis** – **Choledochal cyst** – **Biliary atresia** – **Tumors** (Hepatic, Biliary, Pancreatic, Duodenal)

Investigations of Hepatomegaly

A- Noninvasive Investigations:

- ***Laboratory:***
  1. Stool & urine analysis
  2. CBC
  3. Liver & renal function tests
  4. Disease-specific markers**:** (viral markers,TORSCH screaning, sepsis workup, autoimmune markers, immunological markers, metabolic markers, tumors markers)
- ***Imaging procedures:***
  1. Abdominal ultasound with Doppler
  2. Abdominal CT or MRI
  3. Elastography or FibroScan.

C- Invasive Investigations:

- ***GIT Endoscopy***
  1. Uppper GIT Endoscopy
  2. Colonoscopy
  3. ERCP
- ***Histopathological tissue diagnosis***
  1. Liver biopsy
  2. Lymph node biopsy
  3. Bone marrow aspiration or biopsy).

Practice Questions (Choose one correct answer)

1. ***The preferred type of fat in case of cholestasis is:***
   a. Medium-chain triglycerides.
   b. Long-chain triglycerides.
   c. Both of them.
   d. None of them
2. ***The long-term complications of hepatitis B virus infection include the following except*:**
   a. Cirrhosis.
   b. Chronic hepatitis.
   c. Nephritis.
   d. Hepatic carcinoma.
3. ***The cause of exudative ascitic fluid includes the following except:***
   a. Tuberculosis.
   b. Malignancy.
   c. Liver cirrhosis.
   d. All of the above.
4. ***Most common cause of severe hematemesis in a child is:***
   a. Portal hypertension.
   b. Mallory-Weiss syndrome.
   c. Peptic ulcer.
   d. None of the above.
5. ***Causes of hepatomegaly include the following except:***
   a. Cytomegalovirus.
   b. Cholestasis.
   c. Sepsis.
   d. Prehepatic portal hypertension.
6. ***The investigations for cholestasis include the following except:***
   a. Urine assessment for reducing sugar.
   b. CBC with differential.
   c. Urine culture.
   d. Stool analysis.

7. ***Which of the following is not a known intrahepatic cause of portal hypertension?***
   a. Biliary atresia.
   b. Constrictive pericarditis.
   c. Schistosomiasis.
   d. Congenital hepatic fibrosis.
8. ***The early surgical Kasai procedure of extrahepatic biliary atresia should be done within the first:***
   a. 4 months.
   b. 5 months.
   c. 8 months.
   d. 2 months.
9. ***Splenomegaly without hepatomegaly is found in:***
   a. Tricuspid incompetence.
   b. RT side heart failure
   c. Portal hypertension post neonatal umbilical catheterization.
   d. None of the above.
10. ***The commonest cause of neonatal cholestatic jaundice:***
    a. Extrahepatic biliary atresia.
    b. Idiopathic neonatal hepatitis.
    c. Both.
    d. None of the above.

Chapter 10

Neurologic & Neuromuscular Disorders

Learning Objectives:

By the end of this chapter, students should be able to:

1. Mention the definition, clinical picture, and differential diagnosis of cerebral palsy.
2. Mention the definition and causes of Intellectual Disability.
3. Mention the clinical features of the floppy infant and its DD.
4. Recognize the definition of seizures and the classification of epilepsy.

Contents:

1. Cerebral palsy
2. Intellectual Disability
3. Floppy infant
4. Seizure & epilepsy

Cerebral palsy

Case 1

Male patient aged 2.5 years old complaining of global developmental delay, he developed only head support, active palmer grasp, only recognize mother and only coos .there was history of difficult labor and was incubated for one month on mechanical ventilator immediately after delivery due to severe respiratory distress and cyanosis the child developed attack of convulsion after discharge from incubation which was generalized tonic clonic convulsion, then it was recurrent many times and was investigated by EEG and diagnosed as epilepsy and received antiepileptic drugs and was controlled and the case became stationary .there was past history of repeated hospitalization due to recurrent aspiration that cause recurrent chest infection due to difficulty in swallowing .there is negative consanguinity, no similar condition in the family and he has one brother aged 4 years with good health . By neurological examination he is apathetic; calm, has no speech ,severe mental retarded DQ =50%, regarding motor system he has hypertonia spasticity with muscle power grade1 in both upper limb and grade2 in both lower limb and exaggerated deep tendon reflex and positive Babinski sign.

What is the most likely diagnosis?

A case of spastic double hemiplegic CP most probably post hypoxic ischemic encephalopathy associated with intellectual disability and epilepsy and complicated by aspiration pneumonia.

What is the differential diagnosis?

1. Degenerative CNS diseases
2. Spinal cord tumor
3. Muscular dystrophy

What is the investigation?

1. Brain CT scan or magnetic resonance imaging (MRI)
2. EEG
3. Tests for auditory and visual acuity

What is the appropriate treatment for this condition?

Management of CP is a teamwork aiming at offering the child the best quality of life this needs the cooperation of pediatrician, physiotherapist, orthopedist, speech, Therapist and nutrionist, Treatment consists of:

1. Education: depends on the degree of brain affection
2. Drugs: Muscle relaxant, Anticonvulsant drugs,)

3. Physiotherapy: to avoid contractures.
4. Use of some aids: Sitting: special chairs. And Walking: special calipers.
5. Speech therapist
6. Orthopedic correction of deformities and contractures

Definition:

- 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, intellectual disability, visual/hearing impairment, and / or language delay.

***Etiology*:** CP results from damage affecting motor areas of brain (motor cortex, basal ganglia, and cerebellum) due to:

1- Prenatal factors (10-20 % of cases):

- Intrauterine infection: TORCH, other viruses,
- Prenatal anoxia,
- Fetal irradiation,
- Congenital CNS malformations,
- 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 evolutional stage in the development of spastic CP.

5- Mixed CP.

Spastic Cerebral palsy

- It is the commonest type of CP 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. Intellectual disability,
  2. Seizures,
  3. Swallowing difficulties due to supra nuclear 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, so it is athetoid CP in early life.
- At about one year of age, involuntary movements in the form of choreoathetosis and dystonia appear, and the muscle tone is increased (rigidity)
- Speech is typically affected owing to involvement of the oropharyngeal muscles.
- Seizures are uncommon.

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.

Atonic Cerebral Palsy

- It will be changed into a spastic type after a period of time.
- Generalized hypotonia.
- Exaggerated deep tendon reflexes.
- Intellectual disability.

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 magnetic resonance imaging (MRI),
2. EEG,
3. Tests for auditory and visual acuity.

Associated disabilities with CP:

1- Epilepsy: Occur in 30 % of cases.

2- Intellectual disability and learning problems: 60 % of children with CP have some degree of Intellectual disability.

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.

4- Speech disorders: common and may be due to:

- Hearing loss,
- Intellectual disability,
- Muscular incoordination.

Management of CP: it's a teamwork aiming at offering the child the best quality of life this needs the cooperation of pediatrician, physiotherapist, orthopedist, speech, Therapist and nutrionist.

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

Case 1

An 11-year-old male was referred complaining of delayed speech and defective behavioral skills. He was the first child born to apparently healthy non-consanguineous parents. The mother had an uneventful pregnancy with no history of prenatal exposure to alcohol, drug or tobacco. Though his siblings (7-year brother and 3 years old sister) were phenotypically normal, his paternal cousin-sister was micro cephalic and mentally challenged. No investigations were carried out in the affected cousin-sister. The case was born by normal vaginal delivery. The birth weight was 1.5 kg. Apgar score at birth was within the normal range. The patient was sitting without support at around 1.5 years. He could stand with support by 2 years and independent walking at 2.5 years. His speech development was delayed. He was not able to speak sentences and could not achieve proper bowel and bladder control even at the time of presentation 11 years. His respiratory, cardiovascular and abdominal examinations were unremarkable. CNS examination delayed language development and hyperactivity. His speech and cognitive development were more delayed than his motor milestones, and academic performance was very poor.

What is the most likely diagnosis?

A case of **Intellectual Disability** for further investigations.

What are the diagnostic criteria?

Diagnostic criteria:

1. Sub-average 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.

What are the most common causes?

Some common causes of intellectual disability include:

- Certain genetic conditions, such as Down syndrome, phenylketonuria, or fragile X syndrome.
- Fetal alcohol syndrome.
- Congenital anomalies or brain malformations.
- Some infections, such as meningitis, measles, or whooping cough.
- Exposure to toxins such as mercury or lead.
- Serious head injury.

How can you evaluate such cases?

- Standardized intelligence tests: Intellectual function is measured by the administration of intelligence tests in children >3 yr. of age.
- Brain imaging: Plain x-ray, brain CT scan, MRI.
- Chromosomal studies.
- Thyroid function tests, TORCH, Metabolic screening and Blood lead level.

What is the treatment?

Intellectual disability is a lifelong condition. Although there is currently no cure, most people can learn to improve their functioning over time. Receiving early, ongoing interventions can often improve functioning, thereby allowing someone to thrive. Many services exist to help people with intellectual disability and their families get the support they need. Most of these services allow someone with intellectual disability to function normally in society. Supportive services include:

- Treat the cause if possible.
- Interventions that should be applied early to improve short-term and Long-term outcomes,
- Treat associated diseases e.g., epilepsy, visual, or auditory impairment, malnutrition.
- Specific drug therapy: no drugs have been found to improve intellectual function, except for specific defects as thyroxin for hypothyroidism.

Definition: It is a deficit in intellectual and adaptive functioning presenting before 18 years of age and characterized by IQ less than 70. Adaptive behavior means behavioral skills needed to live independently.

Etiology:

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

- Environmental toxins or teratogens (e.g., alcohol, lead, mercury, Phenytoin, valproate).
- Congenital infections

- Radiation exposure
- Fetal anoxia or trauma.
- Placental insufficiency.

B- Perinatal brain insult:

- Extreme prematurity.
- Neonatal asphyxia.
- Intracranial hemorrhage.
- Birth injuries.
- Neonatal meningo encephalitis.
- Hyperbilirubinemia or Hypoglycemia.

C- Postnatal brain insult:

- Congenital hypothyroidism.
- CNS infections: meningitis, encephalitis, brain abscess.
- Brain trauma
- Hypoxia (e.g., near-drowning)
- Environmental toxins: CO, lead.
- Post-immunization e.g. after rabies or pertussis Vaccination.
- Psychosocial deprivation
- Malnutrition

Grades of Intellectual disability:

IQ	Type	Comment
71-90	**Borderline**	• Not handicapped but have some learning Problems. • Can function independently
51-70	**Mild (educable)**	• May not be apparent till school age. • In special schools, they can attain 4^{th} - 6^{th} grade reading level • Able to function independently as adult.

36-50	**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.
21-35	**Severe**	• Non-educable • Non-trainable. • Minimal self-care, • No language Development.
0-20	**Profound**	• Non educable • Non-trainable. • No self-care • No language development.

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 have been found to improve intellectual function, except for specific defects as thyroxin for hypothyroidism
- Treating associated disorders: ADHD (stimulant medication), self-injurious behavior and aggression (neuroleptics).
- Piracetam may cause some improvement.

Prevention of Intellectual disability

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

Case 1

Female patient was referred to Pediatric consultation at the age of 5 months with extreme hypotonia progressing since birth, marked decrease in spontaneous movement, severe muscular weakness in his trunk and proximal parts of the extremities, with tongue fasciculation. There were repeated episodes of pulmonary infections. There was a history of similar clinical symptomatology in a patient's older brother, suggesting a familial involvement. EMG analysis revealed motor neuron a defect without nerve conduction anomaly a quantitative PCR-based testing demonstrated homozygous deletion of SMN1.

What is the most probable diagnosis?

This is a case of hypotonia most probably **spinal muscular atrophy (SMA)type 1** = severe infantile **(Werdnig-— Hoffman disease)**

What is the cause of this condition?

Spinal muscular atrophy (SMA) describes a spectrum of clinical syndromes caused by a mutation in the survival motor neuron (SMN). SMA causes degeneration of the anterior horn cells and cranial nerve nuclei, resulting in progressive weakness as a consequence of widespread denervation.

What is the differential diagnosis?

Central causes: atonic Cerebral palsy, Chromosomal as Down syndrome, Congenital anomalies of the cerebellum. **Spinal cord diseases**: hypoxic ischemic myelopathy

Neuro-muscular causes: Werdnig-Hoffman, Polyneuropathies: e.g. Gillian Barre Syndrome

Disorders of neuromuscular transmission: congenital myasthenia gravis, primary muscle diseases: congenital myopathy and congenital muscular dystrophy

What is the investigation of such cases?

- A screening work-up was already done by the paediatrician. The availability of specific genetic
- testing for the SMN gene greatly simplifies the evaluation for SMA
- DNA testing is the first recommended step in the evaluation of a child with suspected SMA
- For patients who do not have genetically proven SMA, more conventional testing is warranted.
  - Serum muscle enzymes, EMG, NCS, and muscle biopsy can help to confirm the diagnosis.
  - Serum creatine kinase may be mildly elevated but is usually normal.
  - EMG in severely affected infants demonstrates fibrillations and positive sharp Waves consistent with acute denervation.

How can you differentiate central from peripheral hypotonia?

Central Hypotonia	*Peripheral Hypotonia*
• Dysmorphic features • Cognitive and language delay • Normal strength • Increased reflexes • Seizures • Depressed level of consciousness • Predominantly axial hypotonia	• Muscle fasciculation • Weakness, such as lack of antigravity movements or lack of spontaneous movements • Depressed or absent reflexes • Normal cognitive and language function • Limited eye movement • Decrease muscle bulk or muscle atrophy • Myopathic facies: long, narrow facies with tented upper lip

What is the management of this condition?

- The treatment for spinal muscular atrophy is symptomatic and supportive
- Joint contractures and spinal deformities may be helped with physical and occupational therapy or bracing devices.
- SMA patients are at risk for failure to thrive because of a progressive fatigability and weak suckling. Nutritional support is often required.
- It is also important to observe patients' respiratory status as neurologic deterioration occurs. Involvement of a pulmonologist can be helpful in addressing long-term respiratory issues. Children with SMA should also be evaluated by a geneticist to assist in family counselling and assessment of carrier status.

Definition the infant who has marked generalized Hypotonia since birth and persist.

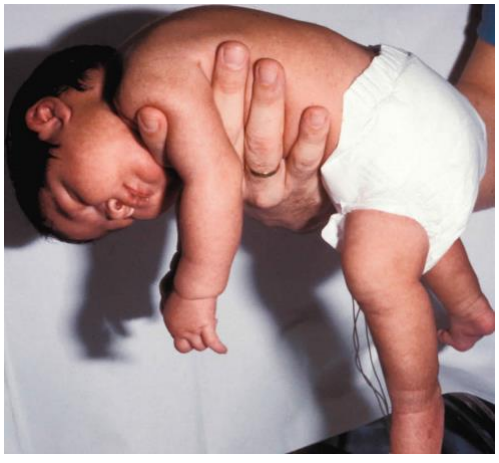
Criteria for diagnosis:

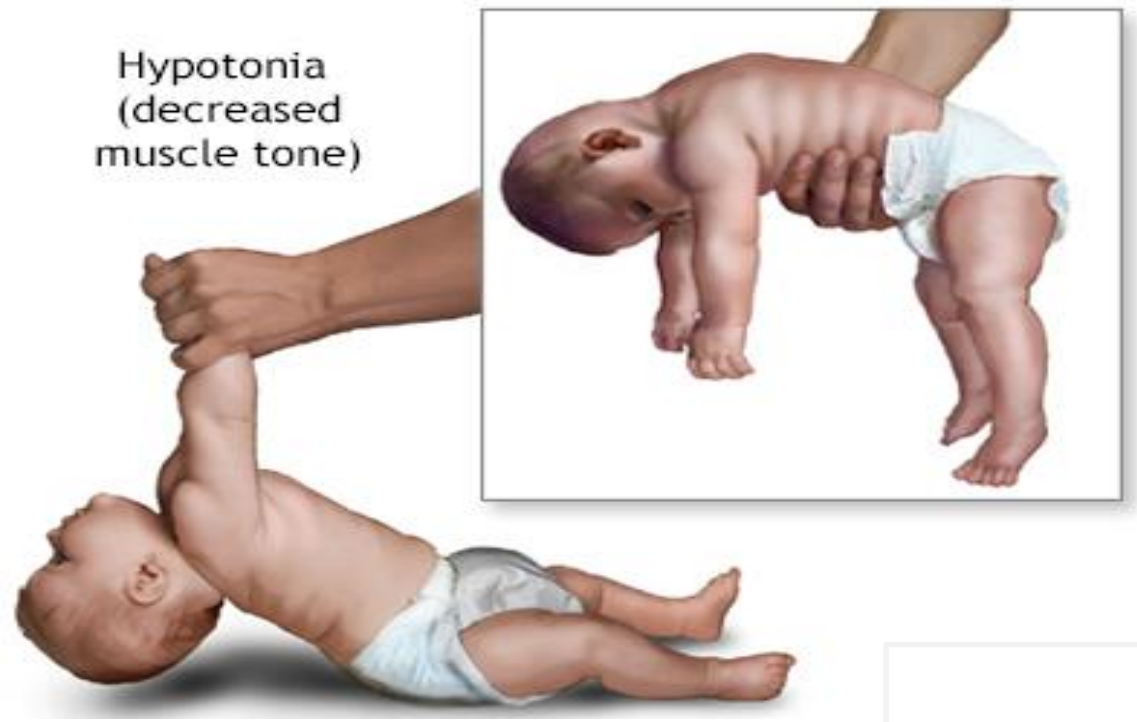
1- **Lying supine**: no spontaneous movements, and Frog-leg position.

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:

I- Central causes:

1- Atonic cerebral palsy.

- Generalized Hypotonia
- Exaggerated deep tendon reflexes
- Intellectual disability

2- Chromosomal as Down syndrome.

3- Congenital anomalies of the cerebellum.

4- 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

II-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 injury of the spinal cord e.g. Breach presentation. **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.

III-Neuro-muscular causes.

1- 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 fasciculation with normal mentality.
- Two thirds of infants die by 2 years of age.
- EMG: is diagnostic

2- Polyneuropathies: e.g., Gillian Barre Syndrome

- Post-infectious (demyelination of spinal roots)
- Bilateral and symmetrical weakness
- Absent deep tendon reflexes
- Glove and stocking hypothesia
- CSF: protein cell dissociation
- Slow nerve conduction velocity
- EMG: normal

Seizures and epilepsy

Case 1

8-month-old boy, presented by some strange episodes he has been having over the previous three weeks. The episodes usually occur soon after he has woken but may sometimes happen as he is about to go to sleep. In these episodes his knees suddenly come up towards his chest, his arms bend at the elbows and his hands may clench. Each episode lasts a few seconds but they may occur repeatedly over many minutes. He is very upset after them.

Over the past two weeks he has become more irritable and has stopped showing any interest in his toys. His birth and perinatal period were normal.

What is the type of seizure?

This case is mostly infantile spasm

What is the investigation?

EEG should be done characteristic EEG pattern (hypsarrhythmia).

Case 2

A healthy 7-year-old boy has been referred for an evaluation several months after starting because his teacher has noted that he frequently have staring spells at school The child seems to come back to responsiveness very quickly, seemingly without confusion His reading and math skills were average but now are slightly below grade level. On questioning, his mother reports that there are times when he stops talking, stares, and blinks his eyes for several seconds. These spells do not seem to bother him, however, and he is fine afterwards.

General Examination: Normal.

Neurologic Examination: Mental Status: Alert. Language: His speech is fluent without dysarthria. Cranial Nerves: II through XII intact. Motor: He has normal bulk and tone with 5/5 strength throughout. Coordination: He has normal finger-to-nose testing bilaterally. Sensory: There are no sensory deficits. Gait: He has a normal heel, toe, flat, and tandem gait. Reflexes: 2+ throughout with bilateral plantar flexor.

Briefly summarize this case.

The patient is a healthy 7-year-old boy who presents with a decline in academic performance and staring spells.

What is the diagnosis?

This case is mostly Childhood absence epilepsy.

What is the differential diagnosis?

1. The differential diagnosis of a child with difficulties in school and daydreaming includes various types of absence, as well as complex partial seizures in contrast to typical absence seizures:
   - Complex partial seizures may begin with an aura.
   - They tend to last more than 1 minute and have more prominent
   - Automatisms, such as lip smacking and semi purposeful hand movements.
   - Complex partial seizures are also more often associated with a postictal state.
   - The EEG in Complex partial seizures demonstrate focal rather than generalized epileptiform discharges.
2. Nonepileptic conditions such as learning disabilities, attention deficit disorder, Daydreaming, depression, and other behavioral disorders must be considered. In these cases, a detailed history of the spells may help differentiate them from Seizures.

Discuss an appropriate diagnostic work-up.

1. A child with suspected absence seizures may be hyperventilated in the office, which will often provide the diagnosis. However, an EEG with hyperventilation and photic stimulation should be performed to confirm the diagnosis
2. EEG should be done characteristic EEG pattern (3 per second spike and wave pattern).
3. Psychological and educational testing should be performed through the school system to rule out an underlying learning disability

Discuss the management of this patient.

1. Treatment with anticonvulsants is indicated in childhood absence epilepsy because seizures are frequent and ongoing seizure activity can adversely affect cognitive function. Accidents may also occur during seizures.
2. Treatment options include ethosuxcimide, valproic acid, and lamotrigine.

Case 3

Healthy 2-year-old boy was brought to the emergency room after experiencing a new-onset seizure. The parents report that the child has had a decrease appetite with slight irritability for the last 12 hours. While taking a nap, he experienced the sudden onset of rhythmic jerking of the upper and lower extremities with his eyes rolling back into his head for approximately 1 minute. This prompted his parents to bring him to the emergency room where he experienced a second event. On review of

developmental milestones, he walks and runs well, speaks in short phrases, and identifies body parts. An older sister experienced a similar seizure at 18 months of age. Vital Signs: Temperature, 103°F. Mild tachypnea. **General Examination**: No dysmorphic facial features. No nuchal rigidity. **Neurologic Examination**: Mental Status: Sleepy but arousable. Cranial Nerves: His pupils are equal, round, and reactive to light. He tracks objects in all directions when awake. His face is symmetric. The tongue is midline. Motor: He has normal bulk and tone. He moves all four extremities against gravity. Coordination: He grabs objects without dysmetria. Gait: He has a normal toddler gait without ataxia. Reflexes: 2+ Throughout with bilateral plantar flexor responses.

Briefly summarize this case.

The patient is a healthy, developmentally normal 2-year-old boy who presents with two generalized seizures that have been provoked by a fever (complex Febrile seizures). Although he is sleepy, his neurologic examination is normal. The family history is significant for febrile seizures.

What is the most likely diagnosis?

Complex febrile seizures

Febrile seizures are very common, occurring in approximately 5% of children ages 6 months to 5 years. The peak incidence occurs at 18 months. Approximately 60% to 70% of febrile seizures are simple, whereas 30% to 40% are complex. By definition, simple febrile seizures are primary generalized seizures that last less than 15 minutes and do not recur within a 24-hour period. Complex febrile seizures are focal, last more than 15 minutes, or occur more than once within a 24-hour period

What is the differential diagnosis?

Alternative diagnoses must be considered in any child presenting with a febrile seizure:

-First, children who are predisposed to having seizures or who have underlying epilepsy may seize because the fever lowered their seizure threshold.

-Also, an underlying meningitis or encephalitis should be considered. In children with fever, focal seizures and/or focal neurologic deficits

-HSV encephalitis should be recognized as a potentially treatable infection that must be ruled out.

Discuss an appropriate diagnostic work-up

-In the emergency room, an evaluation should be performed to identify the source of fever in any child who experiences a febrile seizure.

-Laboratory studies such as a CBC, serum electrolytes, calcium, magnesium, phosphorus, and glucose are not routinely recommended unless clinically indicated

-In this case, the patient presents with tachypnea so a chest radiograph is indicated

- Any child with nuchal rigidity, photophobia, mental status changes, lethargy, irritability, or a bulging fontanel should promptly undergo a lumbar puncture to rule out meningitis and/or encephalitis.

Discuss the management of this patient.

1. Aborting the attack of convulsion with diazepam 0.3 mg/kg slowly intravenously or rectally. This dose can be repeated after10minutes if needed
2. Lowering the body temperature with tepid sponges (no ice or alcohol) and antipyretics.
3. Treating the cause of fever
4. Exclude intracranial infection by lumbar puncture and CSF examination if any doubt exists.

Seizure: a period of symptoms due to abnormally excessive or synchronous neuronal activity in the brain. Outward effects vary from uncontrolled shaking movements involving much of the body with loss of consciousness (tonic-clonic seizure), to shaking movements involving only part of the body with variable levels of consciousness (focal seizure), to a subtle momentary loss of awareness (absence seizure). Seizures may be provoked and unprovoked.

Convulsion: This means a motor seizure and consists of abnormal involuntary muscular contractions which may be:

- Sustained (tonic).
- Interrupted (colonic)
- Brief, jerk-like (myoclonic)

Epilepsy: is present when at least 2 unprovoked seizures occur >24 hours apart**.**

Causes of convulsions:

I-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:

- Prenatal or perinatal asphyxia's
- Severe Broncho pulmonary disease
- Hyper cyanotic attacks of congenital cyanotic heart disease.

6- Metabolic: hypocalcaemia, hypomagnesaemia, hypoglycemia, hypernatremia, alkalosis, post-acidosis.

7- Toxic agents as:

- Bacterial toxins of shigella, salmonella, tetanus
- Poisons: insecticides, lead.
- Drugs: theophylline, corticosteroids

8- Intracranial neoplasm (brain tumor)

9- Cerebrovascular:

- Embolism (subacutebacterial endocarditis).
- Thrombosis (cyanotic heart disease, dehydration).
- Hypertensive encephalopathy

II- Chronic (recurrent) convulsions *i.e. epilepsy:*

1- Primary (idiopathic)

2- Secondary.

FEBRILE SEIZURES

- An 18-month-old child is brought to the emergency center after having generalized tonic-colonic seizure that lasted approximately 5 min. The parents say that the child had been previously well but developed cold symptoms earlier today with a temperature of 39°C (102°F)
- Occurs between age 6 months to 5 years; incidence peaks at age 14–18 months and may reoccur with fever
- Usually positive family history
- Temperature usually increases rapidly to >39°C (102°F)

Types:

a) Typical:

- Generalized tonic-clonic seizures.
- Age from 6 mo - 6 yr.
- Brief postictal period
- Single during the same febrile illness.
- A few seconds to10 minutes in duration
- No neurological abnormalities in the child
- EEG is normal in between the attacks.

b) Atypical:

- >15 minutes
- more than one in a day
- and focal findings
- Simple febrile seizure has no increased risk of epilepsy

Management:

1. Aborting the attack of convulsion with diazepam 0.3 mg/kg slowly intravenously or rectally.
2. This dose can be repeated after10 minutes if needed
3. Lowering the body temperature with tepid sponges (no ice or alcohol) and antipyretics.
4. Treating the cause of fever e.g. antibiotics for otitis media
5. Exclude intracranial infections by doing lumbar puncture and CSF examination if any doubt.

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.

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
- Called idiopathic because the etiology is unknown. The only important factors hereditary. In more than 90 % of cases 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, brain abscess, parasitic causes as neurocysticercosis

3*- Congenital infection*: e.g., toxoplasmosis and cytomegalovirus (CMV**)**

4- Post traumatic

5- Post hypoxic

6- Post-hypoglycemic

7- Post-toxic (e.g. after kernicterus)

8- Degenerative brain diseases.

Classification of epileptic seizures:

I-Partial (Focal) Seizures

a. ***Simple partial*** (consciousness is retained)

- Motor
- Sensory
- Autonomic
- Psychic

b. ***Complex partial*** (consciousness is impaired).

c. ***Partial seizures with secondary generalization***

II-Generalized Seizures

a. Absence:

- Typical
- Atypical

b. ***Generalized tonic-clonic:***

- Tonic
- Clonic
- Tonic-colonic
- Myoclonic
- Atonic (A kinetic)

III-Unclassified seizures the best example is subtle neonatal

Generalized tonic-clonic seizures (Grand Mal Epilepsy)

- Both cerebral hemispheres are involved
- Consciousness is usually lost
- EEG show generalized epileptic activity

Clinical presentation:

- Loss of consciousness, eyes roll back, tonic contraction, apnea
- Then clonic rhythmic contractions alternating with relaxation of all muscle groups
- ***Tongue-biting, loss of bladder control***

- ***Post-ictal stage:*** After the attack, the patient falls asleep or suffers from headache, confusion and on rising he is completely normal.

Treatment:

- Valproic acid, phenobarbital, phenytoin, carbamazepine, and other add- ons.

What triggers an epileptic seizure?

Some cases are able to identify things or situations that can trigger seizures. A few of the most commonly reported triggers are:

- lack of sleep
- vigorous exercise
- illness or fever
- stress
- bright lights, flashing lights, or patterns
- Drugs as theophylline, psychotropic drugs, and methylphenidate
- Sudden withdrawal of anti-epileptic drugs
- skipping meals, overeating, or specific food ingredients

Diagnosis of epilepsy:

Doctor will review symptoms and medical history and may order several tests to diagnose epilepsy and determine the cause of seizures. The evaluation may include:

- **Neurological exam**: assessment of behavior, motor abilities, mental function and other areas to diagnose the condition and determine the type of epilepsy
- **Laboratory investigations:** blood sampling to check for signs of infections, genetic conditions or other conditions that may be associated with seizures.
- Tests to detect brain abnormalities, such as:
  - ***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.
  - ***Magnetic resonance imaging (MRI)*** to create a detailed view of the brain

Differential diagnosis:

- Breath holding attack - Syncope - Pseudo seizures (Psychogenic).

Treatment of epilepsy:

1- 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 10minutes.

2- Long term therapy with antiepileptic drugs (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- Common AEDs are:

I- Conventional AEDs

1-Phenobarbital oral dose is 2-6 mg/kg/day used in:

- Generalized tonic- clonic seizures
- Partial seizures.
- Status epilepticus.
- Neonatal seizures
- **Most common side effects**:
  - Drowsiness
  - Dizziness
  - Lack of energy
  - Depressed mood
  - Impaired cognition
  - Nausea, vomiting
  - Hyperactivity
  - Feeling restless or excited

2-Phenytoin oral dose is 5-8 mg/kg/day used in:

- Generalized tonic- clonic seizures

- Partial seizures.
- Status epilepticus.
- **Most common side effects:**
  - Hirsutism.
  - Partial Gum hypertrophy.
  - Ataxia.
  - Skin rash.
  - Vitamin K and folate deficiency
  - Hormonal dysfunction
  - Rickets.
  - Impaired cognition.
  - Nausea, vomiting
  - Headache, dizziness, fatigue
  - Slurred speech
  - Acne
  - Bone marrow hyperplasia and osteoporosis if taken over a long time

3- Carbamazepine oral dose is 10-30 mg/kg/day used in:

- Partial seizures.
- Generalized tonic- clonic seizures
- **Most common side effects:**
  - Drowsiness., confusion, agitation
  - Blurred vision or double vision
  - Twisting movements of the body
  - Nausea, vomiting, lack of appetite
  - Liver dysfunction.
  - Hematological abnormalities: Aplastic anemia and agranulocytosis
  - Fatal dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported
  - Continuous back-and-forth eye movements
  - Irritability, lack of interest
  - Poor concentration, tiredness
  - Trouble sleeping

4- Sodium valproate oral dose is 10-60 mg/kg/day used in:

- Generalized tonic- clonic seizures
- Partial seizures
- Absence
- Atonic seizures
- Myoclonic
- **Most common side effects:**
  - Weight gain
  - Alopecia
  - Tremor
  - Dizziness
  - Nausea, vomiting
  - Irritability
  - Long-term use can cause bone thinning, ankle swelling and menstrual irregularity.

- Hearing loss, liver damage, pancreatitis and low platelet counts are more dangerous but rare side effects.

5- Ethosuxcimide oral dose is 20-40 mg/kg/day used in:

- Absence
- **Most common side effects:**
  - GIT disturbances
  - Skin rash.
  - Liver dysfunction.
  - Leucopenia.

6-Clonazepam oral dose is 0.05 - 0.2 mg/kg/day used in:

- Absence
- Myoclonic.
- Infantile spasm
- Partial seizures
- **Most common side effects:**
  - Drowsiness.
  - Irritability, restlessness
  - Behavioral abnormalities.
  - Depression.
  - Cardiovascular or respiratory depression
  - Excessive salivation
  - Ataxia
  - Loss of appetite

II- ***Second line AEDs:*** e.g., oxycarbazepine, topiramate, vigabatrin, lamotrigine, leviteracetam

Status Epilepticus (SE)

Definition: Generalized convulsive and nonconvulsive status epilepticus (SE) are neurologic and medical emergencies defined as 5 or more minutes of either continuous seizure activity or repetitive seizures with no intervening recovery of consciousness. Traditionally established SE was defined as a continuous convulsion lasting greater than 30 min, or the recurrence of serial convulsions between which there is no return of consciousness; however, this time frame has been reduced to 5 minutes to emphasize the seriousness of the condition and the need to treat it urgently.

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 long-standing 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.

Early status epilepticus within 10 minutes of onset:

- ***If no IV line available:***
  - Midazolam (in dose 0.2mg/kg) IM or IN or Buccal (0.2-0.5mg/kg) maximum 10 mg
  - or rectal diazepam (0.2-0.5mg/kg) maximum 20mg
- ***If IV line available:***
  - IV Diazepam (0.15-0.2mg/kg) maximum10mg can be repeated once.
  - Or IV lorazepam (0.1mg/kg) maximum 4mg can be repeated once.

Established status epilepticus (10-30 minute of seizure)

- ***Phenytoin*** infusion: IV dose 20 mg/kg slowly over 30 min, can repeat 5-10mg/kg.
- Or IV ***leviteracetam*** 30-60 mg/kg maximum 4500mg, can repeat 30 mg/kg if needed.
- Or IV ***valproic acid*** 20 mg/kg maximum 3000 mg, can repeat 20 mg/kg if needed.
- Or IV ***Phenobarbital*** 20 mg/kg (may repeat 5-10 mg/kg if need).

General anesthesia and assisted ventilation is given if the above measures are failed.

Pactice Questions (Choose one correct answer)

1-In Spastic cerebral palsy area of lesion is:

a) Basal ganglia
b) Cerebellum
c) Motor cerebral cortex
d) cerebellum

2-the most common cause of extrapyramidal cerebral palsy:

a) Congenital infection
b) Kernicterus
c) Hypoxia
d) Brain tumour

3-The most common type of cerebral palsy is:

a) Ataxic CP
b) Extrapyramidal CP
c) Spastic CP
d) Atonic CP

4-recrrent seizures unrelated to fever is the definition of:

a) Convulsion
b) Epilepsy
c) Athetosis
d) dystonia

5-loss of coniousness is present in all of the following except:

a) Simple partial seizure
b) Absence
c) Grand mal epilepsy
d) Complex partial seizure

6-all of the following are signs of floppy infant except

a) Frog leg position
b) Marked head lag on pull to sit
c) Inverted U shape on ventral suspension
d) spasticity

7-Fasciculation of the tongue is diagnostic in:

a) Gillian barre syndrome
b) Werdnig -Hoffman disease
c) Congenital myopathy
d) Atonic CP

8-In case of border line intelligence:

a) IQ 90-71
b) Cannot live independently
c) Non educable
d) Non trainable

9-all of the following are diagnostic of intellectual disability except:

a) Defect in adaptive behaviour
b) Age of onset before 18 years of age
c) Language delay
d) Delayed walking

Chapter 11

Neonatology

Learning Objectives:

By the end of this chapter, students should be able to:

1. Define prematurity and common problems associated.
2. Enumerate birth injuries, causes and management.
3. Understand different neonatal disorders, clinical picture, diagnosis, and management.

Contents:

1. Definitions
2. Prematurity.
3. Birth injury.
4. Neonatal Disoreders
    a. Neonatal respiratory distress.
    b. Neonatal hyperbilirubinemia.
    c. Haemorrhagic diseases of newborns
    d. Neonatal sepsis.
    e. Neonatal seizures.

Definitions

Newborn	First **4 weeks** of life.
Preterm	Live born < **37** weeks pregnancy.
Full term	Live born **37-42** weeks pregnancy.
Post-term	Live born > **42** weeks pregnancy.
Appropriate for gestational age (AGA)	Baby weighting **between the 10th and 90th** percentile for expected for his gestational age.
Small for gestational age (SGA)	Babies weighting **below 10th** percentile for expected for his gestational age.
Large for gestational age (LGA)	Babies weighting **above the 90th** percentile for expected for his gestational age.
Low birth weight (LBW)	Babies weighting **1500-2500 gm** at birth.
Very low birth Weight (VLBW)	Babies weighting **1000-1500 gm** at birth.
Extremely low birth weight (ELBW)	Babies weighting less **than 1000 gm** at birth.
Gestational age	The age of an embryo or fetus (or newborn infant) from the first day of the woman's last menstrual period (LMP).

Case 1

A pregnant woman presents to the hospital with spontaneous rupture of membranes and contractions. Her obstetrician orders antenatal steroids and antibiotics. Although tocolysis is attempted, her labor progresses and she delivers a preterm infant at 28 weeks' gestation with a birth weight of 1,200 g.

The baby is then brought to the Neonatal Intensive Care Unit for further care. The neonatal nurse places the infant on a radiant warmer and assesses the infant's vital signs. The resident orders laboratory studies, a chest radiograph, and an intravenous solution containing total parenteral nutrition. The resident meets with the family to discuss the results of these studies and the management plan.

Of the following, the term that best describes this infant is:

A. Normal birth weight
B. Low-birthweight (LBW) infant
C. Very low-birthweight (VLBW) infant
D. Extremely low-birthweight (ELBW) infant

Answer: (C)

Of the following, the current issue that is least likely to be present in this 1-hour-old infant is:

A. Anemia of prematurity
B. Hypoglycemia
C. Hypothermia
D. Hypoxemia

Answer: (A) Preterm infants usually develop anemia of prematurity at ~1 to 2 months of age. This finding is not apparent soon after birth. Preterm infants have decreased glycogen and fat stores, increasing their risk for hypoglycemia.

Preterm infants are at increased risk for hypothermia because of:

- Decreased skin thickness
- Low amount of subcutaneous fat
- Immature nervous system
- Increased surface area to body weight ratio

Premature infants are at increased risk for surfactant deficiency. Thus, it is important to monitor a preterm infant's respiratory status, including arterial oxygen and carbon dioxide concentrations, soon after birth.

Of the following, the laboratory studies that were most likely sent on this infant are:

A. Blood urea nitrogen and serum creatinine
B. Complete blood cell count and blood culture
C. Serum electrolytes
D. Serum transaminases

Answer: (B) The reason for a spontaneous preterm birth is often unknown. However, because chorioamnionitis is a commonly known cause of preterm labor, neonatal providers will usually evaluate a preterm infant for infection by obtaining a complete blood cell count and blood culture.

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. polyhydraminos, uterine malformations, vaginal bleeding, and premature rupture of membranes (PROM).

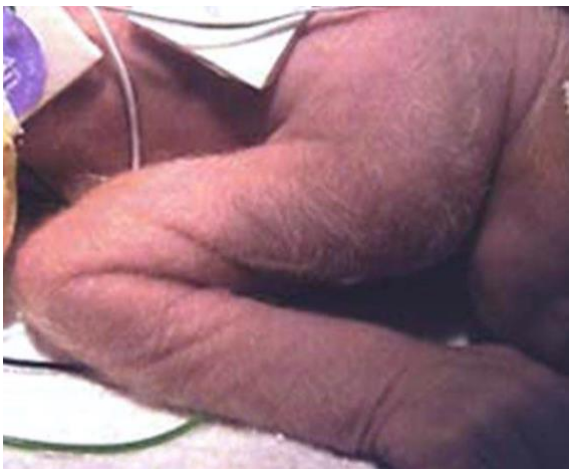
Physical characteristics:

I. Anthropometric measurements:

- Birth weight: < 2500 gm.
- Birth length: < 47 cm.
- Birth head circumference: < 33 cm.
- Chest circumference :< 30 cm.
- The head is relatively larger than body but the neck and extremities are relatively short.

II. Signs of physical immaturity:

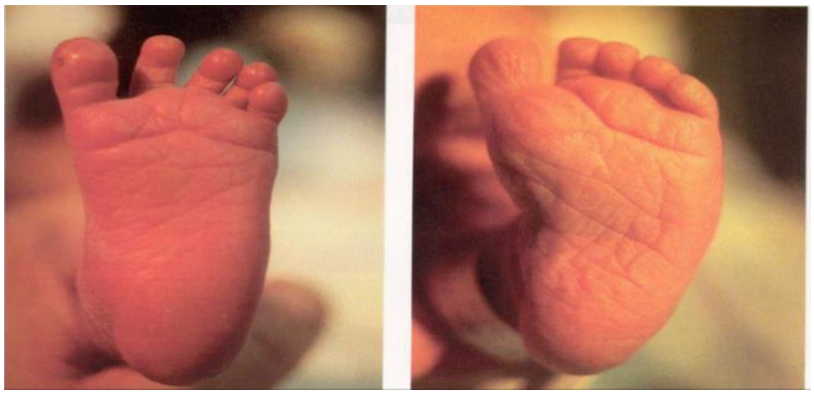
- ***Cry:*** poor crying with poor suckling.
- ***Behavior:*** hypoactive and sleeps more.
- ***Skin:***
  - Thin, smooth and red skin.
  - Little subcutaneous fat: triangular face and loose skin over limbs.
  - Abundant lanugo hair that may cover the whole body.
  - Frequent occurrence of edema in hands and feet



Abundant lanugo hair

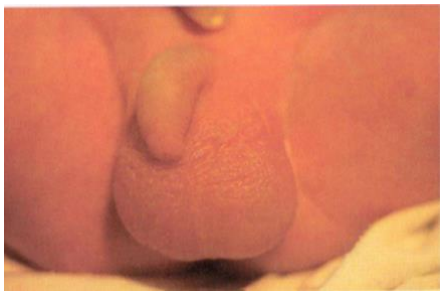
- ***Chest:*** Irregular respiration with periodic spells of apnea (weak respiratory muscles).
- ***Abdomen:*** prominent with thin wall and visible peristalsis.
- ***Breast:*** not palpable nodule, with diminished areola and nipple formation.

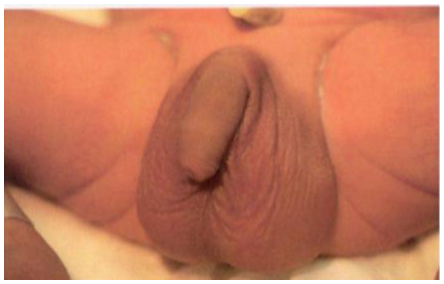
- ***Ear:*** soft, easily folded with absent cartilage.
- ***Plantar Surface:*** creases don't exceed anterior 2/3 of the sole.



Anterior 2/3 (32 weeks) **Entire foot (36 weeks)**

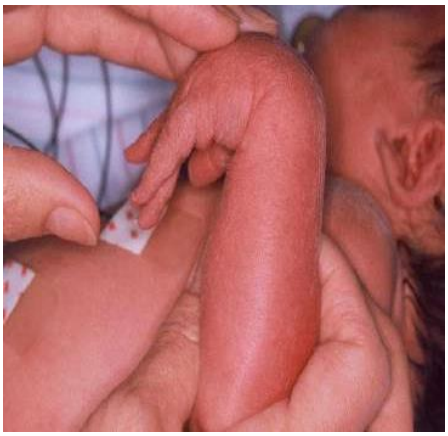
- ***Genitalia:***
  - **Male:** light colored, smooth scrotum with absent rugae, and undescended testes.
  - **Female:** widely separated labia majora with prominent labia minora and clitoris.



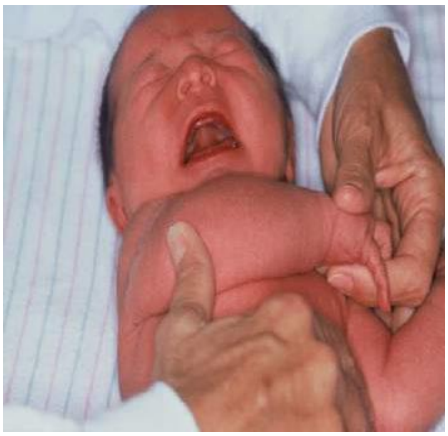


III. Signs of neuromuscular immaturity:

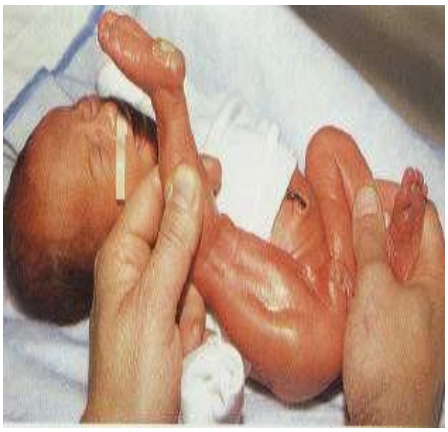
- ***Posture:*** Limp hypotonic (frog position).
- ***Heel to ear maneuver:*** heels can be brought easily by the side of the ears.
- ***Popliteal angle:*** wide
- ***Arm recoil:*** diminished.
- ***Square window:*** wide.
- ***Scarf sign:*** arms can round easily around the neck, elbow can cross midline.



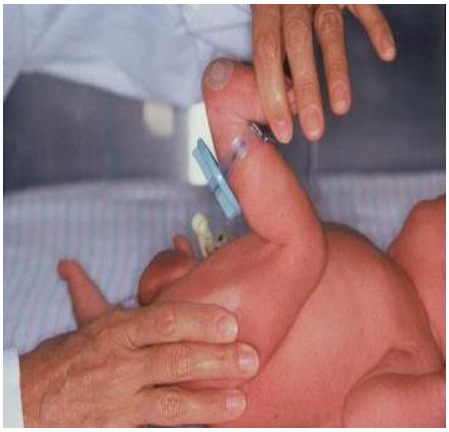
Square window



Scarf sign



Heal to ear



Popliteal angle

Complications of prematurity:

1. **Respiratory:**
   - ***Respiratory distress syndrome (RDS):*** due to surfactant deficiency.
   - ***Apnea of prematurity:*** due to immaturity of respiratory center.
2. **Cardiovascular:**
   - ***Patent ductus arteriosus (PDA):*** that may result in heart failure.
   - ***Hypotention and bradycardia:*** due to hypovolaemia or cardiac dysfunction.
3. **Hematological:**
   - ***Bleeding tendency:*** increased vascular fragility with diminished coagulation factors.
   - ***Anemia of prematurity:*** due to iron and folic acid deficiency.
4. **Neurologic:**
   - ***Intracranial hemorrhage.***
   - ***Hypoxia-ischemic encephalopathy.***
5. **Gastrointestinal:**
   - ***Necrotizing enterocolitis (NEC).***
   - Poor suckling, swallowing, digestion and absorption.
   - Decreased stores of vitamins and minerals.
6. **Renal:**
   - More prone to ***dehydration and acidosis:*** decreased capacity to concentrate urine.
7. **Metabolic:**
   - More prone to ***hypocalcaemia and hypoglycemia.***
8. **Hypothermia:**
   - Large surface area: that leads to excess heat loss.

- Low subcutaneous fat.
- Immature heat regulating centre.

9. **Immunologic:**
   - More prone to ***infection:*** deficiencies in both humoral and cellular im- mune response.

Long-term problems of prematurity:

1. **Developmental disability:**
   - Major handicaps (cerebral palsy, mental retardation)
   - Sensory Impairments (hearing loss, visual impairment)
   - Minimal cerebral dysfunction (language disorders, learningdisability, hyperactivity, attention deficits, behavior disorders)
2. **Retinopathy of prematurity (ROP).**
3. **Chronic lung disease: bronchopulmonary dysplasia (BPD).**
4. **Poor growth.**
5. **Increased risk of congenital anomalies.**
6. **Increased risk of child abuse and neglect.**
7. **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 if suspicting infection.
- ***Immunization:*** Routine immunization should be given on the regular schedule at standard doses.

Birth Injuries

Case 2
Male full term after normal vaginal delivery presented with soft swelling over the presenting part which was associated with ecchymosis of skin.
What is the most likely diagnosis? Caput Succedaneum
What is the appropriate treatment for this condition? No treatment, just reassurance

Case 3
Female neonate after forceps delivery was normal at birth, after 6 hours from birth firm localized swelling appeared gradually over the parietal bone and the baby has gradual pallor.
What is the most likely diagnosis? Cephalhematoma
What is the appropriate treatment for this condition? Admission to incubator Treat anemia (blood transfusion). Treat jaundice (phototherapy). Treat infection (antibiotic).

I- Neurological Birth Injuries:

A- Cranial Injures:

1. Extracranial injures*:*

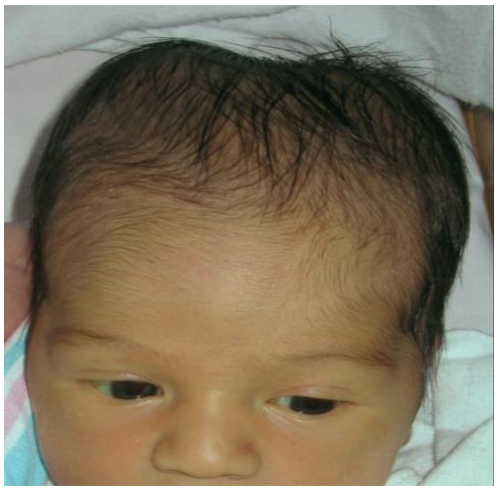
- Caput succedaneum.
- Cephalhematoma.
- Fracture skull.
- Subconjunctival hemorrhage.
- Abrasion, ecchymosis.

2. Intracranial injures: Intracranial hemorrhage.

B- Spine and Spinal Cord Injuries:

1. Vertebrae: fractures and dislocations.

2. Spinal cord: Hemorrhage, edema and transection.



C- Peripheral Nerve Injures:

1. Facial nerve palsy.

2. Brachial birth palsy.

3. Phrenic nerve palsy.

II- Non-Neurological Birth Injuries:

A-Visceral injures:

- Rapture liver with subcapsular hematoma
- Rapture spleen with subcapsular hematoma
- Adrenal hemorrhage

B- Sternocleidomastoid injury:

- Sternomastoid hematoma (tumor).

C- Bone injuries:

- Clavicle fracture
- Extremities: Fractures, dislocation.

	Caput Succedaneum	**Cephalhematoma**
Nature	Subcutaneous extraperiosteal edema.	Sub-periosteal blood collection.
Site	Over presenting part	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) / Jaundice (phototherapy) / Infection (antibiotic). - No aspiration: due to risk of infection (except if infection occurs)

Intracranial Hemorrhage (ICH):

Causes:

1. Birth trauma e.g., forceps.
2. Birth asphyxia.
3. Congenital vascular anomalies.
4. Bleeding disorders.
5. Spontaneous: especially in preterms.

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:

1. History of traumatic delivery.

2. Clinical manifestations.

3. Investigations:

a- Cranial ultrasonography.

b- CT scan or MRI.

c- Lumber puncture: to exclude CNS infection or diagnose subarachnoid hemorrhage (hemorrhagic CSF).

Management:

Supportive treatment:

- Incubator care.
- Minimal handling of the baby.
- Oxygen supply.
- Vitamin K: 1-5 mg I.M help arrest of bleeding

Symptomatic treatment:

- Convulsion: Phenobarbital,3:8mg/kg/Day
- Anemia: Fresh blood transfusion: 10 ml/kg

Surgical treatment:

- Subdural hemorrhage.
- Post-hemorrhagic hydrocephalus:
- Serial lumbar Punctures.
- Shunt operation.

Case 4

A mother of male neonate after difficult forceps delivery noticed that her baby do not move his left arm and he prefer to maintain it internally rotated with outward direction of the palm of his hand.

What is the most likely diagnosis?

Erb's palsy (C5, C6 injury)

What is the appropriate treatment for this condition?

1-Relaxation of the paralyzed muscles in opposite position:

Abduction at the shoulder.

External rotation of arm

Supination of the forearm.

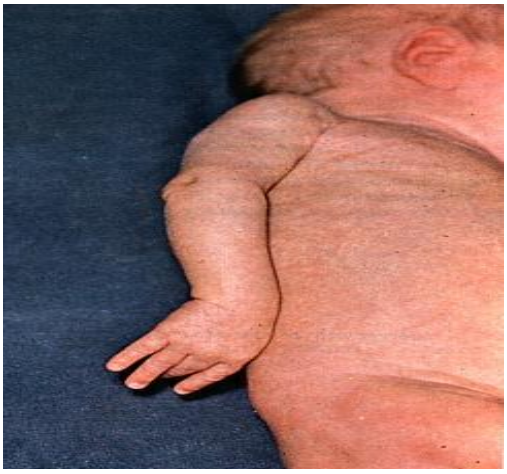
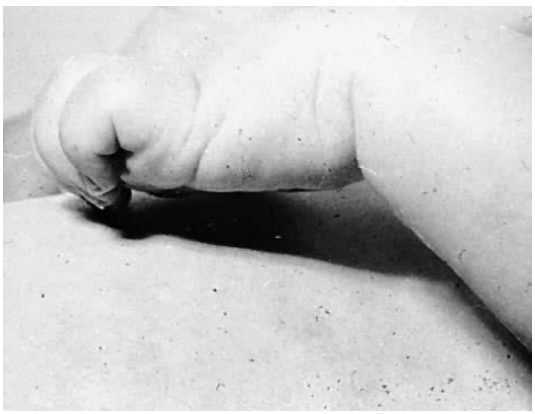
(Holding of the wrist to the head of the bed)

2-Physiotherapy after 2 weeks.

3- Neuroplasty (nerve graft)

If no response after 3:6 months

Brachial Palsy:

	Erb's palsy	**Klumpke's palsy**
Incidence	Common	Rare
Injury	C**5**, C**6**	C**7**, C**8**, T**1**
Deformity	Adduction at the shoulder. Internal rotation of the upper arm. Pronation of the forearm. Outward direction of the palm **(waiter's tip posture)**	Paralysis of all intrinsic muscles of the hand. (**Claw hands**)
Reflexes	Moro: absent / Grasp: present	Moro: present / Grasp: absent
Association	Impaired sensation on the outer side of the arm. Phrenic nerve palsy (C**3**, C**4**, C**5**)	Horner syndrome: injury to sympathetic fibers of T1. (Ptosis, miosis,anhydrosis, enophthalmos)
Prognosis	Favorable	Less favorable
Treatment	1-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)** 2-Physiotherapy after 2 weeks. 3- Neuroplasty(nerve graft) If no response after 3:6 months	1-Relaxation of the paralyzed muscles in opposite position: **(Holding pad of cotton in the fist)** 2-Physiotherapy. 3- Neuroplasty.
		

1.Traction on the head in cephalic presentation.

2.Traction on the shoulders in breach presentation.

Injury of the visceral organs:

The Liver or spleen:

Clinically:

1. The infant usually appears normal for the first 1-3 days.
2. Manifestations of blood loss: severe pallor up to hypovolemic shock (if ruptured capsule into peritoneal cavity)
3. Abdominal distension.

Diagnosis: abdominal ultrasonography is diagnostic.

Treatment:

Blood transfusion in marked anemia or shock.

Surgical repair may be required.

The Adrenal Gland

Clinically:

1. Pallor Profound shock
2. Flank mass, 90% are unilateral, mainly on right side.
3. Adrenal insufficiency (vomiting, shock)

Diagnosis: abdominal ultrasonography is diagnostic.

Treatment:

Blood transfusion in marked anemia or shock.

Treatment of acute adrenal failure (fluid, steroid).

Respiratory Distress in the Newborn

Case 5

The patient was born via cesarean section 1 hour ago to a G1P0 mother with no gestational complications at 39 weeks. The mother had routine prenatal care and no medical problems during her pregnancy. The mother states that patient appears to not be breathing well. HR, 145 beats/min; RR, 70 breaths/min

Which of the following is the most likely diagnosis?

- Transient tachypnea of the newborn.
- Meconium aspiration.
- Spontaneous pneumothorax.
- Pneumonia
- Hyaline membrane disease of the newborn
- Diaphragmatic hernia.

Answer: A Transient tachypnea of the newborn (TTN)

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:
     a. Shallow, irregular respiration, apnea and cyanosis.
     b. Bulging anterior fontanelle, disturbed consciousness, and seizures.

Transient tachypnea of the newborn (TTN)

Self-limited respiratory distress affects mainly full-terms.

Etiology: Delayed clearance of fetal lung fluid.

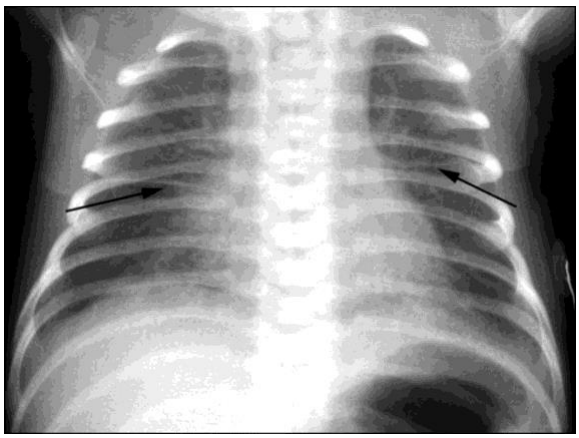
Risk factors:

- 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.**



Increased broncho-vascular markings.
Fluid in fissure and costophrenic angle.
Hyperinflation of the lung.

Treatment:

Incubator care.

Respiratory support (oxygen therapy).

Respiratory distress syndrome (RDS) (Hyaline membrane disease)

Case 6

A mother rushes her baby into the emergency department (ED), stating that she just gave birth in the car. She was having severe cramps, but the baby was only at 29 weeks of gestational age. She did not think she could deliver the baby this early. The baby was born about 10 minutes ago. The mother is a 17-year-old G1P0 with minimal prenatal care. Chest: Intercostal retractions, tachypnea, grunting, nasal flaring, poor air movement

Q1: How to assess degree of respiratory distress?

✓ **Answer: by Scoring System (Downes' score)**

Score	0	1	2
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% O2**
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.**

Q2: Which of the following is the most likely diagnosis?

a. Transient tachypnea of the newborn (TTN)

b. Meconium aspiration

C. Hyaline membrane disease of the newborn

D. Diaphragmatic hernia

Answer: C. Hyaline membrane disease (syndrome of respiratory distress occurs almost always in preterm infants due to lung surfactant deficiency.

Incidence and severity of RDS are related inversely to the gestational age.

Q3: Which of the following is the next step in the management after oxygenation?

a. Administration of ampicillin and gentamicin

b. Administration of surfactant

c. Administration of corticosteroids

Answer: B

Produced by: type II pneumocytes start at 20 weeks and become mature at 35 weeks of gestation.

Lung surfactant:

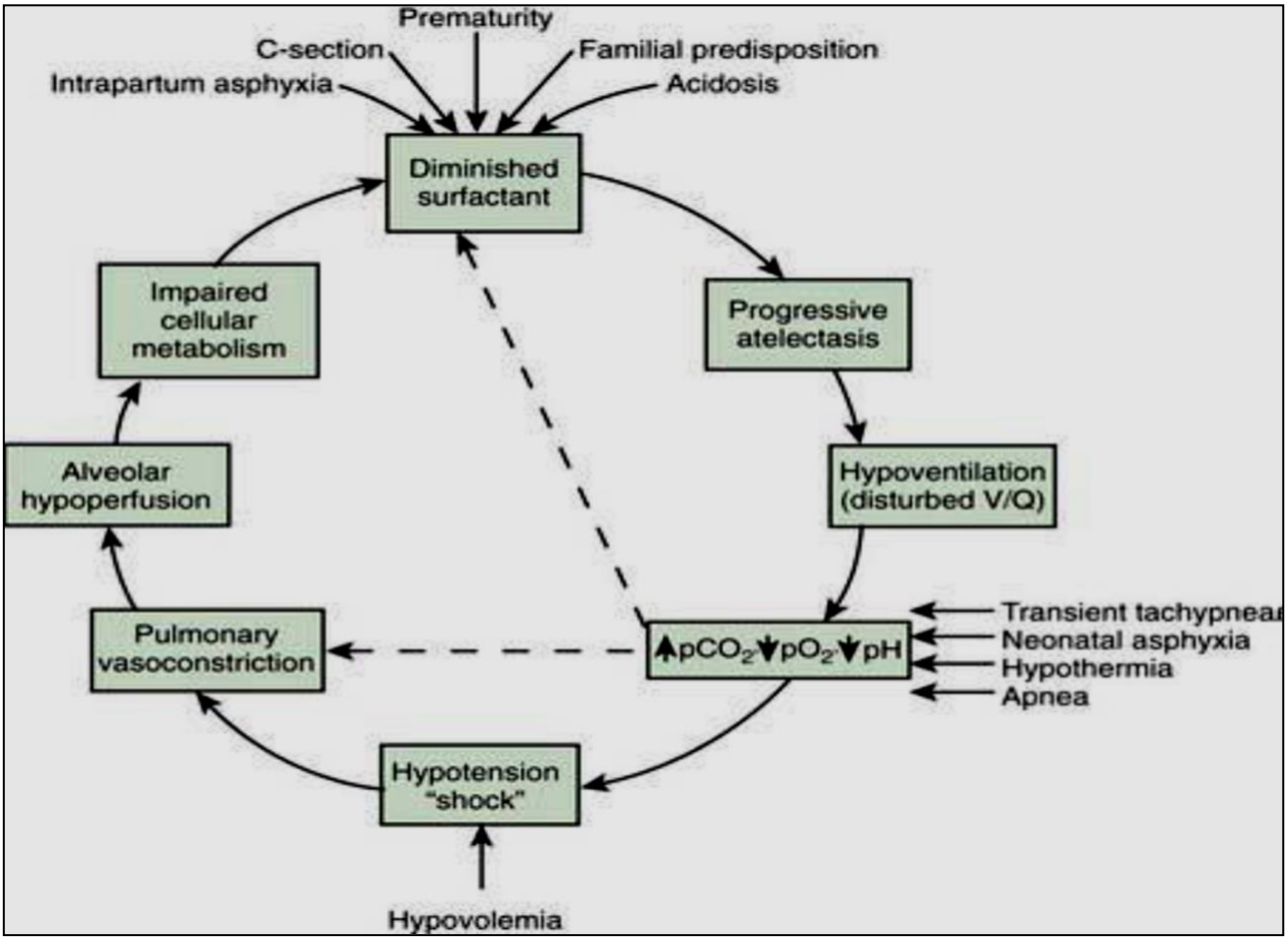
Composition: mixture of phospholipids and surfactant proteins.

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:



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 picture:

- ***Onset:*** within minutes to hours after birth.
- ***Course:*** progressive course

  Mild: gradual improvement after 3 days (reappearance of surfactant).

  Severe: complications or death.

- ***Signs of respiratory distress:***

  Grade I: tachypnea and working alae nasi.

  Grade II: retractions (intercostal and subcostal).

  Grade III: grunting.

  Grade IV: central cyanosis.

Investigations:

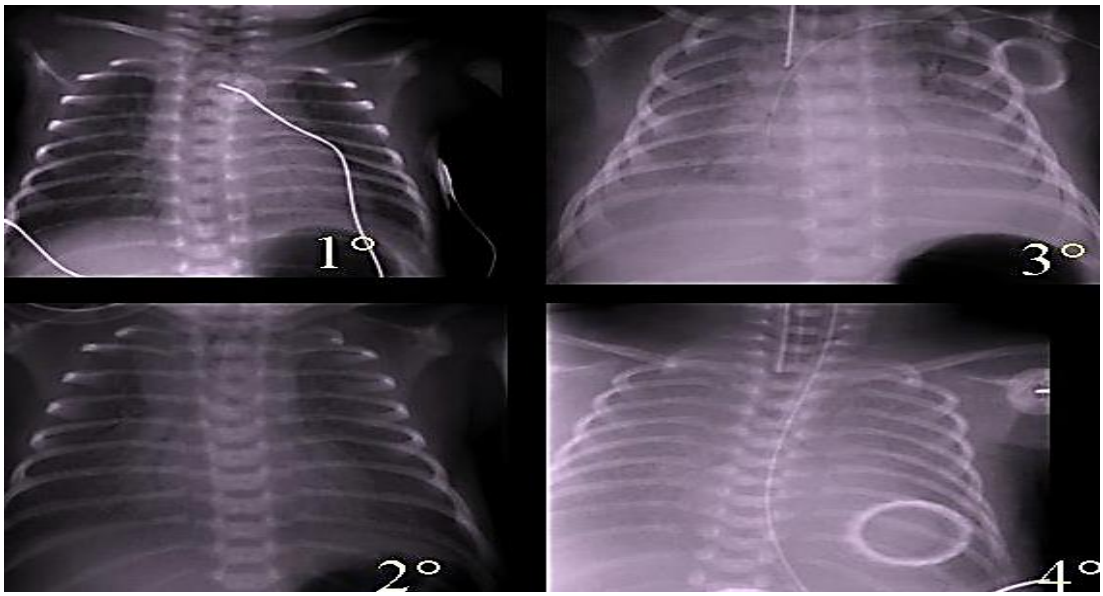
1. Chest X-ray:

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.



2. **Blood gases:** respiratory and metabolic acidosis with hypoxia.
3. **Echocardiography:** to exclude PDA.
4. **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:

A. Supportive treatment:

- Incubator care.

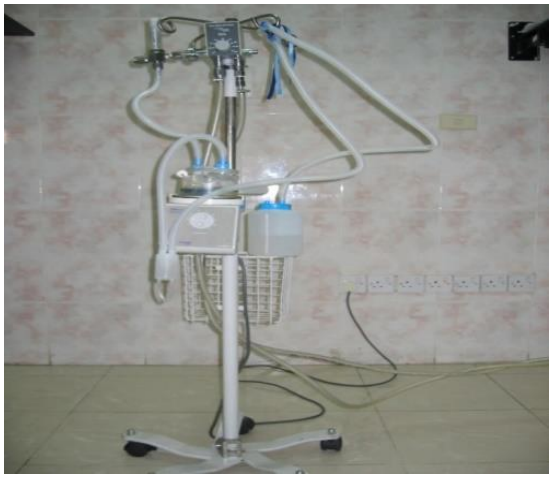
- Support circulation: IV. Fluids, plasma, dopamine.

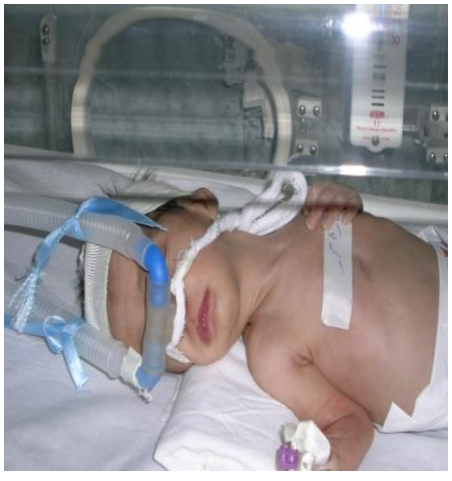
- Support nutrition: oral or parenteral feeding.

-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

1. Incubator oxygen.
2. Head box.
3. Nasal cannula.
4. Continuous positive airway pressure: CPAP keeps the alveoli open at the end of expiration





Indications of mechanical ventilation:

1. PO2 < 50 mm , PCO2 > 60 mmHg, < 7.20 despite using 100% oxygen.
2. Frequent apnea.
3. Marked retractions.
4. Cyanosis.

B. Specific treatment: *(Surfactant therapy)*

1. Four ml/kg/dose via endotracheal tube.
2. Side effects: apnea, bradycardia and pneumothorax

Complications:

A. Acute:

- Air leak syndromes (pneumothorax, pneumomediastinum)
- Infections.
- Intracranial hemorrhage.
- PDA with increasing left-to-right shunt may complicate the course of RDS.
- Heart failure.
- Pulmonary hemorrhage: especially following surfactant therapy.

B. Chronic:

- Bronchopulmonary dysplasia (BPD).
- Retinopathy of prematurity (ROP).
- Neurologic impairment.
- Familial psychopathology

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:

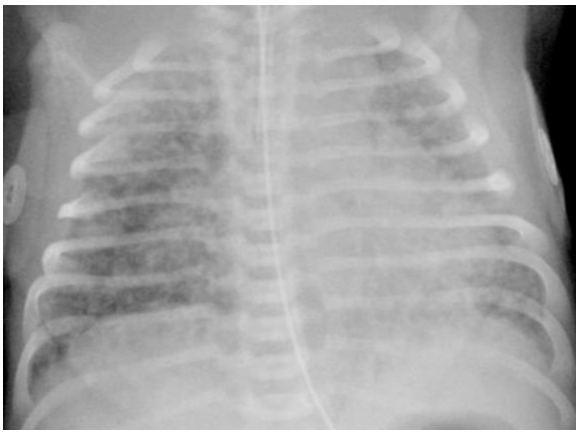
- Complete airway obstruction → atelectasis.
- Partial airway obstruction → air trapping → pneumothorax.
- Chemical pneumonitis and secondary bacterial infection.

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:

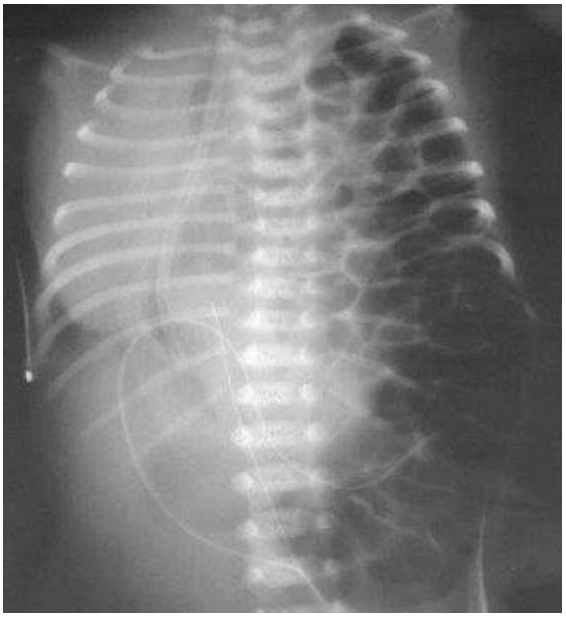
Defect in the diaphragm between the peritoneum and pleura, allowing intestine to herniate in the pleural space.

Clinical manifestations:

- Significant respiratory distress after birth.
- Decreased air entry on the same side.
- Scaphoid abdomen.
- 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:

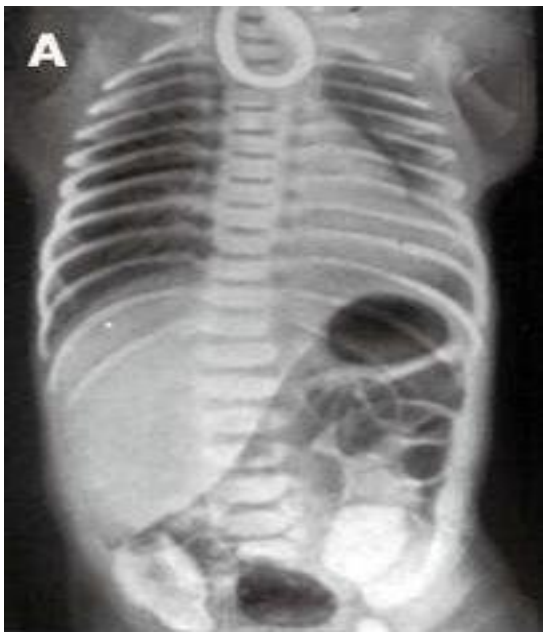
- **Surgical repair.**

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

Case 7

A 2-day-old infant is noticed to be jaundiced. He is nursing and stooling well. Indirect bilirubin is 11.2 mg/dL; direct is 0.4 mg/dL. Physical exam is unremarkable except for visible jaundice.

What is the most likely diagnosis?

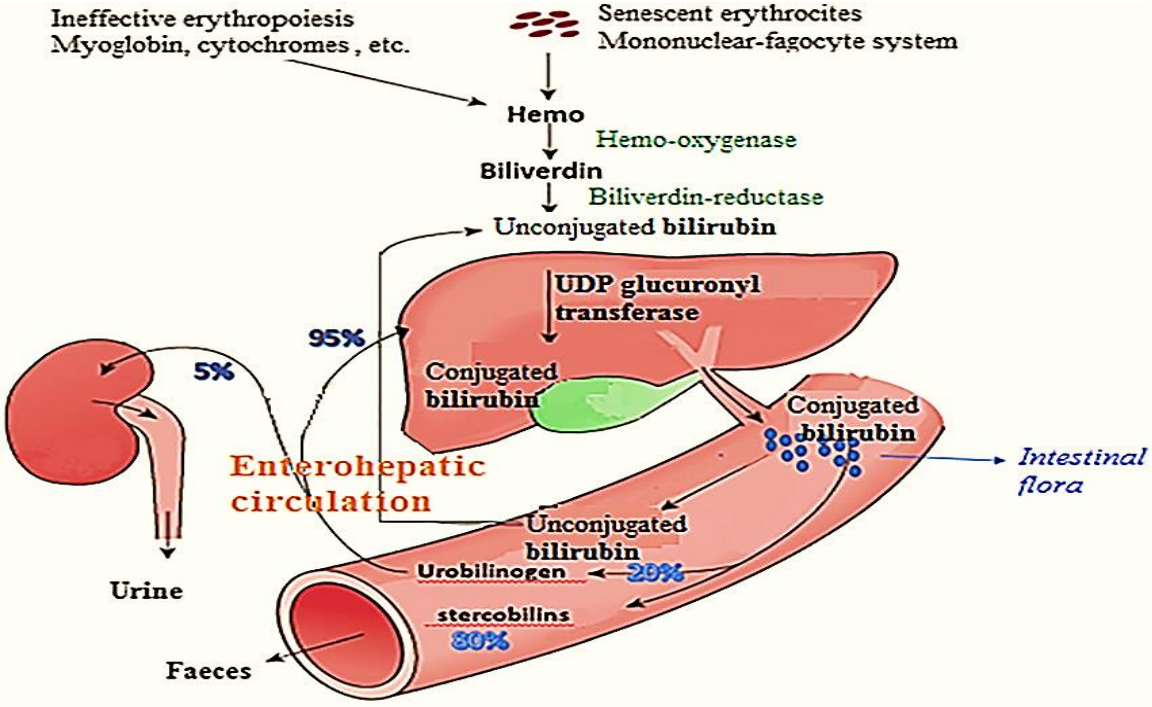
Answer: physiological jaundice: yellowish discoloration of skin, mucous membrane and sclera due to increased serum bilirubin. Jaundice appears clinically when serum bilirubin >5mg/dl in newborn, while > 2mg/dl in older children and adults. It occurs in about 60% of full term and 80% of preterm during the first week of life.

What is the mechanism of physiological jaundice?

- **Bilirubin production:** Increased due to:
  a. Large RBCs volume.
  b. Short life span of RBCs.
  c. Increased entero-hepatic circulation.
- **Uptake** of bilirubin by the liver: Defective
- **Conjugation:** Defective
- **Excretion** into bile: Defective

Definition:

- Yellowish discoloration of skin, mucous membrane and sclera due to increased serum bilirubin. Jaundice appears clinically when serum bilirubin > 5mg/dl in newborn, while > 2 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.



Hyperbilirubinemia either:

- Unconjugated hyperbilirubinemia (Physiological or pathological).
- Conjugated hyperbilirubinemia.

Unconjugated hyperbilirubinemia:

1. *Physiological jaundice:* It is the most common cause of jaundice in neonates.

Mechanisms:

- *Bilirubin production:*

Increased due to:

Large RBCs volume.

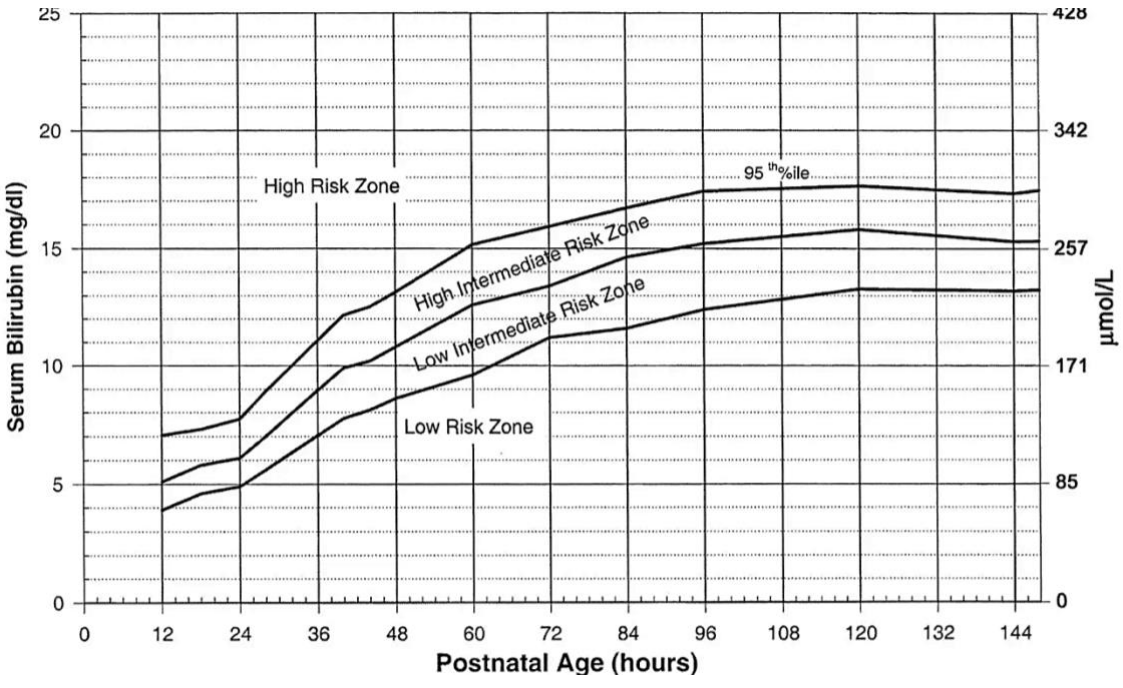
Short life span of RBCs.

Increased entero-hepatic circulation.

- *Uptake of bilirubin by the liver:* Defective.
- *Conjugation:* Defective. - *Excretion into bile:* Defective.

Exclusion criteria for physiologic jaundice:

1. Total serum bilirubin level > **95th** percentile for age in hours based on nomogram for hour- specific serum bilirubin concentration.
2. Bilirubin level increasing at a rate > **5** mg/dl/day, or > **0.2** mg/dl/h.
3. Jaundice in the **first 24 hours** of life.
4. Conjugated bilirubin > **2** mg/dl or > **20 %** of the TSB.
5. Clinical jaundice persisting > **2** weeks in full-term.



2. *Pathological jaundice*

Causes:

A- Common causes:

1. Hemolytic anemia (Rh and ABO incompatibility).
2. Breast milk jaundice.
3. Neonatal infection (congenital or acquired)
4. Increased RBCs content (polycythemia – cephalhematoma -twin-twin transfusion)

B- Rare causes:

1. Congenital hemolytic anemia: G6PD deficiency, hereditary spherocytosis.
2. Endocrine disorders: Maternal diabetes, hypothyroidism.
3. Other disorders: Down syndrome.
4. Glucoronyl transferase defect:
   - Congenital: Grigler-Najjar syndrome (type I, II), Gilbert syndrome.
   - Acquired: Lucey-Driscoll syndrome
5. Metabolic disorders: Galactosemia.
6. Increased entero-hepatic circulation: ileus, intestinal obstruction.
7. Drugs: Aspirin, sulphonamides and furosemide.

Rh incompatibility:

- 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 hemolysis 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 (at a dose of 300 µg I.M).

ABO incompatibility:

- If **mother** group is O and **baby** group is A or B.
- **Antigens** present on the surface of RBCs react with plasma **antibodies** causing **hemolysis**.
- **First** baby is affected.

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. ▪ Stool stasis & ↑ entero-hepatic circulation	**Unknown** may be: ▪ Pregnandiole, ↑ Fatty acids,or Glucuronidase in breast milk → ↑ entero-hepatic circulation
Treatment	Frequent breast feeding	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 wave length 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.**

Side effects:

- Dehydration: due to insensible water loss.
- Diarrhea. (Due to increased bile and indirect bilirubin in bowel)
- Hyperthermia.
- Genital and retinal damage.
- Skin rash and photosensitivity.

- Bronzed-baby syndrome: due to exposure to conjugated bilirubin to phototherapy.
- Loss of maternal infant bond.
- Rebound hyperbilirubinemia.
- Hypocalcemia: may occur especially in preterm, due to decreased secretion of parathyroid hormone.

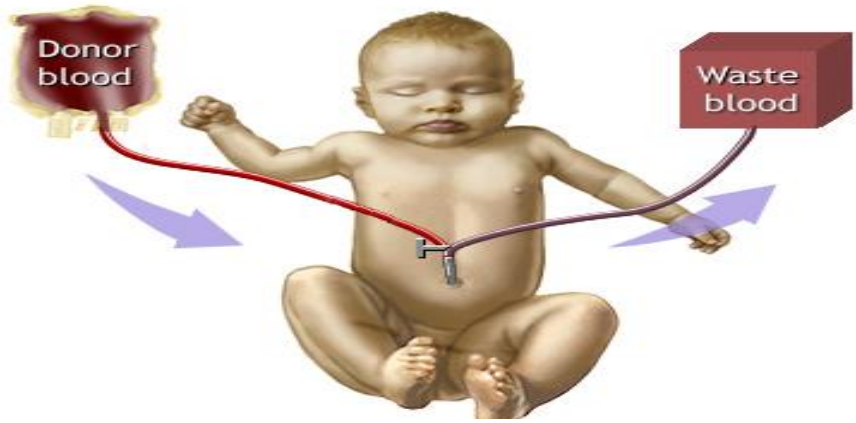
II- Exchange transfusion

Mechanism:

- Remove excess bilirubin.
- Remove antibodies from circulation.
- Correct the anemia.

Indications:

- Failure of phototherapy to prevent rise in bilirubin to toxic levels.
- When exceed the level for exchange transfusion on the exchange transfusion chart.



Side effects:

- Umbilical catheterization: Embolization, thrombosis, infarction.
- Cardiac: Heart failure, arrhythmia, or arrest.
- Hematological: Thrombocytopenia, anemia.
- Electrolyte disturbances:(hypocalcemia, hypoglycemia, hyperkalemia).
- Infections: HIV, CMV, Hepatitis.
- Graft- versus-host disease.
- Hypothermia.

III- IVIG:

***Indications*:** ABO & Rh incompatibility.

Mechanism: Occupy Fc receptors in RES. Prevent 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:

- Bilirubin level: differ according to gestational age and postnatal age.
- Duration of exposure to high bilirubin.
- Factors increase free bilirubin: (hyopalbuminemia, drugs e.g sulfa)
- Factors increase permeability of blood brain barrier (BBB): (Prematurity, hypoxia)

Clinical manifestations:

A. Acute bilirubin encephalopathy:

- Phase I: (1:2 days) Hypotonia, poor feeding, irritability, seizures.

- Phase II: (3:7 days) Hypertonia, opisthotonus, retrocollis, fever.

- Phase III: (after 1 week) Hypertonia and may die or survive with apparent recovery for 2:3 months.

B. 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.

Hemorrhagic Disease of the Newborn (HDN)

Case 8

A newborn aged 5 days, GA 37 wks. BW: 2700 gm, presented to NICU by hematemesis and dark stool, with no other bleeding.

Invest showed Hb = 12 gm /dl, platelet 350 000 mm, WBCs = 8500 mm, coagulation time 16 min, bleeding time 8 min, PTT: 60 Sec, PT: 25 Sec.

What is the possible diagnosis?

Hemorrhagic Disease of the Newborn (HDN)

what are lines of ttt? Vitamin K1 &Fresh frozen plasma.

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	**1st day**	**2:7 days**	**2 wks :6 mons**
Causes	Maternal drugs that inhibit Vit K synthesis: Anticonvulsants. Anti-tuberculous drugs.	Decreased intake: breast milk is poor in vit K	Absence of bacterial intestinal flora (that form vitamin K): Total **parenteral nutrition.**
		Immaturity of the liver	Broad-spectrum antibiotics.
		Decreased vit K stores: common in preterm	Malabsorption: Biliary atresia. Cystic fibrosis.
Incidence	Very rare	2% of neonate not given Vitamin K at birth	Dependent on cause

Clinical picture:

- Hemorrhagic anemia (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:

I. Causes of hemorrhage in newborn.

II. 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:***

    a. Infant blood (HbF): resist denaturation by alkali, stay **(pink).**

    b. Maternal blood (HbA): it forms hematin, turns **(yellow).**

Neonatal sepsis

Case 9

A 3-week-old infant presents with irritability, poor feeding, temperature of 38.9°C (102°F), and grunting. Physical examination reveals a bulging fontanel, delayed capillary refill, and grunting.

Definition: **a clinical** syndrome characterized by **systemic** signs and symptoms of infection with **evidence** of bacteremia. The most important cause of **neonatal deaths** in the community.

Etiology:

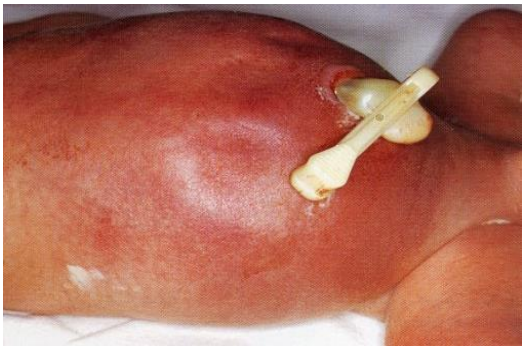
	Early- onset sepsis	**Late- onset sepsis**
Onset	In the 1st week usually before 3rd day	After the 1st week
Risk factors	Prematurity. Low birth weight. Prolonged rupture of membranes. Chorioamnionitis. Maternal fever. Maternal UTI.	Prematurity. Hospitalization. Invasive procedures: Umbilical catheterization 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

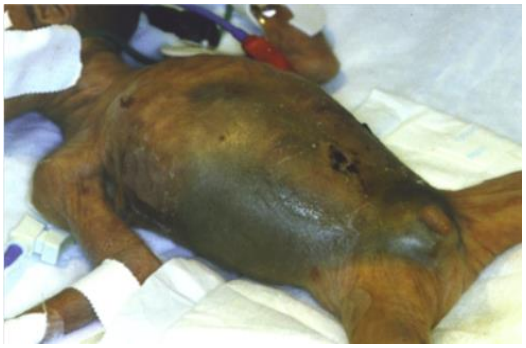
Clinical features: **(Nonspecific** and can simulate other diseases, so **a high index of suspicion is needed for early diagnosis)**

1. ***General:***
   - Not doing well and lethargic
   - Poor feeding and Poor temperature control (hypothermia is more common than fever)
   - Scleroderma (hardening of the skin).
2. ***Gastrointestinal manifestations:***
   - Abdominal distension.

- Anorexia, vomiting, diarrhea.
- Necrotizing enterocolitis (NEC).
- Hepatomegaly.

3. ***Respiratory manifestations:***
   - Tachypnea and flaring.
   - Retractions.
   - Grunting.
   - Cyanosis and apnea.
4. ***Cardiovascular manifestations:***
   - Tachycardia and arrhythmias.
   - Hypotension.
   - Pallor, cyanosis, and mottling.
   - Cold skin.
5. ***CNS manifestations:***
   - Irritability.
   - Hyporeflexia.
   - Tremors, seizures.
   - Full or tense fontanels.
   - Abnormal Moro reflex.





6. Hematological manifestations:

- Pallor.
- Jaundice.
- Splenomegaly.
- Petechiae, purpura.
- Bleeding and DIC.

Investigations:

1. ***Hematological signs:***
   - **Leucopenia** (total leucocyte count **< 5000 per cmm**)
   - **Neutropenia is more predictive** of neonatal sepsis than neutrophilia
   - **Absolute neutrophil count (ANC) is < 1800 per cmm**.
   - **Immature neutrophils** (Band cells + myelocytes + metamyelocytes) **to total neutrophils ratio (I/T) > 0.2** means that immature neutrophils are over 20% of the total neutrophils because bone marrow pushes even the premature cells into circulation, to fight infection.
   - **Thrombocytopenia** (Platelet count < 100,000 /cmm)
2. ***Acute phase reactants:*** C-reactive protein is often elevated neonatal sepsis.
3. ***Direct method Isolation of microorganisms:*** From blood, urine, stool, CSF, pleural fluid, or pus culture is **diagnostic**.
4. ***Imaging:*** CXR, cranial sonar, CT and MRI may be needed.

Treatment:

1. 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**.

2. 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

Case 10

A PT male, 30 wks GA, aged 15 days, presented with convulsions & RBS was 25.

What's the possible diagnosis?

- Hypoglycemia

What's the proper TTT?

- Glucose conc 10% 2 ml\kg IV shot .

Case 11

A FT male. 38 wks GA, was born to an epileptic mother, delivered cyanosed and needed PPV on resuscitation, presented with convulsions 6 hours after birth., serum electrolytes & RBS were normal.

What's the possible diagnosis?

- Hypoxic-ischemic encephalopathy (HIE).

Etiology:

1. Central nervous system: (Commonest)

- Hypoxic-ischemic encephalopathy (HIE)
- Intracranial Hemorrhage.
- CNS infections e.g., meningitis, encephalitis.
- CNS malformation e.g., cerebral agenesis.

2. Metabolic:

- Hypoglycemia.
- Hypocalcemia.
- Hypomagnesaemia.
- Hyponatremia and hypernatremia.
- Inborn error of metabolism e.g., vitamin B6 deficiency, organic acidemia, hyperammonemia.

3. Others:

- Local anesthesia during labor.
- Drug withdrawal e.g., maternal narcotics.
- Familial.
- Fifth-day fits.

4. Unknown causes.

Clinical manifestation and classification:

1. 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.

2. Tonic seizures(%5) :

- Sustained rigid posture of the body.
- May be ***focal or generalized.***

3. Clonic seizures(%25:30) :

- Rapid alternating contraction and relaxation of the muscles.
- May be:
  - ***Focal.***
  - ***Multifocal:*** migrating from limb to limb.
  - ***Rarely generalized.***

4. 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**, then 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 sequale percentage*
Normal	Less than 10%
Severe abnormalities	More than 90%
Moderate abnormalities	Approx.. 50%

Treatment:

- **Stabilize vital signs:** (**A**irway, **B**reathing, **C**irculation)
- **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:*** 50 mg IV 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 diseases 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. The normal heart rate of New born is:

a) 60-80/ minute.
b) 70-120 / minute.
c) 80-110 / minute.
d) 120-160 / minute.

2. All are true about preterm neonates except:

a) The birth weight is low.
b) Liable for respiratory distress syndrome.
c) Less liable to develop infantile rickets.
d) Increased susceptibility to infections.

3. A neonate delivered by difficult forceps delivery was noticed not to move his left arm and prefers to maintain it internally rotated with palm directed outwards, what's the injury type?

a) Cranial Injures
b) Spine and Spinal Cord Injuries
c) Peripheral Nerve Injures
d) Non-Neurological Birth Injuries

4. Unconjugated hyperbilirubinemia occurs in all of the following EXCEPT:

a) physiological jaundice.
b) Rh incompatibility.
c) breast milk jaundice.
d) biliary atresia.

5. what investigation to 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 12

Respiratory & Allergy

Learning Objectives:

By the end of this chapter, students should be able to:

1.Demonstrate understanding of upper airway obstruction from foreign bodies, congenital anomalies, and acute inflammatory upper airway obstruction.

2.Answer questions about inflammatory and infectious disorders of small airways.

3.Apply knowledge of bronchial asthma to diagnose and describe treatment.

Contents:

1. Upper respiratory tract disorders:
    a. Tonsillo – pharyngitis
    b. Congenital anomalies of the larynx:
        i. Laryngomalacia
        ii. Subglottic stenosis
    c. Croup
    d. Epiglottitis
2. Lower respiratory tract disorders:
    a. Bronchiolitis
    b. Pneumonia:
        i. Bronchopneumonia
        ii. Lobar pneumonia
3. Acute bronchial asthma:
4. Pleural diseases:
    a. Pleural effusion
    b. Empyema
    c. Pneumothorax

I. Upper respiratory tract disorders

a. Tonsillo – pharyngitis

Case 1

An 8-year-old girl complains of acute sore throat of 2 days' duration, accompanied by fever and mild abdominal pain. Physical examination reveals enlarged, erythematous tonsils with exudate and enlarged, slightly tender cervical lymph nodes.

What is the most likely diagnosis?

Acute pharyngitis

What is the commonest causative organism?

1. ***Viral*** in > 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.

What are the possible 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:
    i. Rheumatic fever
    ii. Acute glomerulonephritis.

Definition:

It is the acute inflammation of the pharynx and the tonsils.

Clinical presentation:

I. Streptococcal pharyngitis:

- Rapid onset,
- Severe sore throat and fever,
- Headache and gastrointestinal symptoms frequently,
- ***Examination:*** Red pharynx, tonsillar enlargement with yellow, blood-tinged exudate, petechiae on palate and posterior pharynx, strawberry tongue, red swollen uvula, increased and tender anterior cervical nodes.

II. Scarlet fever:

- **Caused by** GABHS that produce one of three streptococcal pyogenic exotoxins (SPE A, B, C); exposure to each confers a specific immunity to that toxin, so a person can have scarlet fever up to three times.
- Findings of pharyngitis plus circumoral pallor.
- Red, finely papular erythematous rash diffusely that feels like sandpaper.
- Pastia's lines in intertriginous areas.

III. Viral pharyngitis:

- more gradual; with typical URI symptoms; erythematous pharynx, no pus.
- **Pharyngoconjunctival fever (adenovirus).**
- **Coxsackie:**
  - ***Herpangina:*** small 1–2 mm vesicles and ulcers on posterior pharynx.
  - ***Acute lymphonodular pharyngitis:*** small 3–6 mm yellowish-white nodules on posterior pharynx with lymphadenopathy.
  - ***Hand-foot-mouth disease:*** inflamed oropharynx with scattered vesicles on tongue, buccal mucosa, gingiva, lips, and posterior pharynx →ulcerate; also, on hands and feet and buttocks; tend to be painful.

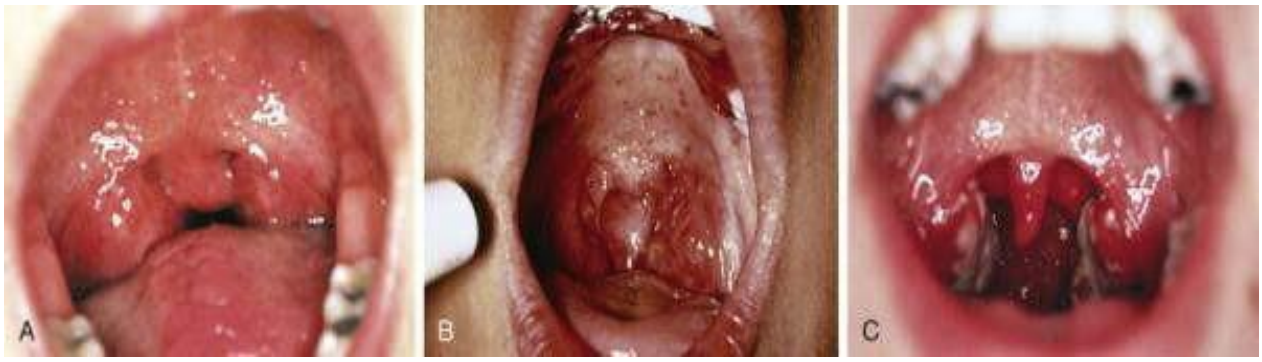
Investigations:

1. In both viral and bacterial cases there is polymorphnuclear leucocytosis.
2. Streptococcal infection can be ***diagnosed by:***
   i. Rapid antigen detection test of throat swabs (needs only 2 hours).
   ii. 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:
   i. Rheumatic fever. ii. 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:

A- Symptomatic:

1. ***Rest.***
2. ***Antipyretics and analgesics***. Paracetamol 10-15 mg/kg/dose or ibuprofen 10-15 mg/kg/dose.
3. ***Diet:*** milk pudding, fruit juice and warm fluids. Then give small amounts of other foods as appetite improves.

B- Antibiotics: If streptococcal etiology is confirmed or highly probable give a ten days course of penicillin or erythromycin.

1. ***Penicillin:***

- 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.

- 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.

2. Other antibiotics:

- 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

- 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.

- Azithromycin: 12 mg/kg/day as single dose for at least 5 days.

- Cephalosporin (cephalexin or cefadroxil) for 10 days.

Prevention:

- Avoid overcrowded places and school class.
- Avoid contact with patients.
- In patients with rheumatic fever, benzathine penicillin injection is given to prevent streptococcal pharyngitis and rheumatic recurrences. The above doses of are given every two weeks till the age of 20 years or older.
- Removal of the tonsils does not reduce the frequency or complications of pharyngitis.

Indications of tonsillectomy:

- Severe obstruction of airways
- Tonsillitis more than six times in the last year.
- Chronic tonsillitis e.g., chronic enlargement of tonsillar lymph nodes or chronic hyperaemia of anterior pillars.
- Peritonsillar abscess.

B- Laryngeal Obstruction

Manifestation:

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 O_2 and increased arterial CO_2 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.

N.B. Laryngeal obstruction is more common in infants and young children due to small size of larynx, soft cartilage, loose submucosa and rich nerve supply.

I. Congenital Laryngeal Stridor (Laryngomalacia)

- ***The onset:*** 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.

II. 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.

III. Acute Viral Laryngitis

Age: 3 months – 5 years, More common in males, and in cold seasons.

Etiology:

- About ¾ of cases are caused by parainfluenza viruses, and the remaining ¼ 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).

IV. 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.

V. Croup

Case 2

A 3-year-old girl awakes from sleep with a barking cough, inspiratory stridor, and dyspnea. The parents think that their child is suffocating and immediately bring the child to the emergency department. As you examine the pale and anxious girl. You notice a strong inspiratory (resting) stridor and marked inter- and subcostal retractions. The rectal temperature is 36.5•c.

What is the most likely diagnosis?

Croup

What is the differential diagnosis?

• Inhaled foreign body
• Anaphylaxis
• Epiglottitis
• Rare causes include:
- Bacterial tracheitis - Severe tonsillitis with very large tonsils,
- Inhalation of hot gases (e.g., house fire) - Retropharyngeal abscess.

What is the treatment?

The first step in the treatment of croup is oral dexamethasone. A less frequently used alternative is nebulized budesonide. If 2–3 hours later the child has improved and the oxygen saturation is >95% in air, the child can be discharged. In some cases, a further dose of steroids can be administered 12–24 hours later. If the child deteriorates then nebulized adrenaline can be administered.

Definition: Acute laryngotracheobronchitis.

Etiology:

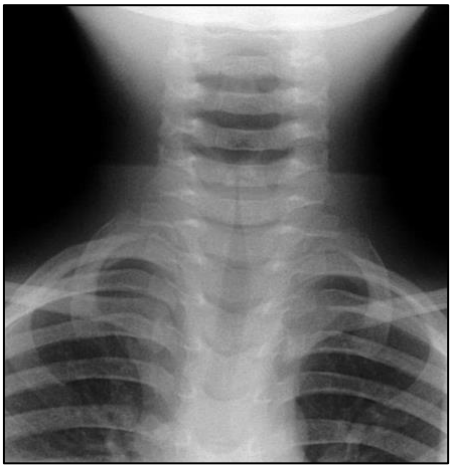
- ***Parainfluenza viruses*** (types 1, 2, 3) are responsible for about 80% of croup cases.

- ***Age:*** 3 months – 5 years; most common in winter; recurrences decrease with increasing growth of airway.

Clinical manifestations:

- Upper respiratory infection 1–3 days, then barking cough, hoarseness, inspiratory stridor; worse at night, gradual resolution over 1 week.

- The patient has moderate to high fever.
- Signs of laryngitis and laryngeal obstruction.
- Signs of bronchial obstruction e.g., wheezy respiration.
- Dyspnea is marked (inspiratory and expiratory).
- Chest examination reveals rhonchi and crepitations.
- Secondary bacterial infection may occur.
- Recurrence occurs in young children.



Complications:

- Hypoxia only when obstruction is complete.

Diagnosis:

- Clinical, x-ray not needed (steeple sign if an x-ray is performed).

Treatment:

Supportive:

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.

plus:

- ***Mild:*** corticosteroid then observe; if improved, then home but if worsens, treat as moderate.
- ***Moderate:*** nebulized epinephrine + corticosteroid, then observe; if improved, then home but if worsens, repeat epinephrine, and admit to hospital.
- ***Severe:*** nebulized epinephrine and corticosteroid then admit to hospital (possibly PICU).

VI. Epiglottitis

Case 3

A 2-year-old child presents to the emergency center with her parents because of high fever and difficulty swallowing. The parents state that the child had been in her usual state of health but awoke with fever of 40ºC (104°F), a hoarse voice, and difficulty swallowing. On physical examination, the patient is sitting in a tripod position. She is drooling, has inspiratory stridor, nasal flaring, and retractions of the suprasternal notch and supraclavicular and intercostal spaces.

What is the most likely diagnosis?

Epiglottitis

What is the most common causative organism?

Haemophilus influenzae type B (HiB)

What is the treatment?

- Establish patent airway (intubate).
- Antibiotics to cover staphylococci, HiB, and resistant strep (antistaphylococcal plus third generation cephalosporin).

Epidemiology:

- ***Age:*** 2-7 years. - ***Sex:*** More common in males

Etiology:

- Haemophilus influenzae type B (HiB) no longer number one (vaccine success).
- Now combination of streptococcus pyogenes, streptococcus pneumoniae, staphylococcus aureus and mycoplasma.
- ***Risk factor:*** unimmunized child

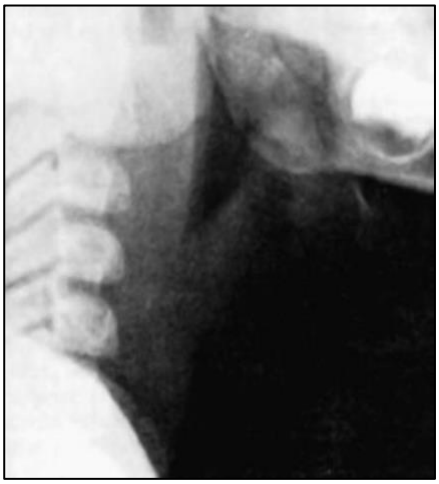
Clinical manifestations:

- Dramatic acute onset.
- High fever, sore throat, dyspnea, and rapidly progressing obstruction.
- Toxic-appearing, difficulty swallowing, drooling, sniffing-position.
- Stridor is a late finding (near-complete obstruction).

Complications:

- Complete airway obstruction and death.

Diagnosis:



Clinical first (do nothing to upset child), controlled visualization (laryngoscopy) of cherry-red, swollen epiglottis; x-ray not needed (thumb sign if x-ray is performed) followed by immediate intubation.

Treatment:

- Establish patent airway (intubate).
- Antibiotics to cover staphylococci, HiB, and resistant strep (antistaphylococcalplus third-generation cephalosporin)

VII. 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.

VIII. 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 wakens 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 >>> Treat viral nasopharyngitis an dgive Promethazine HCl (Phenergan) 0.5 mg/ kg. Before bedtime.

IX. 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.

X. Acute Tracheobronchitis

Definition:

- Acute catarrhal inflammation of the trachea and bronchi.

Etiology:

- 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.
- 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 39C. 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.

6. ***Chest Signs:***
    - Breath sounds may become harsh.
    - Rhonchi may be heard especially in infants with or without few scattered crepitations.
7. ***X-ray chest:*** Free or shows prominent bronchovascular shadows.

Course And Prognosis:

- The condition gradually subsides within 7-15 days.
- Complications occur in malnourished or rachitic patients e.g., otitis media, sinusitis, or bronchopneumonia.
- Recurrent acute bronchitis occurs if predisposing factor is not treated.

Treatment:

- Bed rest with frequent change of position in infants to facilitate drainage of mucus.
- Warmth.
- Adequate fluid intake especially warm fluids.
- Antipyretic e.g., Paracetamol 50 mg/kg/day, or Ibuprofen 20 mg/kg/day.
- If cough is distressing and interfering with sleep or feeding a cough suppressant may be prescribed.
- If bacterial super infection is present an antibiotic is given.
- Mucolytic e.g., Carobcysteine or Ambroxol syrup (one ml /10 kg) 4 times daily.
- Expectorant e.g., Syrup Ipecac (1 ml /10kg) 4 times daily.

Lower respiratory tract disorders

a. Bronchiolitis

Case 5

A 6-month-old infant presents to the physician with a 3-day history of a runny nose and bit of a cough 2 days ago but has become progressively more chesty and has now gone off his feeds and is having far fewer wet nappies. He has two older siblings who also have colds. He was born at 34 weeks' gestation. On physical examination, the patient has a temperature of 37.8°C, respirations of 60 breaths/min, nasal flaring, and accessory muscle usage. The patient appears to be air hungry, and the oxygen saturation is 92%.

What is the most likely diagnosis?

This baby has the characteristic clinical features of acute bronchiolitis, a seasonal viral illness occurring from early autumn to spring, principally affecting infants.

What is the commonest causative organism?

The commonest causative organism is respiratory syncytial virus (RSV), which is responsible for about 80 % of infections. In hospital, a nasopharyngeal aspirate (NPA) may be sent for viral immunofluorescence, polymerase chain reaction (PCR) or culture. This is largely for infection control and epidemiology and does not affect acute management.

What are the indications for referral to hospital?

- Apneic episodes (commonest in babies 2 months and may be the presenting feature)
- Intake 50 % of normal in preceding 24 hours
- Cyanosis
- Severe respiratory distress – grunting, nasal flaring, severe recession, respiratory rate > 70/min
- Congenital heart disease, pre-existing lung disease or immunodeficiency
- Significant hypotonia, e.g., trisomy 21 – less likely to cope with respiratory compromise
- Survivor of extreme prematurity
- Social factors

What is the management in hospital?

- Babies usually deteriorate over the first 48–72 hours. Hence there is a low threshold for admitting any baby 2 months of age on day 1–2 of their illness as they may deteriorate and become exhausted and apneic.
- Management is supportive.

• Investigations are rarely indicated; A chest X-ray is only needed if the clinical course is unusual and often leads to unnecessary antibiotic prescriptions. Blood tests are only required if there is diagnostic uncertainty, e.g., if the infant has a temperature ≥ 39°C and a superadded bacterial respiratory infection is suspected.

• Oxygen saturations should be kept at ≥ 92 per cent and the infant should be nasogastrically fed if they cannot maintain >50 per cent of normal intake. Intravenous fluids are used in severe cases.

• All fluids are restricted to two-thirds of maintenance.

• Nasal and oral suction is helpful.

• There is no evidence that bronchodilators, oral or inhaled steroids modify the clinical course or any important outcomes such as the need for ventilation or the length of stay.

• A capillary blood gas should be checked if the infant is deteriorating. Every season a small proportion of infants need high-dependency or intensive care – most respond well to continuous positive airways pressure (CPAP), avoiding the need for intubation.

• Babies are discharged when they are well enough to continue recovering at home, but many continue to cough and wheeze for weeks and get similar symptoms with subsequent upper respiratory tract infections.

• Response to conventional asthma treatment is variable. Leukotriene antagonists may have a role. Exposure to tobacco smoke must be avoided.

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:*** Inflammation of the small airways (inflammatory obstruction: edema, mucus, and cellular debris) → (bilateral) obstruction → air-trapping and over inflation.

Clinical presentation:

- **Signs and symptoms:**
  - Mild URI (often from household contact), decreased appetite and fever, irritability, paroxysmal wheezy cough, dyspnea, and tachypnea
  - Apnea may be more prominent early in young infants.
- **Examination:**
  - Wheezing, increased work of breathing, fine crackles, prolonged expiratory phase, Lasts average of 12 days (worse in first 2–3 days).

Complications:

A. Dehydration
B. Hypoxia
C. Apneic spells
D. Respiratory acidosis
E. Bronchopneumonia
F. Bronchial hyperreactivity and bronchial asthma
G. Death in 1% of cases.

Investigations:

Diagnosis is clinical. Radiography (nonspecific, viral) and lab studies (microbiology) should not be routinely used.

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. Aspiration syndromes; Foreign body, GERD
   b. Heart failure
   c. Anaphylaxis
   d. Congenital airway anomalies: Tracheal stenosis, Vascular ring
   e. Mucociliary clearance defect: Primary ciliary dyskinesia, Cystic fibrosis

Treatment:

- ***Outpatient treatment for mild cases.***
- ***Severe cases:***
  1. Hospitalization
  2. Hydration oral, IV in severe cases.
  3. Humidified oxygen is the most important line of treatment.
  4. Racemic adrenaline inhalation
  5. Nebulised hypertonic (3%) saline
  6. Antibiotics for secondary bacterial infection.
  7. Aspiration of secretions and assisted ventilation may be needed.
  8. Digitalis for heart failure.
  9. Bronchodilators and corticosteroids (as for asthmatic paroxysm) use are controversy
  10. Ribavirin aerosol is useful for severe cases, but costly. *Indicated for:* Cases with acute respiratory failure, co-existing disease e.g., congenital heart disease and cases with low immunity.

Prevention:

Monoclonal antibody to RSV F protein (preferred: palivizumab) in *high-risk infants only*, e.g., oxygen-dependent survivors of prematurity, as it is extremely expensive, infants with hemodynamically significant heart disease.

b. Pneumonia

Case 7

A 3-year-old boy presented to the physician with 4 days history of cough and fever and diagnosed with a viral upper respiratory tract infection (URTI). The following day he returned and was commenced on oral antibiotics. He is now complaining of tummy ache and has vomited once. He has not been immunized but there is no other medical history of note.

Examination showed that the child was miserable, flushed, toxic and febrile (38.8^0C) with a capillary refill time of 2 sec. His pulse is 140 beats/min, his oxygen saturation is 91 % in air and his blood pressure is 85/60 mmHg. He seems to be in pain, especially when he coughs, and his respiratory rate is 48 breaths/min with nasal flaring. There is dullness to percussion in the right lower zone posteriorly with decreased breath sounds and bronchial breathing. He seems reluctant to have his abdomen examined but bowel sounds are normal.

What is the most likely diagnosis?

Right lower lobar pneumonia

What is the commonest causative organism?

The most likely causative organism is Streptococcus pneumoniae. However, a diagnosis is rarely made from sputum analysis as children tend to swallow sputum. Blood cultures may be positive.

What are the steps in management?

• Oxygen to maintain saturation at > 92 %.

• Adequate pain relief for pleuritic pain

• Intravenous antibiotics according to local guidelines, e.g., co-amoxiclav

• Physiotherapy, e.g., bubble blowing. Encourage mobility

• Monitor for development of a pleural effusion. If the chest X-ray is suspicious, an ultrasound will be diagnostic. If present, a longer course of antibiotics is recommended to prevent empyema (a purulent pleural effusion).

• Ensure adequate nutrition

• Arrange a follow-up chest X-ray in 6–8 weeks for those with lobar collapse and/ or an effusion. If still abnormal, consider an inhaled foreign body.

Definition: Pneumonias are inflammatory diseases of the pulmonary parenchyma.

Classifications of pneumonias: *(depending on the morphology)*

- ***Bronchial pneumonia*** is the most frequent form of pneumonia in children. The inflammatory changes affect the respiratory pathways and the neighbouring portions of the pulmonary parenchyma.
- ***Lobar pneumonia,*** the inflammatory changes are limited to the pulmonary parenchyma of a lung segment or lobe.
- ***Interstitial pneumonias,*** it is primarily the perivascular or interalveolar connective tissue that is inflamed.

Etiology:

The pathogen spectrum of community acquired pneumonia varies as a function of age.

- ***1 month to 5 years:*** Principally viruses (RSV, influenza, Para influenza, adenovirus, ECHO-virus, coxsackie-virus, rhinoviruses), bacteria (Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis, Staphylococcus aureus [especially in infants]
- ***New-borns****:* B-Streptococci, Staphylococci, Gram-negative enterobacteria (e.g., E. coli, Klebsiella), Chlamydia.
- ***School children:*** Principally viruses (see above), Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Haemophilus influenza

Clinical Picture:

a. Clinical symptoms of pneumonia are; coughing (first dry, then productive), fever, abnormal breathing (dyspnea, tachypnea, flared nostrils, labored breathing [air is audibly expressed from the lungs], with accompanying obstruction, thoracic retractions), and possible cyanosis (oxygen saturation < 90%) and chest pains (with associated pleuritis).
b. Often there are associated symptoms such as tiredness, vomiting, loss of appetite, and often abdominal pain ("pneumonia stomach" is an accompanying inflammatory reaction of the peritoneum in pleuritis).
c. Note: any case of acute abdomen in children, pneumonia should be considered.
d. Bacterial pneumonia is usually more severe and is associated with high fever and more intense signs of inflammation.
e. Chlamydia trachomatis pneumonia:
    - No fever or wheezing (serves to distinguish from RSV)

- 1–3 months of age, with insidious onset
- May or may not have conjunctivitis at birth
- Mild interstitial chest x-ray findings
- Staccato cough

I- Lobar pneumonia

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:

1. Pneumococcus and H. influenza bacillus:
   - From patient with upper respiratory tract infection, rarely from patient with pneumonia.
   - From contact carrier with the microorganism in his throat.
2. 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:
   - Dyspnea with expiratory grunt.
   - Inverted breathing rhythm.
   - 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.
5) In mild cases, only tachypnea may be present.

C- 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.

D- Chest signs of consolidation

1) ***Inspection:*** normal shaped chest, central mediastinum
2) ***Palpation:*** diminished chest expansion on affected side, central trachea, increased TVF

over the affected lobe, no palpable rhonchii

3) ***Percussion:*** dullness over the affected lobe

4) ***Auscultation:*** bronchial breathing over the affected lobe with increased vocal resonance (bronchophony). Pleural rub may be heard

>>> 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:

- ***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.

- ***Causative microorganisms:***

a. ***Exclusively viral:*** RSV, influenza, parainfluenza, adenovirus and measles.

b. ***Exclusively bacterial:*** The most common organism differs according to the age of child:

- In neonates, Strept. Group B and E. Coli.

- Age 1-3 months, Strept. B and Chlamydia.
- Pneumococcus is the most common after the age of 3 months.
- Staph. aureus in preschool age.
- Streptococcus-A and Mycoplasma, by school age.
- Oral anaerobes at any age in cases of aspiration pneumonia.

c. ***Mixed viral and bacterial superinfection.***

- ***Source of infection:***

a. From patients or carriers (as before).

b. From oral flora in aspiration pneumonia.

c. Neonatal pneumonia from carriers, patients or vaginal flora.

Pathology:

- ***Lungs*** show a mixture of lesions diffusely scattered in one or both lungs:

a. Bronchitis and bronchiolitis with variable degrees of obstruction and secretions.

b. Alveoli: in some lobules they are consolidated, in others collapsed, and in others emphysematous.

c. Inflammatory infiltrate of interstitial tissue.

d. Lung abscess may be present.

- ***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:

- Symptoms and general signs of pneumonia.
- Variable degrees of wheezing, more marked in cases complicating asthma.
- Cough is early and prominent and may be productive.
- In neonatal pneumonia, manifestations of neonatal sepsis may be present.

C- Chest examination:

- **Marked dyspnea:** increased RR, working accessory muscles of resp., & retractions.
- **Breath sounds:** Harsh vesicular breath sounds allover, but if large areas of consolidation are present near lung surface, they cause tubular breath sounds here and there.
- **Added sounds:**
  - Rhonchi: sibilant and sonorous, diffuse and most marked in asthmatic cases.

- 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. Pneumatoceles, empyema, pyopneumothorax and lung abscess.
4. Disseminated infection: Meningitis, pericarditis, peritonitis and arthritis.
6. Heart failure.
7. Respiratory failure.
8. Pulmonary sequelae may complicate bronchopneumonia e.g., flaring of dormant pulmonary T.B., pulmonary fibrosis, and bronchiectasis.

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.
- 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.
- 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.
- Chest X-Ray cannot differentiate between viral and bacterial pneumonia.

B- Blood Picture:

- CBC shows leucocytosis.
- Neutrophilia more common in bacterial cases.
- Lymphocytosis in viral cases.
- Eosinophilia in Chlamydia pneumonia.

C- Definitive diagnosis:

- ***Viral:*** isolation of virus or detection of antigens in respiratory tract secretions; (usually requires 5–10 days); rapid reagents available for RSV, parainfluenza, influenza, and adenovirus
- ***Bacterial:*** isolation of organism from blood (positive in only 10–30% of children with S. pneumoniae), pleural fluid, or lung; sputum cultures are of no value in children.

Treatment of Pneumonia:

- Indications for hospital admission:

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 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.

   Oxygen, if there is severe dyspnea, even in absence of cyanosis, or if O2 sat < 90 %.
5. Bronchodilators for asthmatic bronchopneumonia.
6. Mechanical ventilation for respiratory failure.
7. Digoxin for heart failure.

- ***Depending on the age of the patient, clinical picture and the probable pathogens antibiotics are given till results of culture and sensitivity:***
  - **Pneumococcus, streptococcus A or B:** Penicillin or ampicillin or amoxicillin or first-generation cephalosporin
  - **Staph. Aureus:** Oxacillin or first-generation cephalosporin
  - **H. influenza:** Ceftrixone, cefotaxime
  - **E. coli:** Gentamicin or amikacin
  - **Mycoplasma pneumonia:** Azithromycin or Clarithromycin

Feature	Bacterial	Viral	C. trachomatis	M. pneumoniae
Etiology	S.pneumoniae HIB S. aureus	RSV Parainfluenza Influenza Adenovirus	C. Trachomatis	M. Pneumoniae
Age	Any age Most common reason for lobar is S. pneumoniae	<5 years	1–3 months	>5 years
Timing	Cold months	Cold months	All year	All year; more in winter
Diagnosis Key Words	● Acute ● Severe ● Productive cough ● Dyspnea ● High fever ● Chest pain ● Rhonchi ● Rales ● Decreased breath sounds ● May have empyema	● Insidious ● Often worsening URI ● Lower temperature ● Wheeze ● Cough ● Mild dyspnea	● May have had conjunctivitis as newborn ● Afebrile ● No wheeze ● Staccato cough	● Insidious ● URI symptoms with persistence of cough worsening over 2 weeks ● Rales most consistent finding (lower lobe uni- or bilateral)
Best Initial Test = Chest Xray	- Lobar consolidation	- Bronchopneumonia, interstitial - Hyperinflation with increased Peribronchial markings	- Mild interstitial	- Unilateral lower lobe interstitial - Classically looks worse than symptoms

Most Accurate Test	● Sputum C and S (cannot rely on in child) ● Blood culture ● Pleural fluid culture	● Respiratory secretions for viral or antigen isolation (would not do routinely)	● Sputum PCR (but not needed = classic clinical diagnosis)	● PCR of NP or throat swab (but not usually needed)
Best Initial Treatment and Definitive Treatment	- Admit for IV cefuroxime - Then change if needed based on C and S	- No treatment of viral pneumonia - If uncertain, give oral amoxicillin	Oral macrolide	Oral macrolide

III. Acute bronchial asthma

Case 9

A 5- year-old child comes to ER with grunting complaining of chest tightness and cough with wheeze for 3 days after he visited his grandfather who is heavy cigarette smoker, by history taking; he had past history of recurrence of similar attacks last year, his mother suffering allergic rhino-sinusitis and his elder sister had atopic dermatitis, by examination; bilateral expiratory rhonchi with decreased vocal resonance.

What is the most likely diagnosis?

Acute bronchial asthma moderate to severe attack with RD grade3 (Persistent)

How to approach diagnosis?

By past history of recurrence of similar attacks, family history of allergic diseases in his mother and sister, history of exposure to aeroallergen passive cigarette smoking as a trigger (the offending cause), symptoms (cough/chest tightness) examination; bilateral rhonchi/ ↓VR and Persistent asthma as he had many flares in the last year.

What is the treatment?

- Hospitalization/ Oxygenation/ hydration
- Inhaled albuterol q 20 minutes for one hour—add ipratropium if no good response for second dose
- Give oral prednisolone or intravenous (IV) hydrocortisone. Blood gases (capillary or venous) and a chest X-ray may be required.
- If there is no improvement or the child deteriorates, additional treatment is needed. These include IV salbutamol, IV magnesium sulphate (a smooth muscle relaxant) and IV aminophylline, although the effectiveness of the latter two is still controversial.

How to prevent further attacks?

- Avoid exposure to aeroallergen (passive cigarette smoking)
- Daily use of controller medications (Inhaled corticosteroids/Ieukotriene antagonist)
- Annual influenza vaccination
- Allergen Immunotherapy (Hyposensitization)

Definition: Asthma is a chronic inflammatory disease of the airways. It is characterized by airway hyper - responsiveness to a variety of stimuli, reversible airway obstruction, and bronchospasm.

Epidemiology:

- ***Prevalence:*** 5 - 10 % of children
- ***Sex:*** incidence before puberty, boys to girls, 2: 1 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
  - ✓ 80 – 90 % < 5 years of age

Etiology/pathophysiology:

- ***Chronic inflammation of airways*** with episodic at least partially reversible airflow obstruction
- ***Most with onset age <6 years;*** most resolve by late childhood
- ***Two main patterns:***
  - Early childhood triggered primarily by common viral infections
  - Chronic asthma associated with allergies (often into adulthood; atopic).

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:

- Relatively narrow bronchial lumen.
- Increased number and activity of mucus secreting glands.
- Weak collapsible bronchial walls.

C: Abnormal characteristics of allergic child:

- 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.
- Irritability or hyperreactivity of bronchi (BHR) to various stimuli (physical or chemical).
- 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:

- ***Non antigenic stimuli:*** are common causes of asthma in the 1st five years of life.
  - Viral infections: RSV, parainfluenza, rhinovirus, and influenza virus.
  - Physical irritants: smoke, fumes, dust, strong odors, and cold air, and drinks.
  - Chemical irritants: kerosene, insecticides, and sulfur dioxide.
  - Strenuous exercise especially running.
  - Emotional stress.
- ***Antigenic stimuli:*** are common causes of asthma in older children.
  - Inhalants (aeroallergens): the most common allergens are: house dust mite, animal dander (cats, dogs, birds, cattle, sheep), pollens, fungi, insect parts and house dust.
  - Food: Milk, fish, eggs…etc.
  - Drugs: penicillin, aspirin and some non-steroidal anti-inflammatory drugs.

E: The result of this:

1. ***Non antigenic stimuli i***rritate 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: results in air trapping → generalized obstructive hyperinflation, scattered areas of atelectasis→ labored breathing.

H: Hyperinflation: being non uniform + Atelectasis areas → ventilation/perfusion mismatch → Decreased Pa O2 and increased P a CO2 + respiratory and/or metabolic acidosis.

Pathology:

A: Bronchi:

- Diffuse partial obstruction of small and large bronchi caused by bronchospasm, edema of the mucosa, increased mucus and cellular debris, and thickened walls (due to infiltration by inflammatory cells and deposition of collagen under the basement membrane i.e., remodeling).

B: Alveoli:

- Generalized hyperinflation due to air trapping. - Scattered small areas of collapse.

C: Complications may be found:

- Bronchopneumonia - Pneumothorax - Massive collapse

Clinical picture:

A: The asthmatic paroxysm:

- It is characterized by gradual or sudden onset of mild to severe chest wheeze and cough.
- The majority of attacks are mild to moderate.
- Gradual development of asthmatic paroxysm over a few days is triggered by exposure to irritants or allergens
- The paroxysms are more frequent and are more severe at night and early morning hours.
- 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.

B: In mild attacks, the condition is represented by:

- Complaint of intermittent chest wheeze or rattle.
- Slight increase in respiratory rate (RR)
- End expiratory rhonchi.
- PEFR and O2 saturation are still normal.

C: 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 PEFR and O2 saturation start to fall.

D: In severe paroxysm, there will be:

- Dehydration - Fatigue - Refusal of feed - Cyanosis
- Impaired consciousness - O2 saturation is low.

E: 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
- ***Auscultation:*** vesicular breathing with prolonged expiration, sibilant (±sonorous) rhonchi is present mainly expiratory ± non consonating 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.

F: 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.
- 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%.

G: Severity of Asthma Paroxysm (6 or more of the following criteria are needed)

Criteria	Mild	Moderate	Severe
1- RR (% of normal)	↑ up to 30%	↑ 30-50%	↑ > 50%
2- Alertness	normal	agitated	↓ 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- O2 saturation (%)	>95 normal	95-91	< 91
13- PEFR/FEV1 (%)	> 80 normal	80-50	< 50

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:

1. ***During the attack:*** Bacterial super infection, pneumothorax, and collapse of part or all of the lung and respiratory failure.
2. ***Chronic asthma results in:*** growth failure, chronic bronchitis, bronchiectasis, cor-pulmonale, emphysema, chest wall deformity
3. Badly controlled asthma can have an adverse effect on your quality of life. As it ***results in:***
   - Fatigue
   - Underperformance or absence from school or work
   - Psychological problems including stress, anxiety and depression.
4. Associated diseases may cause difficulty in asthma control:
   - Allergic rhinitis and sinusitis ± infection
   - 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:

- **In children,** neither lab tests nor provocation challenge tests are required for diagnosis; they may support the clinical diagnosis or may be used to follow the patient clinically.

- **Lung function:**

  - ***Gold standard = spirometry during forced expiration.*** FEV1/FVC <0.8 = airflow obstruction (the forced expiratory volume in 1 second adjusted to the full expiratory lung volume, i.e., the forced vital capacity) in children age ≥ 5 yrs
  - ***Bronchodilator response to inhaled beta-agonist:*** improvement in FEV1 to >12%
  - ***Exercise challenge:*** worsening in FEV1 of at least 15%
  - ***Home tool:*** peak expiratory home monitoring (PEF); A.M. and P.M. PEF for several weeks for practice and to establish personal best and to correlate to symptoms; based on personal best, divide PEFs into zones: green (80–100%), yellow (50–80%), red (<50%)

- **Radiology (no routine use):**

  - Hyperinflation: flattening of the diaphragms
  - Peribronchial thickening
  - Use to identify other problems that may mimic asthma (e.g., aspiration with severe gastroesophageal reflux) and for complications during severe exacerbations (atelectasis, pneumonia, air leak)

Classification of asthma severity

- **Intermittent asthma**
  - Symptoms ≤ 2 days/week and ≤ 2 nights/month.
  - No need for daily controller.
- **Persistent asthma**
  - (Mild → moderate → severe) symptoms > intermittent
  - Need daily controller

Class	Daytime Symptoms	Nighttime Symptoms	Treatment
Intermittent	≤2×/week	≤2×/month	-Short-acting β agonist PRN
Mild persistent	>2×/week	>2×/month	- Inhaled steroids - β agonist for, breakthrough
Moderate persistent	Daily	>1×/week	- Inhaled steroids - Long-acting β agonist - Short-acting β for, breakthrough -Leukotriene-receptor Antagonists
Severe persistent	Continual; limited activities; frequent Exacerbations	Frequent	- High-dose inhaled steroid -Long-acting β agonist -Short-acting β agonist -Systemic steroids -Leukotrine-receptor Antagonists

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:

Hospital Admission indicated for: Moderate - severe attacks, Status asthmaticus, complication (bronchopneumonia, pneumothorax, massive collapse .....etc)

- 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) Aerosolized β2 adrenergic agonists:

a. One dose /20 minutes (2-3 doses are usually adequate).

b. In case of status asthmaticus or no response to 3 doses, repeated doses are given (max. = 6 doses) till the attack is controlled β2 agonists can be given either by:

- ***Nebulizer + mask:*** for any age (Salbutamol 0.15 mg/kg in 2 ml saline/dose)
- ***Metered dose inhaler (MDI) with spacer*** is useful for school children. Salbutamol 4 puffs/dose, increase up to 8 puffs/dose if response in inadequate.

2) Corticosteroid therapy:

a. *For moderate paroxysm:* Give oral Prednisone 1 -2 mg / Kg / day divided in 2 doses, for 5-7 days.

b. *For severe paroxysm or status asthmaticus* give IV or IM dexamethasone: 0.1 mg/Kg / dose, repeat /12 hours, or methyl prednisolone 1mg/kg q 12 hours up to 48h then give oral prednisone.

c. *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 β2 agonist is inadequate. Ipratropium bromide; by nebulizer: 250 ug / ml every 20 minutes for 3 doses, then every 2-4 h.

4) Aminophylline: IV infusion: Given for cases of status asthmaticus diluted in 30 ml saline and given by infusion pump.

5) Mechanical Ventilation: Indicated if any of the following occurs:

a. Failure of maximal pharmacological therapy including I.V beta agonist.

b. Exhausted child.

c. Impending respiratory failure (RF).

d. Respiratory or cardiac arrest.

Treatment of Mild Paroxysm

A) Beta-adrenergic agonist.

- For 1 weeks.
- Aerosol 2-4 puffs / 6 hours or by nebulizer

B) Oral aminophylline may be added 2-4 mg / kg / 6h.

C) Oral prednisone: May be added if:

- Otherwise not controlled
- For patient with history of previous severe paroxysms.

D) Antibiotic for febrile cases.

E) Hydration by oral warm fluids.

Control of bronchial asthma:

Children with persistent asthma need to take medication daily to keep their asthma under control after treatment of exacerbations by “Long-term controller medications " to decrease inflammation and to control chronic symptoms and prevent recurrence of asthma attacks:

- Inhaled corticosteroids (fluticasone)
- Leukotriene antagonist (montelukast)
- Long-acting beta-agonists
- Long-acting theophylline
- Monoclonal anti-IgE antibody (Omalizumab) in severe atopic patients.

Prevention of bronchial asthma:

1. Reduction of exposure to various antigenic and non-antigenic stimuli
2. Treat associated upper resp. allergy (URA) by antihistamines.
3. Treat Gastroesophageal reflux (GER) if present.
4. Prevention of exercise induced asthma (EIA):
5. Beta agonist (aerosol) a single dose 15-30 minutes before exercise is adequate.
6. Controller medication for persistent asthma
7. Annual vaccination against influenza virus
8. Allergen Immunotherapy (Hyposensitization): this is the administration of gradually increasing doses of causative allergens to the asthmatic atopic child administrated by injection 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.

IV-Pleural diseases

Pleurisy

Definition: Inflammation of the pleura.

Types:

1- Dry or plastic pleurisy.

2- Serofibrinous pleurisy.

3- Purulent pleurisy (empyema).

1.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:

- Treat underlying disease.
- Analgesic antipyretics.

2. Pleural effusion

Case 10

A 7-year-old boy with a 5-day history of cough, fever, and increased work of breathing. In speaking with the family, he had been healthy, and had received all of his immunizations.

He was seen by his family doctor 3 days ago and started on a course of oral amoxicillin to treat community-acquired pneumonia. They tell you that despite 3 days of antibiotics, he hasn't gotten any better and has still been having fevers at home.

Examination showed a temperature of 38.6^0c, RR 40 breaths /min, HR 120 bpm, his blood pressure is 90/68, and his O2 sat is 89% on room air, so he is given supplemental oxygen by nasal prongs.

Respiratory examination showed that he has mild subcostal and intercostal retractions. He has decreased chest expansion, with reduced movement on the left side. He also has dullness to percussion at the left lung base. On auscultation, there are normal vesicular breath sounds on the right, but they are reduced on the left and absent at the left lung base. Other physical examination was unremarkable

What is the most likely diagnosis?

Left lower lung parapneumonic effusion.

What investigation would you do to confirm the diagnosis?

- Chest x-ray erect to see opacity obliterating left costophrenic angle and rising to the axilla
- Chest ultrasound to detect the mild amount of effusion and see echogenicity of fluid
- CT chest to detect if the effusion is free or loculated
- Intercostal aspiration of pleural fluid to differentiate between exudate and transudate and do culture and sensitivity

What is the 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.

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

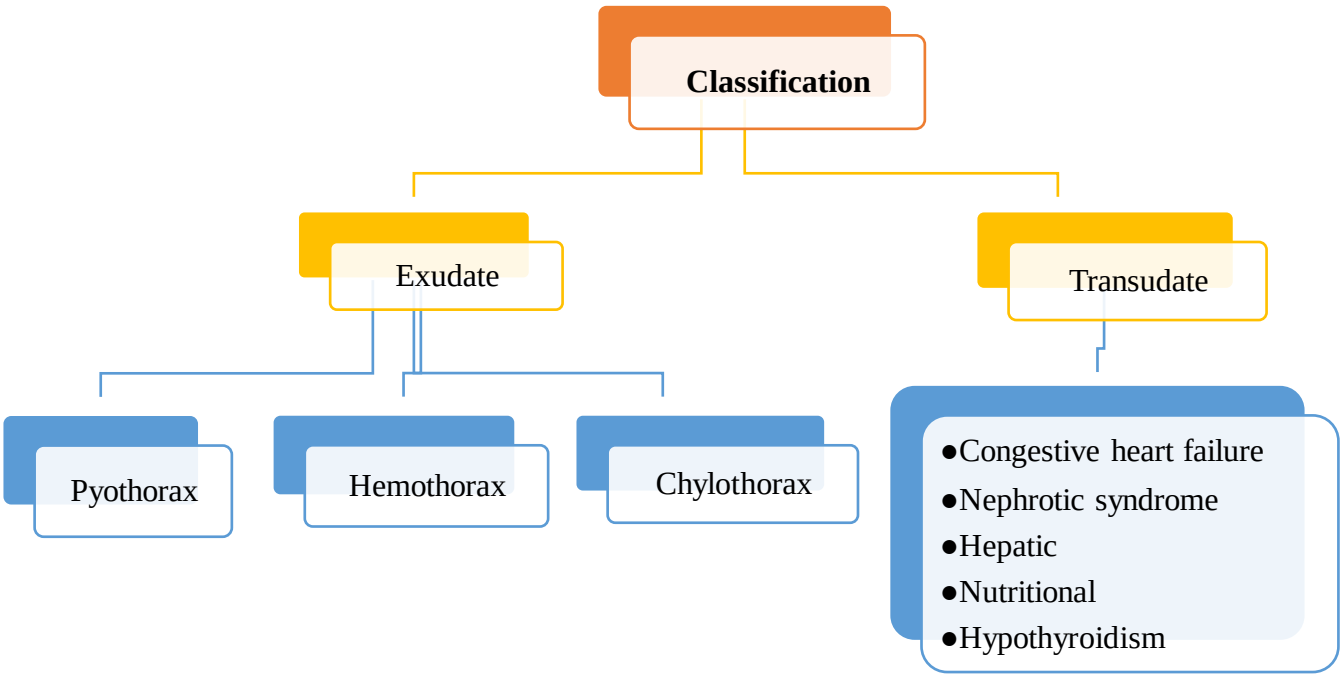
3. Oral antibiotics for 2-3 weeks after IV antibiotics.
4. Symptomatic treatment: Oxygen, analgesic antipyretic and light diet during febrile period.
5. For chronic empyema decortication of the lung and pulmonary exercises are needed to regain lung function.

Definition:

Abnormal (excessive) accumulation of fluid inside the pleural space.

Types:

	Exudate	Transudate
1. Appearance	Cloudy	Clear
2. Protein	> 3gm/dl	< 3gm/dl
3. Specific gravity	> 1016	< 1016
4. Glucose	Less than the serum	Same as serum
5. WBCs	> 1000/ mm3	< 1000/ mm3
6. PH	< 7.2	> 7.2
7. LDH	> 200 u/l	< 200 u/l



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 ▪ Triglycrides > 50mg/dl ▪ Lymphocytes > 5000 /cmm ▪ Becomes clear when shaken with ether	▪ Lymphatic obstruction (tumor) ▪ Thoracic duct injury (trauma) ▪ Chest surgery.

Clinical manifestations:

A. Symptoms and signs of the underlying disease.

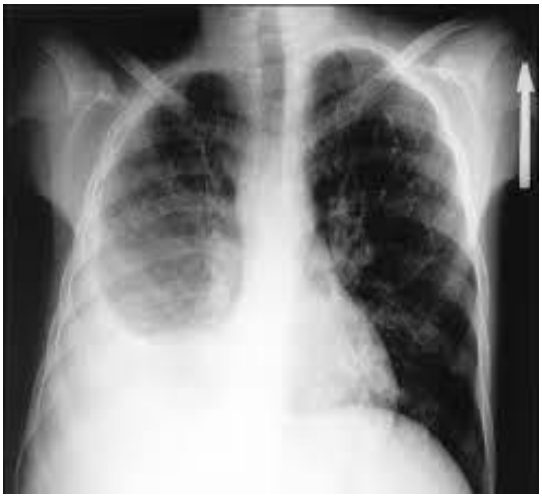
B. Symptoms of pleural disease:

1. Pleural pain early in disease and disappears when fluid accumulates
2. Large amounts can cause cough, dyspnea, cyanosis, retractions, tachypnea or orthopnea

C. Chest Signs of pleural effusion:

1. Inspection

- Limitation of movements on the affected side



2. Palpation

- Large effusions shift the mediastinum to the opposite side
- Decreased tactile vocal fremitus

3. Percussion

- Basal stony dullness rising to the axilla
- Hyper-resonance above the level of effusion

4. Auscultation

- Absent or reduced breath sounds over the area of the effusion
- BB heard over the upper level of effusion

D. Chest X-Ray:

- Small amounts are detected as obliteration of the costophrenic and cardiophrenic angels or widening of the interlobar septa.
- Large collections show homogenous opacity obliterating the angles and ascending to axilla with mediastinumal shift to the other side and lung collapse upwards & medially.

Differential diagnosis:

- Other causes of pleural effusion - Lobar pneumonia
- Massive collapse - Pneumothorax.

Treatment:

- That of underlying disease.
- 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.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 preschoolars.

2- Other causes include rupture of lung abscess, chest trauma, or extension of subphrenic abscess.

Clinical manifestations:

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, culture and sensitivity.

2- Chest X-ray:

- The same in pleural effusion
- When loculated no shift of fluid is observed when the child's position is changed.

Complications:

1. Bronchopleural fistula and pyopneumothorax are common in staphylococcal cases.
2. Purulent pericarditis and lung abscess.
3. Septicemia with osteomyelitis, arthritis and meningitis may occur in H. influenza and pneumococcus cases.
4. Chronic empyema causes pulmonary atelectasis.

Treatment:

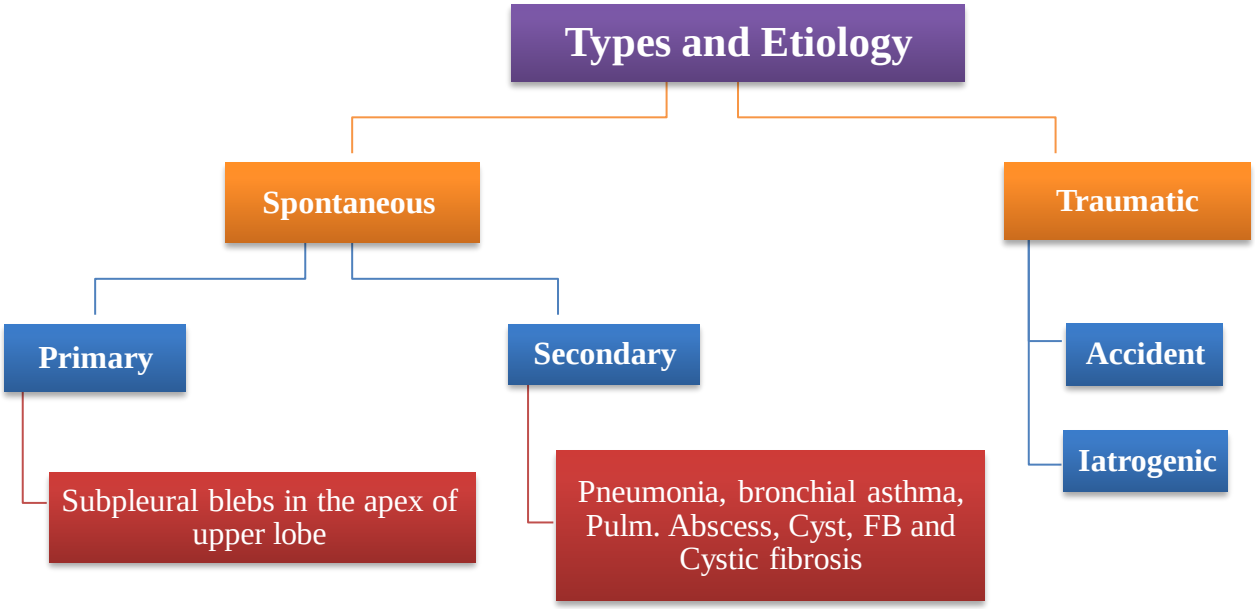
1. ***Drainage:*** the maximum amount of pus should be aspirated. This is followed by continuous closed drainage under water seal through a wide catheter in the pleural cavity for 1-2 wks. More than l tube is needed to drain loculated areas.
2. ***Systemic antibiotics IV or IM:***
    - **Duration:** 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.

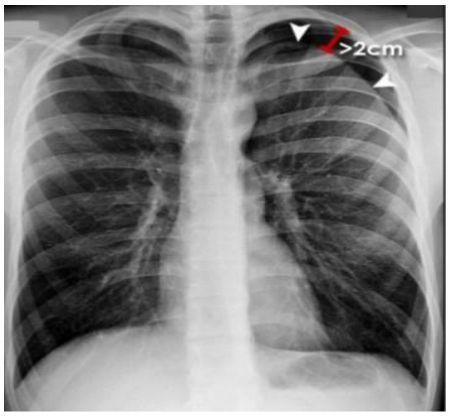
Pneumothorax

Definition: Presence of air in the pleural space.



Clinical manifestations:

- Symptoms and signs of underlying etiology.
- Small amount of air may be discovered on X-ray.
- Larger amounts give varying degrees of:
  - Chest pain.
  - Dyspnea with or without cyanosis
  - Signs of pleural air or signs of pleural air and fluid.



Tension pneumothorax:

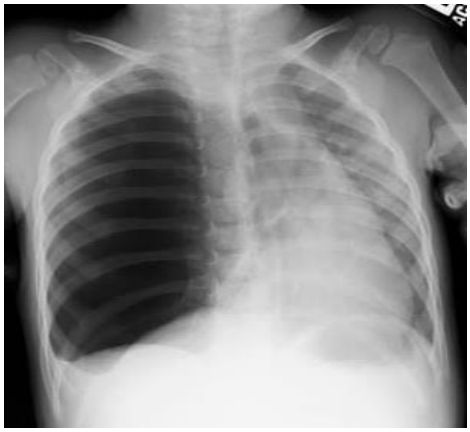
- It is the presence of a large amount of air under tension in the pleural space.
- It results in:
  - Symptoms and signs of pleural air are severe.
  - The expansion of the contra lateral lung is diminished.
  - Interference with venous return results in cardiovascular collapse (shock).

Investigations:

1. **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.
2. **Thoracocentesis:** Air is aspirated. A hiss may be heard in cases of tension pneumothorax.

Differential Diagnosis:

- Pleural fluid
- Pneumonia
- Severe asthma
- Diaphragmatic hernia



Treatment:

1. **General:**
   - O2 therapy if there is tachypnea or dyspnea
   - Analgesics for pleural pain
2. **Drainage:**
   - Mild cases with less than 5% collapse need no treatment, they will absorb spontaneously in about one week.
   - 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.
3. **Treat the underlying condition.**
4. **For recurring cases thoracic surgery is needed**

Practice Questions (Choose one correct answer)

1- The most common cause of acute bronchiolitis is:

a) Respiratory syncytial virus.
b) Influenza.
c) Adenovirus.
d) All of the above.

2- The following is not indication for tonsillectomy:

a) Peritonsillar abscess.
b) Acute tonsillitis.
c) Chronic tonsillitis.
d) Tonsillar abscess.

3- Commonest organism for epiglottitis:

a) Influenza.
b) H. influenza.
c) Staphylococcus.
d) Streptococcus.

4- Which is true in lobar pneumonia:

a) Hyper-resonant note on percussion over the affected side.
b) Diminished air entry over the side and dullness on percussion.
c) Fine crepitation on the affected side is the only chest finding.
d) None of the above.

5- Which is false regarding transudative pleural effusion:

a) Protein < 3gm/dl.
b) LDH<200 U/L.
c) Specific gravity <1016.
d) PH<7.2.

6- ***A 12-year-old girl is diagnosed with asthma. She has nighttime symptoms twice a week and daily daytime symptoms. Which of the following should NOT be part of her long-term treatment?***

a) Inhaled steroids.
b) Leukotriene-receptor antagonist
c) Short-acting beta agonist
d) Oral prednisone
e) Long-acting beta agonist

7- ***A 5-year-old boy has had a low-grade fever, runny nose, non-productive cough, and mild stridor for 2 days. He sounds like a seal when he coughs. He is nontoxic appearing and has no increased work of breathing. What is the next step?***

a) Chest x-ray to evaluate for the steeple sign
b) Discharge with close follow-up if symptoms worsen
c) Nebulized epinephrine
d) Laryngoscopy
e) Parenteral steroids

Chapter 13

Cardiovascular Diseases

Learning Objectives:

By the end of this chapter, students should be able to:

1. Identify tools for cardiovascular diagnosis.
2. Classify different types of congenital and acquired heart disease.
3. Correlate between the clinical presentations and the special nature of each cardiovascular disorder.
4. Formulate a management plan for cardiovascular diseases.
5. Identify common cardiac emergencies.
6. Give counseling to families whose child having a cardiac problem.

Contents:

1. Introduction
2. Common congenital cardiac diseases in pediatrics.
3. Common acquired cardiac diseases in pediatrics.

Chief complaint and presenting symptoms

Case 1
A 15 Year old male with history of chest pain on exertion, 2 episodes of sudden loss of consciousness which were with exercise. His father died suddenly at age of 40. His 20 YO sister working out in gym, collapsed and died. O/E Ejection systolic murmur on base of the heart. ECHO: basal septum measuring upper limits of normal.
What is the most likely diagnosis? A case of syncope, mostly due to hypertrophic cardiomyopathy (HOCM)
What is the most common etiology of this presentation in pediatrics? Vasovagal syncope
What may raise the suspicion of cardiac cause in this patient? • Syncope is associated with chest pain • Syncope is with exercise. • History of sudden death at young age in close family members.

Pulmonary congestion

Definition: Congestion of blood in the lung vasculature due to increase pulmonary blood flow, or fluid back from left side of the heart to lung.

Manifestations

- Tachypnea.
- Dyspnea: increases with exertion.
- Frequent respiratory infections.
- Cough or Wheeze.

Possible causes

- Congenital heart diseases with left to right shunt e.g., Ventricular septal defect (VSD), patent ductus arteriosus (PDA).
- Congenital and acquired lesions of left side of the heart e.g., Mitral valve stenosis and regurge, Aortic valve regurge.
- Other causes of left sided heart failure; myocarditis and dilated cardiomyopathy.

Systemic congestion

Definition: Accumulation of fluid in systemic venous circulation due to impairment of blood return to the right side of the heart.

Manifestations

- Edema; it is pitting, generalized appears in the dependent part and increases by effect of gravity
- In neonates and infants, the first edema seen is generally eyelid edema.
- Dyspepsia and vomiting.
- Right hypochondrial pain.

Possible causes

- Lesions affecting right side of the heart as tricuspid valve regurge, Atrial septal defect (ASD)
- Pericardial effusion - Constrictive pericarditis - Congestive HF.

Low cardiac output

Definition: The heart cannot pump sufficient blood to keep metabolic demand of the body.

Manifestations

- Irritability
- Dizziness.
- Intolerance to exertion, easy fatigability
- Feeding difficulties in infant: prolonged time of feeding, tachypnea, tachycardia and diaphoresis with feeding.
- Failure to thrive.

Possible causes

- Heart failure - Obstructive lesions as aortic stenosis, mitral stenosis, coarctation of aorta.

Cyanosis

Definition: Bluish discoloration of skin and mucus membrane due to increase non-oxygenated hemoglobin in systemic circulation more than 5 gm/dl.

Manifestations

- Cyanosis is more difficult to detect in children with dark pigmentation.
- In a newborn, acrocyanosis may cause confusion.

- In addition, some newborns are polycythemic, which may contribute to the appearance of cyanosis without arterial desaturation.
- Cardiac cyanosis due to congenital cyanotic heart diseases is constant, increases with exertion, improved by squatting position in older children. It is onset may be since birth or few weeks after birth according to lesion.

Differential diagnosis of Central and peripheral cyanosis:

	Central	Peripheral
Mechanism	Diminished arterial oxygen saturation.	Increased extraction of oxygen by peripheral tissue in presence of Normal arterial saturation Diminished blood flow to local part.
Cause	Cyanotic heart disease (right to left shunt, Eisenmenger's syndrome), lung edema. Noncardiac causes: Abnormal hemoglobin Severe chest problems (e.g pneumonia, obstructive lung disease)	Circulatory shock Hypovolemia Heart failure Vasoconstriction from cold
Site	Mucous membrane (palate, Inner side of lips and under surface of tongue), and under nail beds.	Limited to ears, nose, cheeks, hands and feet.
Clubbing and polycythemia	Usually associated	Usually, absent
Temperature	Warm	Cold

Syncope

Definition: Sudden, transient, momentarily, self-limited loss of consciousness due to cerebral hypo-perfusion.

Alarming signs for cardiac syncope:

- Syncope with exertion.
- If associated with chest pain, or other cardiac symptoms.
- Family history of sudden unexplained death.
- Syncope in patients with congenital or already surgically treated heart defects

Possible causes

- Most syncope is benign; reflex syncope or vasovagal syncope.
- Cardiac causes of syncope:
  1. Arrhythmia (e.g., in the context of long QT syndrome),
  2. Obstructive lesions as aortic stenosis
  3. Cardiomyopathy especially hypertrophic obstructive (HOCM) cardiomyopathy.
  4. Eisenmenger syndrome.

Cardiac chest pain

Definition: The presence of abnormal pain or discomfort in the chest, between the diaphragm and the base of the neck.

Manifestations

- Cardiac chest pain is squeezing or sharp retrosternal pain radiating to the left shoulder. May be aggravated by exercise as in HOCM.
- May be relieved by leaning forward as in pain due to pericarditis,

Possible causes

- Myocarditis - Pericarditis - Aortic stenosis and other obstructive lesions - Cardiomyopathy
- Mitral valve prolapse - Coronary artery abnormalities: congenital, or acquired as Kawasaki.

Palpitations

Definition: Awareness of heart beats.

Manifestations

Heart palpitations are heartbeats that suddenly become more noticeable. The heart may feel like it's pounding, fluttering, or beating irregularly, often for just a few seconds or minutes. The patient may also feel these sensations in his throat or neck. >>> This needs a patient that can describe; not just a kid.

Possible causes

1. Paroxysmal or permanent tachyarrhythmias or extrasystoles.
2. Heart failure and active rheumatic carditis.
3. Mitral valve prolapse.
4. Anemia or hyperthyroidism.

Congenital Heart Diseases

Case 1

A 5-month-old male infant presents with tachypnea that worse with feeding, irritability, fever, and cough. His symptoms began 4 weeks ago and have become progressively worse. General examination reveals respiratory distress grade 3, and tachycardia. His weight is 3Kg. Chest examination shows bilateral consonating crepitation, and ronchi. His cardiac examination is significant for gallop rhythm, and harsh holosystolic murmur 2/6 maximal on his left lower parasternal border, propagating all over the precordium.

What is the most likely diagnosis?

A case of congenital heart disease. Mostly, ventricular septal defect (VSD), not compensated, and complicated by bronchopneumonia, and growth failure.

What are the different types of this lesion?

- Perimembranous.
- Inlet.
- Outlet (Infundibular).
- Muscular.

How this condition is confirmed?

By Echocardiography

What is the appropriate management for this condition?

- Medical treatment.
- Possible eventual surgical or trans-catheter closure.

Definition

Congenital heart defects (CHDs) are problems with the heart's structure that are present at birth. CHDs are the most common birth defects occur in almost 1% of births.

Causes and risk factors

- Unknown.
- Genetic, major chromosomal abnormalities.
- History of positive consanguinity.
- Advanced maternal age.

- Rubella infection.
- Teratogen exposure during pregnancy.
- Drug intake and maternal diabetes.
- Alcohol.

Health impact of congenital heart diseases

- CHDs are the most common cause of infant death due to birth defects.
- Approximately 25% of children born with a CHD will need heart surgery or other intervention to survive.
- Surgery is often not a cure for CHDs, many individuals with CHDs require additional operation(s) and/or medications as adults.
- People with CHDs face a life-long risk of health problems such as issues with growth and eating, developmental delays, difficulty with exercise, heart rhythm problems, heart failure, sudden cardiac arrest, or stroke.
- CHDs are now the most common heart problem in pregnant women.
- The recurrence risk with CHD is considerable.

Classification of Congenital Heart Defects

A. *Acyanotic*

- <u>Increased pulmonary blood flow</u>

- Ventricular septal defect.
- Atrial septal defect.
- Atrioventricular canal.
- Patent ductus arteriosus.

- <u>Obstruction of blood flow from ventricles</u>

- Pulmonary stenosis.
- Aortic stenosis.
- Coarctation of the aorta.

B. *Cyanotic*

- <u>Decreased pulmonary blood flow</u>

- Tetralogy of Fallot.
- Tricuspid atresia.

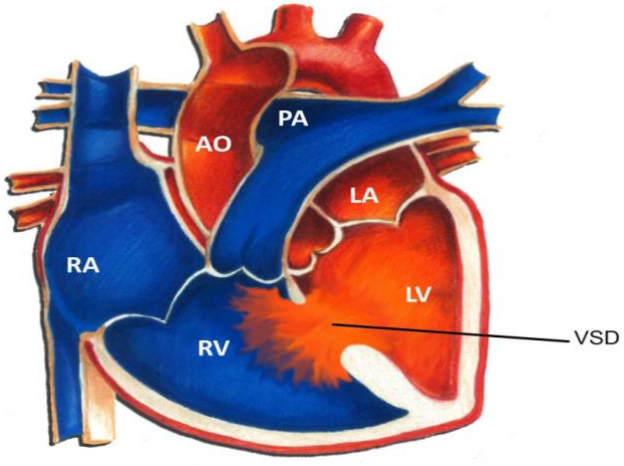
- <u>Mixed blood flow</u>

- Transposition of great arteries.
- Truncus arteriosus.
- Hypoplastic left heart syndrome.

Ventricular Septal Defect – VSD

Anatomy

- Single or multiple communications between the right and left ventricles
- A congenital opening -hole- in the interventricular septum, which connects both ventricles of the heart.
- The most common congenital heart defect excluding bicuspid aortic valve.



Types

VSDs are classified by their location in the septum:

- Perimembranous (most common).
- Infundibular (outlet septum).
- AV canal type (inlet septum).
- Muscular: could be central (mid-muscular), apical, marginal. Single or multiple "Swiss cheese" type.

Classification according to the size of the defect

- Small (restrictive): Diameter of the defect is less than one-third of the size of aortic orifice.
- Moderate (restrictive): Diameter is more than one-third but less that of aortic orifice.
- Large (non-restrictive): Diameter is equal to or more that of aortic orifice.

Hemodynamic effects

- Left to right shunt leads to increase pulmonary blood flow and lung congestion.
- Because of higher pressure in the left ventricle, blood is usually shunted from the left ventricle, across the VSD into the right ventricle, and into the pulmonary circulation.
- ***The flow across the defect is regulated by:***
  - ✓ The relation between systemic vascular resistance, SVR (16 mmHg/L/min/M2) and pulmonary vascular resistance, PVR (2 mmHg/L/min/M2).
  - ✓ 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.
- 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.
- 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 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 presentation

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*****:** due to vasoconstriction of blood vessels secondary to increased sympathetic tone.

III- Cardiac Examination:

1. ***Inspection:***
   - Diffusely increased precordial activity, over RV (parasternal), and over LV (apical) areas.
   - Precordial bulge (large shunt for 4-6 months or longer).
2. ***Palpation:***
   - LV impulse is displaced laterally
   - A palpable systolic thrill along the lower left sternal border.
   - A hyperdynamic apex (LV volume load).
   - RV lift usually felt over the anterior precordium.
3. ***Percussion:***
   - Cardiomegaly, mainly LV enlargement.
4. ***Auscultation:***
   - S1 is normal, S2 is increased pulmonary component, with narrow split (PH).
   - Gallop rhythm may be heard (CHF).
   - A holosystolic, mid-frequency murmur in left parasternal area.
   - 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

1. ***Laboratory findings:***
   - CBC.
   - Blood culture (indicated only when infective endocarditis is suspected).
2. ***Radiological Features:***
   - Generalized cardiomegaly LV enlargement then LV & RV enlargement.
   - Prominence of PA and increased pulmonary vascular markings.
3. ***ECG:***
   - LAH and LVH in early cases.
   - Later on, combined ventricular hypertrophy may develop.
4. ***Echo-Doppler:***
   - The diagnosis of VSD can be confirmed using echocardiography.

Management

Follow up

- Majority of perimembranous and muscular VSD close spontaneously.
- Small muscular VSDs have good chances to close spontaneously.
- Inlet VSDs almost never close spontaneously.
- Prophylaxis against infective endocarditis is indicated.
- All patients with VSD must be advised to maintain good oro-dental hygiene.

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.

Indications and timing of closure:

I. ***Small VSD (no symptoms, normal PA pressure, normal left heart chambers):***

- Annual follow-up till 10 years of age, then every 2–3 years.
- Closure indicated if the patient has had an episode of infective endocarditis.

II. ***Moderate VSD:***

- Asymptomatic: Closure of VSD by 2–5 years.
- Symptomatic: If controlled with medications, VSD closure by 1–2 years.

III. ***Large VSD:***

- Uncontrolled heart failure: As soon as possible
- Controlled heart failure: By 6 months of age.

IV. ***VSD with aortic cusp prolapse*****:**

- Surgery whenever AR is detected.

Contraindications for closure

Severe pulmonary arterial hypertension with irreversible pulmonary vascular occlusive disease.

Method of closure

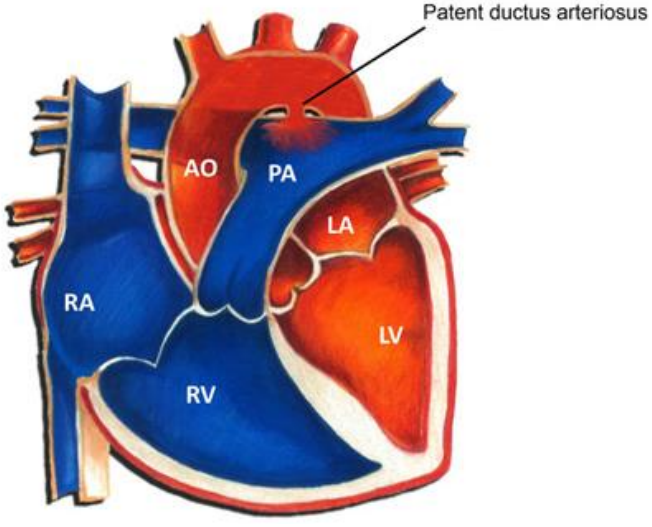
- ***Trans catheter***: in selected types as mid-muscular one.
- ***Surgical closure:*** Early to prevent the development of pulmonary vascular disease ; it is indicated in all patients with large VSD before age of 1 year with the following:

    1. Growth failure.
    2. Life-threatening pulmonary infections.
    3. Recurrent uncontrollable CHF.
    4. PAP>50% SAP.

- ***Palliative:*** pulmonary artery banding may be indicated as primary step to decrease the pulmonary congestion and to keep the baby safe until VSD closure and may be indicated if the defect is too large or multiple and cannot to be closed.

Patent Ductus Arteriosus – PDA

Anatomy



- Communication between the pulmonary artery and the aortic arch; (vessel that normally connects the pulmonary artery and the aorta in fetus).
- The ductus develops from the distal portion of the sixth aortic arch.
- 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.
- It accepted to find PDA in the first 96 hours of life.
- Patency of the duct depends on placental prostaglandin (PGE2) & low pO2.
- If remains patent even after 3 months of birth is called persistent PDA.

Classification according to the size of PDA

- ***Large PDA:*** Associated with significant left heart volume overload congestive heart failure, and severe pulmonary arterial hypertension.
- ***Moderate PDA:*** Some degree of left heart overload, mild-to-moderate pulmonary artery hypertension, and no/mild congestive heart failure.
- ***Small PDA:*** Minimal or no left heart overload. No pulmonary hypertension or congestive heart failure.
- ***Silent PDA:*** Diagnosed only on echo Doppler. These are hemodynamically insignificant, produce no murmur and there is no pulmonary hypertension.

Hemodynamic effect

- Left to right shunting of blood through the patent ductus from aorta to pulmonary results in an increase in pulmonary blood flow.
- Symptoms are determined by the differences in systemic vascular resistance and pulmonary vascular resistance, size and the length of the PDA.

- 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. This leads to wide pulse pressure.

Clinical presentation

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 2nd Left intercostal space or radiate to left sternal border or to clavicle.
- Mid-diastolic rumbling murmur may be audible at the apex in case of large PDA shunt.

Complications

- Repeated chest infection.
- Congestive heart failure (CHF).
- Infective endarteritis is a potential life-threatening complication at any age irrespective of size of the duct.; Small ducts are more prone for vegetations.
- Pulmonary hypertension and pulmonary vascular disease.

Differential diagnosis

- Venous hum.
- AR+MR.
- AR+VSD.
- Any arteriovenous connection.

Investigations

1- ***Laboratory:*** For infective endocarditis.

2- ***X-ray:*** prominent Pulmonary Artery, increased pulmonary vascular markings, and enlarged heart (LA and 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.

Management

- Most PDA has chance for spontaneous closure.
- Spontaneous closure rate of PDA in preterms varies from 35% to 75% in the 1st year of life.
- Prophylaxis against infective endocarditis is indicated.
- All patients with PDA must be advised to maintain good oro-dental hygiene.

Ideal age of closure

1- ***Large/moderate PDA,*** with congestive heart failure, pulmonary artery hypertension: Early closure (by 3 months).

2- ***Moderate PDA,*** no congestive heart failure: 6 months–1 year.

3- ***Small PDA:*** At 12–18 months.

4- ***Silent PDA:*** Closure not recommended.

Those presenting beyond 6 months of life with large PDA, significant pulmonary hypertension and suspected elevated PVR should be referred to a higher center for further evaluation.

Contraindications for closure

Severe pulmonary arterial hypertension with irreversible pulmonary vascular occlusive disease.

Method of closure

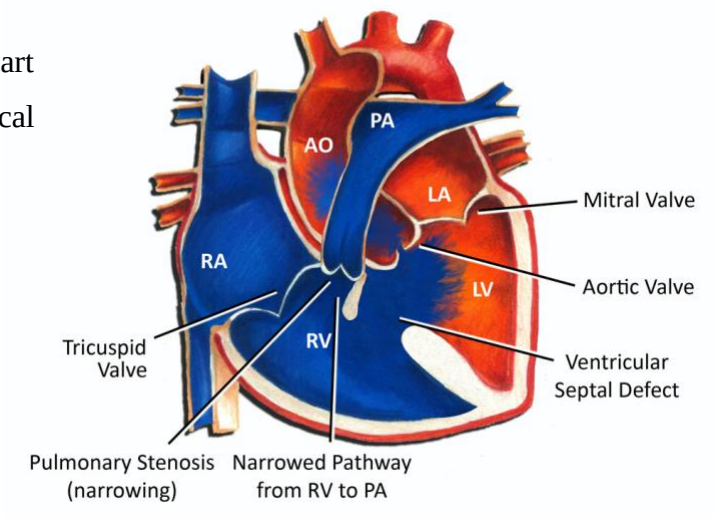
- ***Surgical:*** Ligation/dissection.
- ***Trans catheter:*** device / coil.
- ***Drug therapy:*** trial of PDA medical closure with Ibuprofen or paracetamol in preterm neonates.

Tetralogy of Fallot- TOF

Anatomy

TOF is the most common cyanotic congenital heart disease which consists of four classical abnormalities:

- Ventricular septal defect (VSD).
- Pulmonary stenosis (PS).
- Overriding of aorta.
- Right ventricular hypertrophy (RVH).



Types

- ***Classic Fallot.***
- ***Pink Fallot:*** mild RVOT obstruction.
- ***Extreme Fallot***: critical pulmonary stenosis or atresia of pulmonary valve.

Hemodynamic effect

- High pulmonary vascular resistance and VSD create right to left shunt & right ventricular hypertrophy
- The degree and onset of cyanosis is affected by the degree of subpulmonary stenosis (right ventricular outflow tract obstruction).
- The VSD is usually large, resulting in equal peak systolic pressures in the two ventricles.
- Severe obstruction to RVO leading to:
    a. Decreased pulmonary blood flow and pulmonary hypoperfusion
    b. Shunting of large amount of unsaturated blood to overriding aorta and systemic circulation and persistent cyanosis.
- Persistent systemic unsaturation leading to secondary polycythemia and increased hematocrit and blood viscosity which have serious consequences.

Clinical presentation

I- <u>Symptomatology:</u>

a. Cyanosis:

- Cyanosis usually appears during first month with closure of the ductus arteriosus.
- Cyanosis at birth is not common unless there is pulmonary atresia.

b. 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.

c. 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.

d. 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:

a. Central Cyanosis: Cyanosis occurs, most prominently on the mucous membranes of the lips and mouth and in the fingernails and toenails.

b. Blue Clubbing: Clubbing of the fingers and toes, recognizable in older infants and children, is a manifestation of chronic desaturation.

c. Growth Retardation: Growth is limited in severely cyanotic, unoperated patients.

III-*Heart Examination:*

a. Inspection: The left anterior hemithorax may bulge anteriorly (RVH).

b. Palpation: Substernal right ventricular impulse in 50% of cases, a systolic thrill is felt along the left parasternal area (RVOTO).

c. Percussion: The heart is usually normal in size.

d. 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.

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:

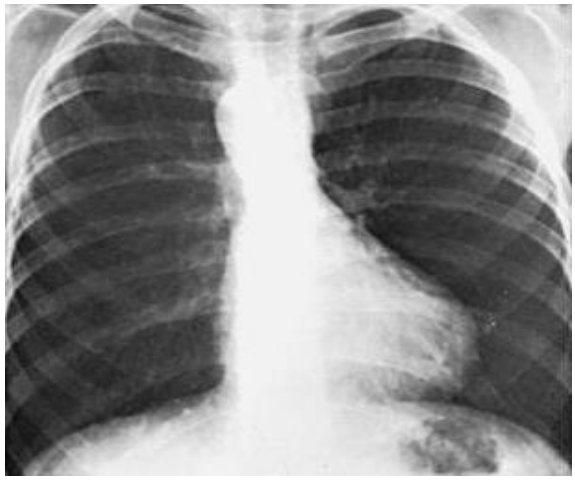
- Decreased pulmonary vascularity.
- Normal sized heart: narrow base (PA segment is deficient), cardiac apex is elevated and rounded

(hypertrophy RV). The cardiac silhouette has been likened to that of wooden shoe (Coeur en sabot).

III-ECG: shows right-axis deviation and right ventricular hypertrophy.

IV-Echo-Doppler.

V- Cardiac Catheterization.



X-RAY: Tetralogy of Fallot

Management

- All patients need surgical repair.
- Prophylaxis against infective endocarditis is indicated.
- All patients with TOF must be advised to maintain good oro-dental hygiene.

Medical

- ***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.
- Propranolol to help prevent future spells.
- Antibiotics prophylaxis against infective endocarditis.
- Maintain Hb >14 g/dL (using oral iron or blood transfusion).

Ideal age of closure

- ***Stable, minimally cyanosed:*** Total repair at 6–12 months of age.
- ***Symptomatic children <6 months with significant cyanosis or frequent spells:*** Palliative systemic-to-pulmonary artery shunt or PDA stenting early.

Method of closure

- ***Surgical:*** total repair; it consists of closure of VSD, and relieving RVOT obstruction.
- ***Palliative:*** 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.
  3. PDA stenting.

Hypercyanotic spells (Blue Spells)

Definition A clinical state of acutely reduced pulmonary blood flow leading to severe hypoxemia and metabolic acidosis.

Causes

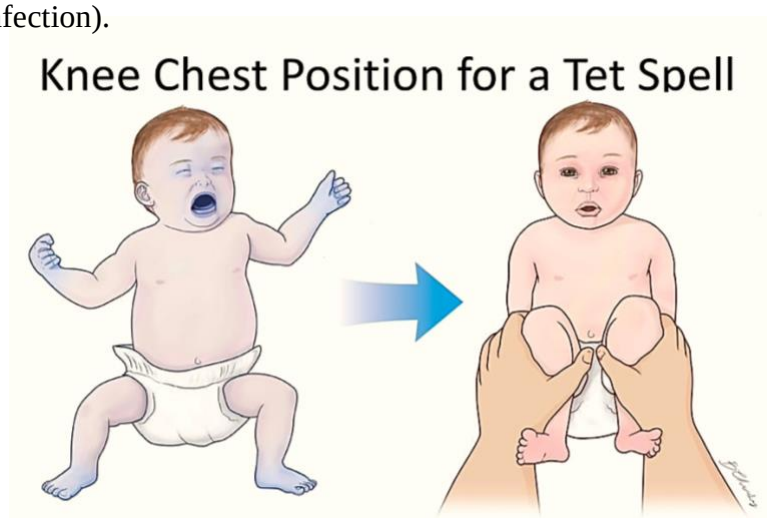
- Infection, dehydration, excessive crying and intramuscular injection are the most frequent precipitating events.
- The majority of these children have tetralogy of Fallot, but other lesions such as pulmonary or tricuspid atresia can also present with spells.
- The mechanisms include spasm of the right ventricular outflow tract, intravascular volume depletion and systemic vasodilation.
- A **'tet'** spell constitutes an emergency, as there is a high risk of hypoxic brain injury, stroke and even death.

Clinical Manifestations

Central cyanosis, irritability, hyperpnoea, syncope and occasionally ending in convulsions and death.

A softer ejection systolic murmur than at baseline and signs of the trigger (e.g. dehydration from gastroenteritis, pyrexia from a respiratory tract infection).

Management



- Keep the child calm and avoid painful procedures.
- Placement of infant in knee chest position.
- O2 administration.
- Adequate sedation (Morphia, 0.2 mg/kg subcutaneously).
- Blood volume expansion 10 ml/kg 0.9% saline IV bolus and repeat as necessary
- Sodium bicarbonate (1-3 mEq/kg IV).
- Beta-blocker (propranolol) 0.1-0.2 mg/kg intravenously, followed by 1mg/kg/day divided every 6 hr orally.
- Discuss with pediatric cardiologist and refer to tertiary center as soon as possible.

Rheumatic Heart Diseases

Case 1

A 13-year-old female was referred to the cardiology clinic by her primary care physician. She had history of sore throat and fever 3 weeks ago. Over the past few days, she has had joint pain and swelling and has felt progressively tired. She first noted joint pain, swelling, and redness in her right knee that resolved just as she began experiencing similar symptoms in the left knee.

Exam: Tempreture 38c, Pulse 140 with average force and volume. There was noticeable redness and swelling of the left knee joint. The right knee appeared to be within normal limits. Cardiac examination revealed distant S1 and S2, gallop rhythm, and a 3/6 soft holosystolic murmur heard over the apical region and propagates to the axilla. Abdominal examination revealed mild tender hepatomegaly.

Investigation: ESR 1st hour 80 mm/h, CRP 24mg/L. 12-lead ECG showed prolonged PR interval. Transthoracic echocardiography revealed dilated left ventricle with mildly decreased systolic function. The mitral valve leaflets were thickened with moderate to severe regurgitation. Trivial aortic regurgitation was noted. There was moderate pericardial effusion.

What is the most likely diagnosis?

A case of rheumatic fever with active rheumatic carditis; moderate to severe mitral regurge, trivial aortic regurge, and pericardial effusion. Decompensated. Not complicated. Associated with rheumatic arthritis.

What is the pathogenesis of this condition?

It is an inflammatory process affecting different tissues. It is due to autoimmune or hypersensitivity reaction, following infection by group A beta hemolytic streptococci, in genetically susceptible individuals.

What is the long-term sequelae of this condition?

Chronic rheumatic heart disease.

What is the appropriate management for this patient?

- Bed rest and treatment of heart failure
- Primary prevention by eradication of infection.
- Medical treatment of inflammatory process by corticosteroid.
- Secondary prevention to prevent recurrence by prophylaxis long-acting penicillin.

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 (tonsils, pharynx, middle ear, sinuses, and carried 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 tthese 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

1- 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.

2- 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.

3- ***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***

- Persistent tachycardia out of proportion to fever (disproportionate tachycardia).
- Dyspnea.
- Cardiomegaly.
- Arrhythmias.
- Gallop rhythm.
- 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.
- Usually affects these large joints, knees, ankles, wrists, elbows, hips, and shoulders (by this order)
- 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 back of 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, 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 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.

1- **Clinical diagnosis** The presence of the clinical characteristics of any presentation of ARF, i.e., arthritis, carditis, chorea, skin manifestations, or any combinations.

2- **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:

- ***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.

- ***Throat culture:***
  - It may be negative due to the presence of a latent period between streptococcal infection and the appearance of ARF.

3- **ECG Diagnosis:**

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.

4- **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.

5- **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 SLE.
- ***Acute leukemia***: suspected if 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):

A. General treatment for all presentations:

1- *Bed Rest:* it is important especially in case of carditis to lessen the cardiac work and load.

- 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 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 a diet, which is easily digested and rich in vitamins.

B. Specific Treatment:

1- Carditis:

- **Prednisone** 2 mg /kg / day, oral (tablet = 5 mg), in 4 divided doses after meals for 2-3 weeks.

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 %.

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:

General Measures: Good nutrition, proper housing, and ventilation, prevention of overcrowding and socio–economic development.

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 → 600,000 IU.
  - Patients > 27 kg→ 1,200,000 IU.

2. *Sulfadiazine:*

- Given orally if the child is sensitive to penicillin.
- The dose according to weight is:
  - Patients ≤ 27 kg → 0.5 gm once a day.
  - Patients > 27 kg → 1 gm once a day.

3. *Penicillin V:*

- Given orally, in a dose of 250 mg twice/day.

Duration of secondary prophylaxis:

I. ***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.

II. ***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.

Infective Endocarditis

Case 1

A 6-year-old girl presents with 2-week history of intermittent fevers. She was initially seen in the first week of illness by her physician and was diagnosed with otitis media. She received oral amoxicillin for a week, but continued to have spikes of fever. In addition she complains of headaches, abdominal pains, and daily fevers with sweating. The patient's mother reports that she appears less active than usual. Her past history is significant for a heart murmur that was thought to be benign.

Physical exam: Physical examination reveals a temperature of 39°c, respiratory rate of 24/min, pulse rate of 121 bpm and BP of 93/51 mmHg, and oxygen saturation of 98% on room air. The patient appears pale and ill, but awake. Cardiac examination is significant for regular rate and rhythm with no thrill; normal S1 and narrow splitting of S2. There is a 2/6 systolic ejection murmur at right upper sternal border and 2/4 early diastolic murmur at left mid-sternal border. The peripheral pulses are bounding. The patient is noted to have extensive dental caries.

Investigative studies: A complete blood count is obtained with a white cell count of 11,000/UL, 80% neutrophils; hemoglobin of 10.5 g/dL and a platelet count of 271,000. ESR is mildly elevated at 35 mm/h. Chest radiography reveals mild cardiomegaly with no pulmonary infiltrates. A 12-lead ECG is consistent with sinus tachycardia and left ventricular hypertrophy.

What is the provisional diagnosis?

This patient is presenting with the complaint of a 2-week history of fever and lethargy. History suggests an infectious process. Her physical examination is significant for systolic and diastolic murmurs. These findings, coupled with the laboratory studies are suggestive of Infective endocarditis (IE). These auscultatory findings are most consistent with a stenotic and insufficient aortic valve.

What would be the most suspected etiology of this condition?

– Due to the rather insidious onset in this particular patient, Strep viridans would be the most likely infectious etiology, but other causes such as S. aureus, fungal pathogens, and gram-negative organisms must be considered.

How can the diagnosis be confirmed?

- Echocardiography
- Blood culture

Definition

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 .

Cause

Infection: By bacterial organisms as streptococcus viridans, staphylococcus aureus, enterococci. Other nonbacterial organisms as viruses, and fungi.

Sources of bacteremia: As dental procedures with poor dental hygiene, and non-sterile surgical instrumentation of GIT, respiratory tract, or genitourinary tract.

High risk groups including:

- Children with congenital heart disease (especially if associated with high velocity of blood) as Tetralogy of Fallot, VSD, PDA.
- Children with rheumatic heart disease (left -side valvular lesions) as mitral or aortic lesions.
- Survivors of cardiac surgery, especially those with prosthetic material or valves.
- Patients without pre-existing heart disease (rare) who have immune deficiency.

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 ***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.***

History

- Prior congenital or rheumatic heart disease.
- Preceding dental, intestinal, or urinary procedure.

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.

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).

Complications

- Heart failure and cardiogenic shock.
- Embolic phenomena (cerebral abscesses, mycotic aneurysms, CNS hemorrhage, or hematuria).
- Metastatic infections (arthritis, meningitis, pericarditis, or septic pulmonary emboli).

Investigations

Laboratory Diagnosis

- Blood culture: It is the most important for diagnosis and treatment, and it is positive in about 90% of cases within 48 hours.
- Anemia, leukocytosis and elevated ESR and C-reactive protein.

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; Amoxicillin 30 minutes before 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 + Gentamicin	200,000 – 300,000 U/kg/day (every 4 hr) 5 mg / kg / day (every 8 hr)	4 - 6 2
2- Enterococcus	Ampicillin + Gentamicin	300 mg / kg / day (every 4 hr) 5 mg / kg / day (every 8 hr)	4 - 6 4 – 6
3- Staph. aureus	Oxacillin or Vancomycin	200 mg / kg / day (every 6 hr) 50 mg / kg / day (every 8 hr)	6 – 8 6 - 8

Congestive heart failure

Case 1

An 8-year-old boy presents to the medical emergency department with respiratory distress, unable to lie flat. He has a 10 cm liver, displaced apex beat with a tachycardia and a loud apical pansystolic murmur. His mother says he has recently been tiring easily and was treated for tonsillitis in the previous month. You then notice his swollen left knee. What is the diagnosis?

What is the most likely diagnosis?

The above mentioned patient is in obvious HF, probably due to acute rheumatic mitral regurgitation.

What are the causes of congestive heart failure and the cause in this condition?

Many congenital and acquired heart diseases may present with heart failure (HF). The main acquired causes present acutely and include myocarditis, dilated cardiomyopathy, valvular dysfunction from infective endocarditis or acute rheumatic fever, acute glomerulonephritis, prolonged tachyarrhythmias and heart block. In contrast HF secondary to congenital heart disease is usually a more insidious process and can occur at any age but most often presents in infancy e.g. at 4 - 6 weeks (or earlier in premature infants) for large L to R shunts.

In this case the most probable cause is valvular dysfunction (mitral reguge) from acute rheumatic fever

How is this condition diagnosed?

By echocardiography which is useful for diagnosis of underlying pathology e.g. rheumatic carditis and determination of systolic and diastolic functions of the heart.

Systolic function is assessed by Ejection Fraction (EF) and diastolic function is assessed by E/A

What is the appropriate treatment for this condition?

Hospitalization, Bed rest with elevated head, O2 therapy, Treatment of underlying cause (Prednisone for active rheumatic carditis in this case) and start medical treatment in the form of diuretic (furosemide) and ACE inhibitor (captopril).

Definition

Is a clinical syndrome in which the heart is unable to pump enough blood to the body to meet its needs, to dispose of systemic or pulmonary venous return adequately or a combination of the two.

Causes

Congenital Heart Diseases

- 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.

Acquired Heart Diseases

- *RHD (ARF).*
- *Viral myocarditis*
- *Dysrrhythmias (SVT).*
- *Secondary cardiomyopathies: metabolic diseases.*
- *Anemic HF (hemolytic anemia).*
- *Hypertensive HF (PSAGN).*

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 after- load.
- 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.

Clinical Manifestations

- Manifestations of pulmonary venous congestion
- Manifestations of systemic venous congestion
- Manifestations of low cardiac output.
- **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 week, 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.

- **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 soft, tender and may be pulsating due to tricuspid regurgitation.
- **Cardiac Examination:**
    a. ***Inspection & Palpation:*** Precordial activity may be decreased (impaired cardiac output) or increased (volume loading).
    b. ***Percussion:*** Cardiomegaly (ventricular dilatation to compensate impaired cardiac function).
    c. ***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**
    a. ***Acute:*** Pulmonary edema, pulmonary infections, dysrhythmias, and Acute renal failure.
    b. ***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:** an excellent tool for assessing cardiac size, pulmonary congestion & edema.
3. **ECG.**
4. **Echo-Doppler:** Diagnosis of underlying pathology e.g. rheumatic carditis.

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

General Measurements

- **Hospitalization .**
- **Bed rest** with elevated head.
- **O2 therapy.**
- **Diet:** adequate calories with low salt or completely restricted salt .
- **Treatment of underlying cause.**

Specific Therapy

- ***Preload reduction***: Diuretics (furosemide) .
- ***Afterload reduction*:** ACE inhibitor (captopril) .
- ***Inotropic agents***: Digitalis (digoxin) which is indicated in Systolic Heart Failure.
- ***Beta-blocker therapy*** (e.g. Carvedilol).

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

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.

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:

1. Including Pericardial Tamponade & Constrictive Pericarditis.
2. Decubitus: Sitting and leaning forward (relieving posture).
3. 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).
4. 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.

5. 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.
6. 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:

1. Other causes of chest pain: e.g., pleurisy, and spontaneous pneumothorax.
2. Differential diagnosis of the causes: by specific manifestations.

Treatment of Pericarditis

I. Specific lines:

- ***Viral or Allergic pericarditis:***

  - Mild: Aspirin (spontaneous recovery) - Severe: NSAID or corticosteroids.

- ***Purulent (pyogenic) pericarditis:***
  - IV antibiotics (according to culture & sensitivity).
  - Closed pericardial aspiration first (for diagnosis, culture & decompression).
  - Then open pericardial paracentesis (for treatment of pericardial tamponade).
- ***TB pericarditis:***

  Anti-tuberculous drugs. - Corticosteroids.

- ***Constrictive pericarditis:***
  - Radical pericardiectomy (surgical removal of the thick pericardium).

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 and Atrial fibrillation (AF).
- Ventricular tachycardia and 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).

Practice Questions (Choose one correct answer)

1- All of the following may be life-threatening causes of syncope except:

a) Ventricular arrhythmias due to long QT syndrome.
b) Hypertrophic obstructive cardiomyopathy.
c) Severe aortic stenosis.
d) Vasovagal syncope.

2- In 10 years, old boy presented with recurrent attacks of sudden palpitation. He felt dizziness during the attacks. The child is completely normal after and in between the attack. Which of the following is the first line investigation?

a) 12 lead Electrocaediogram and ambulatory ECG recording (Holter).
b) Cardiac MRI
c) Cardiac catheterization
d) Echocacardiography.

3- Which is not true about central cyanosis due to congenital cyanotic heart diseases?

a) Constant and persistent cyanosis
b) Increases in infant with feeding or crying.
c) In all cases it must be presented at birth.
d) It is due to right to left shunt.

4- Which of the following is true about rheumatic heart disease:

a) Significant active carditis is usually treated by 2 weeks of steroid.
b) Long acting penicillin is given for 5 years as a prophylaxis in patient with residual chronic heart disease.
c) Mitral valve regurge is the commonest lesion.
d) Aortic valve regurge is the commonest lesion.

5- What is not true about infective endocarditis?

a) Patients with large VSD has high risk for infective endocarditis.
b) Prophylaxis is not necessary in 1 year infant with large PDA before circumcision.
c) IV antibiotic according to culture and sensitivity must be given for 4-6 weeks.
d) Surgical removal of the vegetation and valve replacement may be indicated in patients with extensive valve destruction.

Chapter 14

Hematologic and Oncologic Disorders

Learning Objectives:

By the end of this chapter, students should be able to:

1. Classify different types of anemias, coagulation and bleeding disorders and common childhood malignancies.
2. Correlate between the clinical presentations and the special nature of each hematological disorder.
3. Enumerate findings in hematological investigations in different diseases.
4. Formulate a management plan for hematological disorders.

Contents:

1. Childhood anemia:
    a. Iron deficiency anemia
    b. Hemolytic anemias:
        i. Acute: G6PD deficiency.
        ii. Chronic: thalassemia, sickle cell anemia.
    c. Aplastic anemia.
2. Approach to a bleeding child:
    a. Coagulation disorders: Hemophilia.
    b. Bleeding disorders:
        i. ITP.
        ii. HSP.
3. Childhood leukemia and lymphoma.

Childhood 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:

- Infection, chemical and physical agents, and metabolic products.
- 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-Intracorpuscular defects:

- Sickle cell disease, Thalassemia, Spherocytosis and Elliptocytosis.
- Hemolytic anemia due to enzyme deficiencies.

B-Extracorpuscular factors:

- Auto immune hemolytic anemia.
- Miscellaneous: infection, chemical and physical agents, hypersplenism.

Physiologic Anemia of Infancy

Decreased Hb level to 10-11 gm% at 2-3 months.

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)

Case 1

A 2 years old female toddler presented to the clinic with the mother complaining of 2 weeks' history of her baby having pale face and poor appetite. She also started to notice that her baby tends to eat mud. There is no history of any past illness, and the patient was fed by absolute breast feeding till age of 9 months followed by introduction of yogurt and mashed potatoes. Examining the patient revealed pale lips and conjunctiva, tachycardia, no organomegaly or lymphadenopathy.

Initial investigations revealed Hb 6.5 g/dl, MCV 55 fl, MCH 22 pg, Retic. 0.5% WBCs 6600/mm^3 and platelet count: 550.000/mm^3.

What is the most likely diagnosis of this case?

This is most probably a case of iron deficiency anemia. The patient is aged 2 years with presence of dietetic error in the form of delayed weaning. There is tendency to eat strange objects like mud, a condition called pica, and this is one of the neurological manifestations of iron deficiency. No organomegaly or lymphadenopathy and no history of previous illness or previous blood transfusion. The CBC shows microcytic hypochromic anemia with normal reticulocytic count, normal white blood cells count and thrombocytosis.

The differential diagnosis of this case: (Causes of microcytic hypochromic anemia)

- Iron deficiency anemia.
- Thalassemia.
- Lead posoning
- Anemia of chronic disease.

How is this condition diagnosed?

A serum ferritin less than 10 ng/ml is diagnostic for iron deficiency anemia. Other investigations are needed to search for the cause of iron deficiency like stool analysis for parasites and occult blood in stool to detect any GIT bleeds.

What is the appropriate treatment for this condition?

Oral iron therapy in the form of Ferrous fumarate, sulphate, or gluconate oral solutions (30, 20, 10% elemental iron subsequently) in a dose of 6mg/kg/day for 1- 3 months after correction of Hb to the normal for the age and sex is the standard of care therapy in such cases.

Packed RBCs transfusion in a dose of 10 ml/kg if the patient is hemodynamically unstable or in case of Hb < 5g/dl for fear of anemic heart failure.

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:
   - Fetal hemorrhage into maternal circulation or one to another.
   - Retroplacental bleeding.
   - 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- Exessive demands for iron:

A-Blood loss e.g., hemorrhage and parasitic infestation.

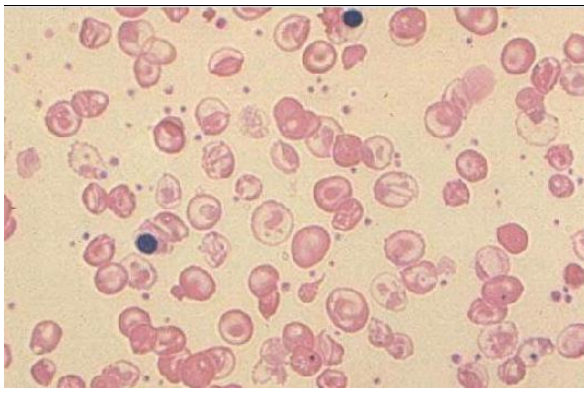
B-Increase growth rate e.g., premature and adolescence.

Clinical picture:

a. General manifestation of anemia:

- Pallor, General weakness and Headache.
- Easy fatigability and Blurring of vision.
- Spooning of nails.

Atrophic glossitis



Microcytic hypochromic anemia

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 with iron therapy start.

-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)

3- Stool analysis: searching for ***parasitic infestation*** and ***occult blood***.

4- Therapeutic test: give iron 6 mg/kg/day and closely monitor the percentage of reticulocyte count after 72 hours, if it increased, the case is iron deficiency anemia.

5- 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- Sidroblastic 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- Parenteral iron therapy (either IM or IV infusion):

Parenteral 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 Anemias

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 in blood film.
- Decrease life span-special tests e.g. autohemolysis and osmotic fragility test.
- Pigmented gallstones.

Causes of hemolytic anemia:

1-Intrinsic abnormalities 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 (Extra-corpuscular 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.

B. Non immunologic disorders:

- Toxic from drug and or chemicals.
- Infection as malaria and clostridium.

Case 2

A mother came to the ER with her baby boy aged 2 years. She said that her baby woke up with pale skin, yellow sclera, excessive crying and two attacks of vomiting. "My son was very well and was playing actively yesterday", added the mother. Asking about any medications or strange food in the previous few days, she answered that he only has eaten fava beans for the first time yesterday morning. There was no any previous history of any illness. The mother has a brother with similar condition in his childhood period. By examination, the patient is pale, jaundiced with HR=170b/min without crying and gallop rhythm on cardiac auscultation. No hepatosplenomegaly but the urine sample of the baby is dark colored.

CBC shows Hb 3 g/dl, MCV 85fl, MCH 27pg, corrected retic.10%, WBCs 12.000/mm^3 and platelets 350.000/mm^3. The direct and indirect coomb's tests are negative.

How to approach the diagnosis of this case?

It appears that this is a case of acute hemolytic anemia as the patient presents with acute onset of pallor, jaundice and dark colored urine hours after ingestion of fava beans, the triad of pallor, jaundice and dark urine is characteristic to acute hemolytic anemia. CBC shows normocytic normochromic anemia with reticulocytosis.

The cause of acute hemolysis is usually due to G6PD deficiency (Favism) as the patient is male and the symptoms appeared shortly after fava beans ingestion and there is family history in a maternal uncle of a similar condition.

So this is a case of Favism with acute hemolysis and anemic heart failure.

How is this condition inherited?

G6PD deficiency is inherited in an X-linked recessive form, so males are more affected, but females may be affected in few certain conditions.

Diagnostic test of this case:

A deficient G6PD level is diagnostic. Other investigations to detect the precipitating factor as liver function tests to exclude hepatitis.

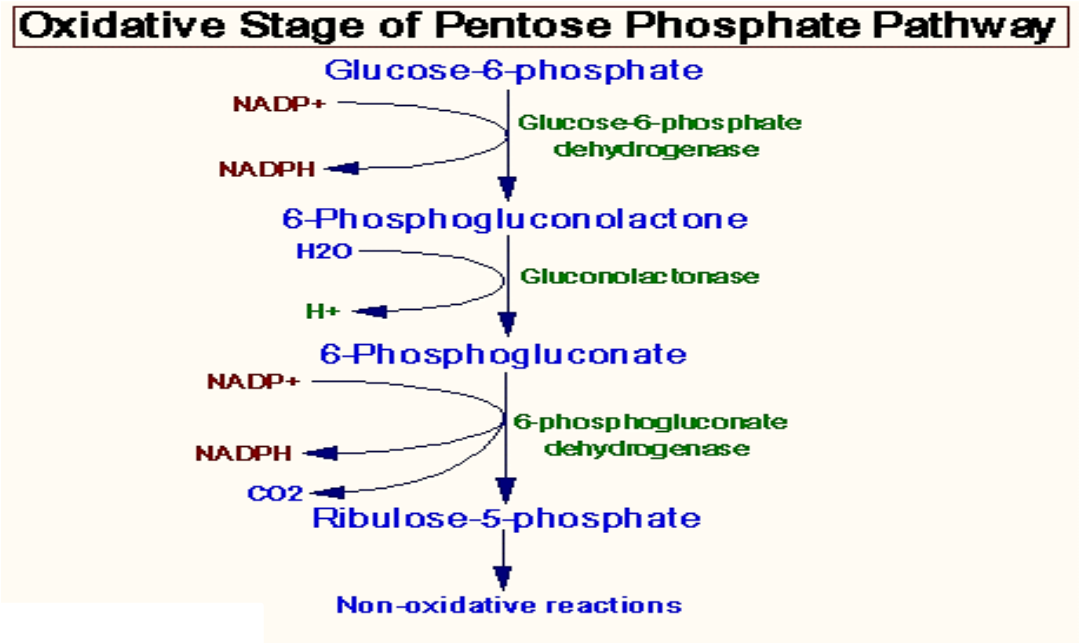
What is the appropriate treatment for this condition?

Packed RBCs transfusion in a dose of 5-10 ml/kg is the treatment, while in this patient with heart failure fractionated transfusion of smaller doses over a longer duration is indicated. I.M. injection of desferioxamine 20-40 mg/kg single dose as an antioxidant and future avoidance of the precipitating factors.

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.



Precipitating Factors:

1. Drugs & chemicals:

- Antipyretics, all except paracetamol.
- Antibiotics: e.g chloramphenicol, sulphonamide, macrodantin.
- Anti-malarial drugs.
- Drugs containing sulpha.
- Vitamins e.g synthetic vitamin k.
- Organophosphorus compounds e.g insecticides.
- Naphthalene.

2. Diet: An ingredient in the fava beans (vice fava=favisim).

3. 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.

  1- It may be one of the causes of neonatal hyperbilirubinemia.

  2-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:

  1- Intense pallor

  2- Jaundice

  3- 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).

Case 3

An 11-month-old boy is brought to the clinic by his parents, who have noticed that the baby has been pale and dyspneic for about 3 weeks. The mother denies any previous illness with her son but he has a cousin with repeated blood transfusion history. Examination revealed pallor and tachycardia. Hb is 5.5 g/dl, MCV 57 fl, retic 0.6% and the serum ferritin is 400 ng/ml.

What is the most likely diagnosis?

This is a case of microcytic anemia with high serum ferritin and family history of repeated blood transfusion, Thalassemia is the most likely diagnosis. β-thalassemia is a genetically transmitted disease due to mutation in the b-globin gene of hemoglobin and is prevalent in Mediterranean populations, while α thalassemia is due to a-globin genes deletion and is most commonly present in Southeast Asians and blacks.

How to diagnose this condition?

Hemoglobin electrophoresis 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%.

Diagnosis of α thalassemia is made by genetic testing as electrophoresis is normal in this condition.

Differential diagnosis of this case:

Iron deficiency anemia as it is the most common microcytic anemia, but high ferritin level can differentiate between iron deficiency anemia and thalassemia.

Other causes of microcytic anemia enter in differential diagnosis as chronic lead poisoning and anemia of chronic illness.

How to prevent this inherited disease?

Genetic counselling with pre-marital detection of carriers is the corner stone of preventing this disease as the carrier rate of beta thalassemia in Egypt is high (around 10%). Decreasing cases of consanguineous marriage also plays a role in prevention as the risk of thalassemia increases with consanguinity and positive family history.

Hemoglobinopathies

Thalassemia Syndromes

Definition: Thalassemia is genetic disorder with absence of or defect in genes responsible for production of different hemoglobin chains (hemoglobinopathy).

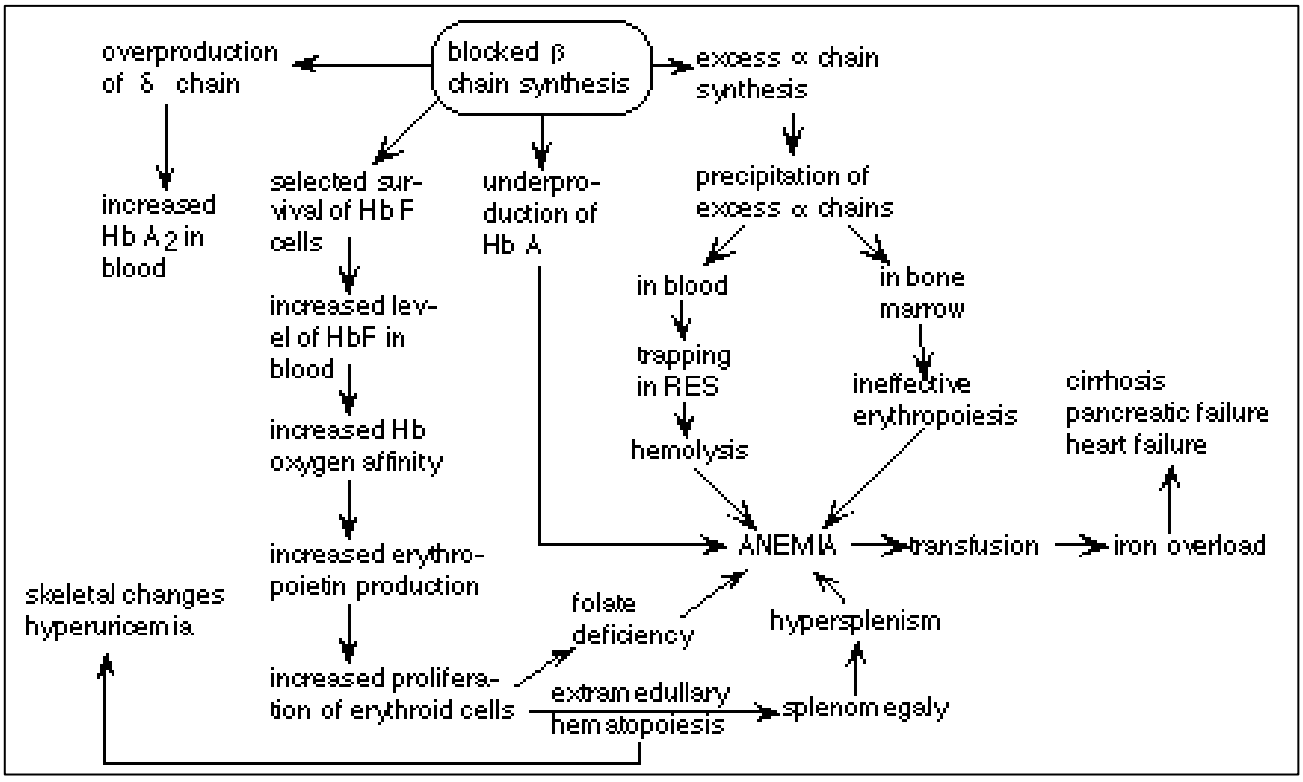
Mode of transmission

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 an excessive free alpha chain, 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.

β - 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 7 g/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.

a. Manifestations of anemia: Pallor, anorexia, easy fatigability, dyspnea on effort, dizziness and may be hemic murmurs and cardiac enlargement and cardiac decompensation.

b. Manifestations of hemolysis: jaundice, dark urine and dark stools and enlarged spleen.

c. 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.

d. Manifestations of extramedullary hemopoiesis: Hepatosplenomegaly leading to abdominal enlargement.

e. 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 entrocolitica. 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 occurs.

13- Rare complications: as chronic leg ulcers and aplastic crisis.

Investigations of thalassemia

A. Hematological investigations:

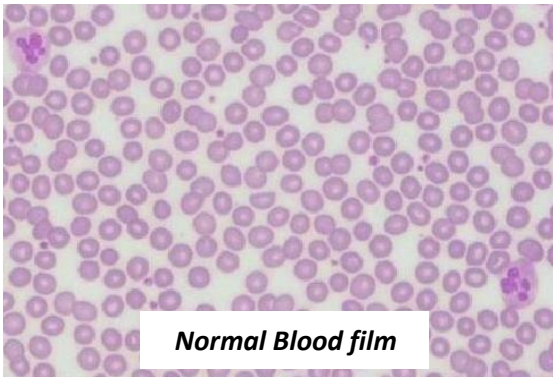
- ***Complete blood picture (CBC):***

  1-***Microcytic hypochromic*** anemia.

  2-Increased reticulocyte count.

  3-Normoblasts (immature RBCs) are increased.

  4-***Target cells*** on blood film.



Normal Blood film

- ***Iron status:***

  1-Increased serum ferritin.

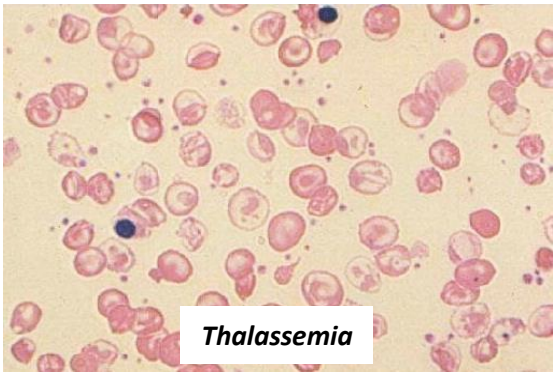
  2-Increased serum iron.

  3-Decreased total iron binding capacity.

- ***Hemoglobin electrophoresis:***

  1-This is the diagnostic test for beta thalassemia.

  2-There is a compensatory increase in Hb F.



Thalassemia

3-Hemoglobin electrophoresis is also important in carrier screening. Beta thalassemia carrier has Hb A2 equal to or greater than 3.5%.

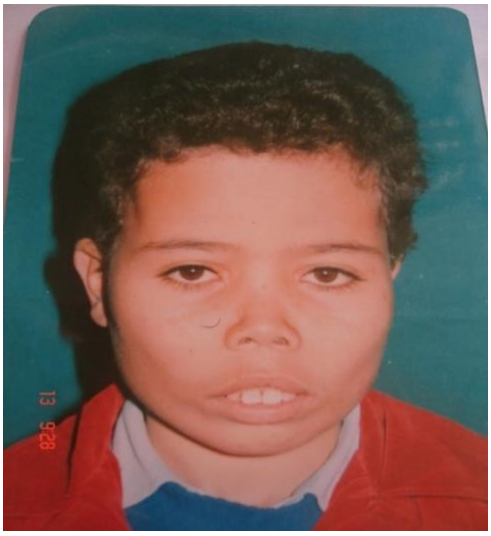
- ***Liver function tests***

  1-Increased serum indirect bilirubin to 2-4 mg /dl.

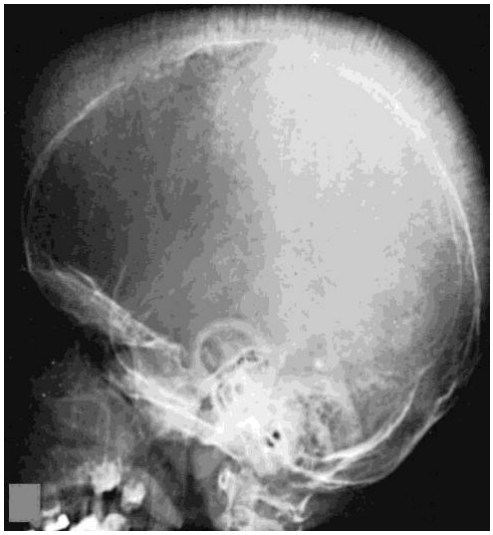
  2-Increased S.G.O.T. and S.G.P.T. due to hepatic damage due to iron overload or associated hepatitis infection from repeated transfusion.

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.



Thalassemic Facies



X-ray: skull

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
  - Corrected by splenectomy.

II- Huge spleen: If the lower pole of the spleen reaches the level of the umbilicus.

- **Precautions:**
  - Age >5 years.
  - Preoperative vaccination with Hemophilus Influenza, meningococcal and pneumococcal.
  - 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 - for 5-6 nights/week - over 8-12 hours/day.

  - Given by 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.

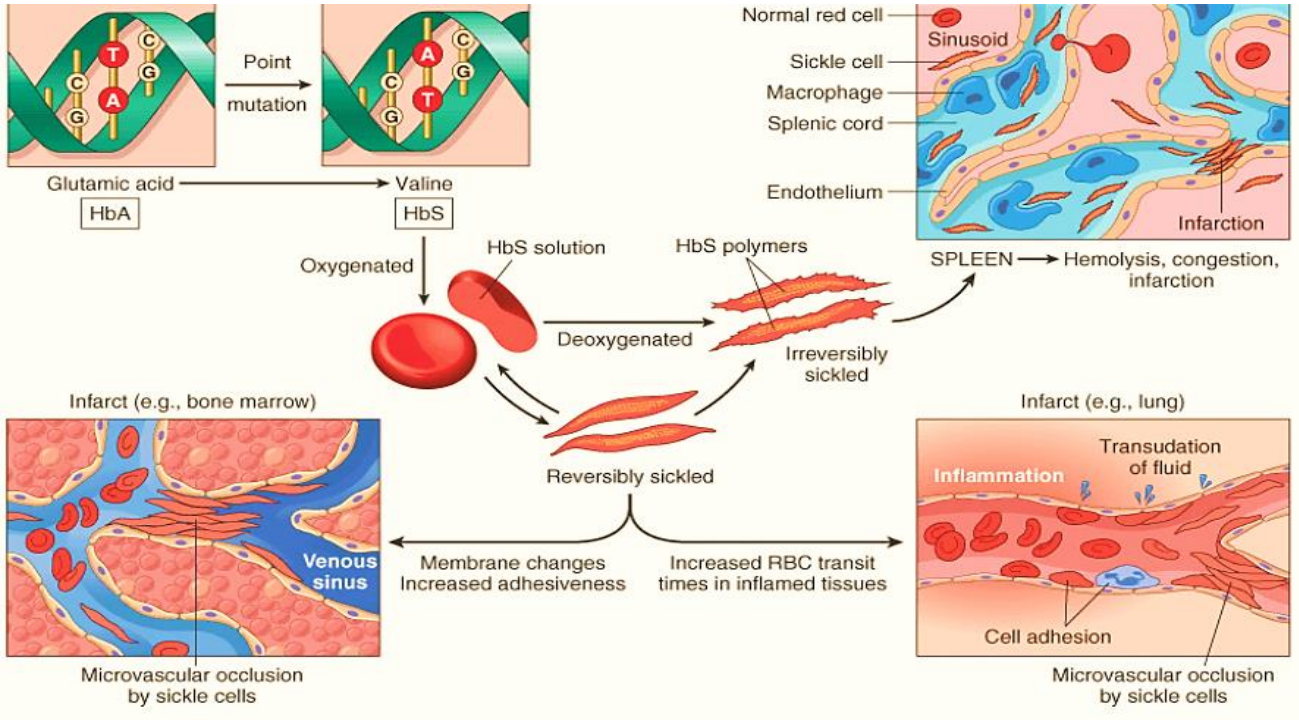
  3- Liability to post-splenectomy infection may be another cause of death.

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-oclusive crisis: Extremely painful, transient episodes that result from ischemic damage to tissue. Infection, acidosis, fever, and dehydration may precipitate vaso-oclusive 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.

Treatment:

I. General line of treatment as thalassemia plus:

II. General measures:

1. Folic acid

2. Prophylactic transfusion: Decreases frequency of crisis but require desferoxamine to prevent iron overload.

3. Avoidance of precipitating factors:

- Sudden exposure to cold. - High altitude. - Occupation that require heavy manual work.

4. Vaccination: Especially with Pneumococal and Hemophillus influenza vaccine.

III. Specific treatment:

1-Painful crisis:

- Keep the patient warm.
- Alkalization 88 meq NaHCO3/L
- Adequate hydration 2250 ml/m^2/day.
- Exchange transfusion is indicated in:

► Anemic crisis. ► Pregnancy.
► Acute chest syndrome. ► Prior to surgery.
► Prolonged painful crisis. ► Priapism.
► Cerebrovascular accidents.

2- Drugs that decrease hemolysis by increasing fetal Hb:

- Hydroxy urea,
- Ara-C,
- Interferon,
- Erythopoietin,
- Piracetam.

3- Drugs that have anti-sickling effect:

- Ca-channel blockers as verapamil and nifedipine.
- Vitamins as pyridoxine (B6) or Minerals as Zinc.

4- Treatment of other crisis: Aplastic, sequestration and hyperhemolytic, by blood transfusion.

5- Bone marrow transplantation:

Aplastic Anemia

Case 4

A male patient aged 12 years came to the emergency room with bilateral bleeding per nose. The patient has history of being easily fatigued with several attacks of headache few weeks before presentation. Physical examination reveals pallor, petichea in the mucous membrane of the mouth and dried blood around both nostrils. There're also multiple ecchymotic patches on the trunk and lower limbs. No organomegaly or lymphadenopathy and no history of any previous illness. Hb 6.2 g/dl, MCV 88 fl, MCH 28 pg, Retic. 0.2%, WBCs 2000/mm^3 and platelets 15.000/mm^3

What is the most likely diagnosis of this case?

This is a case of pancytopenia with reticulopenia, mostly acquired aplastic anemia. The patient is aged 12 years with no previous history of any other disease and presented by pancytopenia with no organomegaly, lymphadenopathy or evidence of any congenital anomaly. Reticulopenia which means that it is central pancytopenia not due to peripheral destruction.

The differential diagnosis of this case:

Pancytopenia with reticulopenia:

1- Acquired aplastic anemia: There is no history of previous disease and there is no evidence of any congenital anomaly.
2- Acute leukemia: If organomegaly or lymphadenopathy is present, this raises the suspicion of malignancy.
3- Congenital aplatic anemia: If there's any congenital anomaly like poly or syndactly or positive family history of similar condition.
4- Megaloblastic anemia: B_{12} or folic acid deficiency may give the picture of pancytopenia with macrocytosis and megaloblastoid changes in the bone marrow. Neurological manifestations of vit. b 12 deficiency may be present.

Pancytopenia with reticulocytosis:

1- Hypersplenism: Splenomegaly with pancytopenia and reticulocytosis is suspicious of hypersplenism due to any cause.
2- Acute leukemia.

Other investigations to confirm the diagnosis:

Bone marrow aspiration shows hypocellular bone marrow with fatty infiltration and reduction of all cellular elements with normal appearance of the remaining few cells. Bone marrow biopsy to detect

the bone marrow cellularity accurately and to detect the severity of the disease to decide the best treatment options.

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:

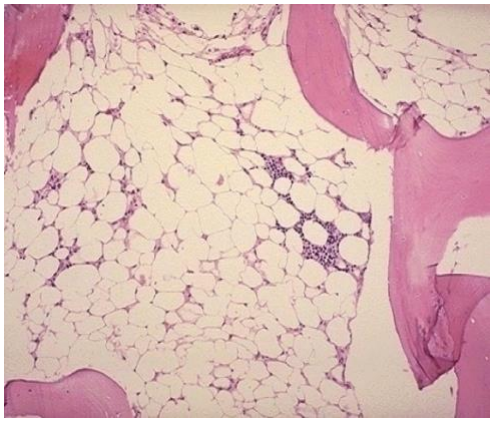
- Fanconi anemia.
- Dyskeratosis congenita.
- Shwachman-Diamond syndrome.
- Reticular dysgenesis.
- Amegakaryocytic thrombocytopenia.

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 reticulocytoenia.

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/mm3

- Absolute reticulocyte count of less than 40,000/mm3
- Absolute neutrophil count of less than 500/mm3.

- **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/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 receive transfusions ± drug therapy ± 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- **<u>Blood component transfusion:</u>**

a) Red Cells transfusion: To correct anemia. However, with repeated transfusions, patients accumulate toxic amounts of iron with iron overload which may be fatal.

b) Platelets: To correct thrombocytopenia and prevent fatal hemorrhage. However, transfused platelets survive only a few days.

5- **<u>Bone marrow transplantation:</u>** BMT is indicated for any case with severe aplastic anemia with matched sibling donor. In absence of matched sibling donor, and after failure of immune therapy, haploidentical transplantation from one of the parents may be the only lifesaving option.

6- **<u>Immunosuppressive therapy:</u>**

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%.

Approach to a bleeding child

Case 5

A 15-month-old boy was brought to the emergency department by his mother for oozing blood from his mouth following a fall nearly 6 hours ago. His mother stated that he tended to bleed for prolonged periods from his immunization sites with history of recurrent bruising. She reported that during his circumcision, he seemed to bleed for an extended amount of time as well. There was a known family history of a bleeding disorder in his brother. Physical examination was significant for two small lacerations on the inside of lower lip, oozing blood with multiple bruises in his lower limb. Relevant laboratory findings include a platelet count of 368,000/mm^3, a normal bleeding time, a PT of 12 seconds, and a PTT of 65 seconds.

What is the most probable diagnosis?

Hemophilia which is an X - linked recessive disease caused by decreased level of factor VIII in hemophilia A and factor IX in hemophilia B).

What are the clinical manifestations of hemophilia?

According to 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 form of hematoma after injection, bleeding after circumcision. After trauma excessive bruising, hemarthrosis commonly occur. Internal bleeding as hematuria, G.I.T. bleeding and intracranial hemorrhage may also present.

How to diagnose hemophilia A?

APTT: Prolonged F VIII: Decreased

PT, TT, bleeding time, platelet count, vWF, and fibrinogen are normal.

What are the appropriate treatments for this condition?

- Prevention of trauma.
- Factor VIII concentrates 25-50 I.U. /kg/12 h.
- Fresh frozen plasma.
- Cryoprecipitate one bag/5kg (bag=75:125 IU).

In mild cases of hemophilia A, desmopressin transiently increases the factor VIII level.

Coagulation Disorders

a. Inherited disorders:

- Hemophilia A, B and C,
- VonWillebrand disease,
- Other factor deficiencies.

b. Acquired disorders:

- Liver diseases.
- DIC.
- Vitamin K deficiency/warfarin overdose.

HEMOPHILIA A

Etiology: An X - linked recessive disease caused by decreased level of factor VIII in the plasma.

Clinical manifestations:

- Depend on the level of factor VIII deficiency 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, and fibrinogen** are normal.

Treatment:

1. **Prevention of trauma.**
2. **Avoid aspirin.**
3. **When there is bleeding.**
   - *Local cold application and pressure*
   - *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**

Bleeding Disorders

Case 6

A 6-years-old girl presented to the clinic with a two-week history of red spots and ecchymosis allover her body. She had an episode of epistaxis three weeks prior. There was a history of upper respiratory viral infection 2 weeks before the epistaxis. The patient's past medical and surgical history was insignificant. There is no family history of bleeding disorders. Physical examination was significant for purpuric spots and ecchymosis allover her body, no hepatosplenomegaly. Her laboratory results were as follows:

WBC 6500/µL, Hemoglobin 12.5 g/dL, Platelets 25,000/µL, Bleeding time: 15 minutes, PT: 14 seconds and PTT: 28 seconds.

What is the most likely diagnosis?

Immune thrombocytopenic purpura (ITP), a disease that is characterized by thrombocytopenia, shortened platelet survival, presence of platelet auto-antibodies is the most likely diagnosis. The patient presents with isolated thrombocytopenia (normal WBC and Hb), prolonged bleeding time , normal PT , PTT , and given her age, ITP is the most common cause of thrombocytopenia.

What are the different causes of thrombocytopenia?

1. Decreased production: Hypoplastic or aplastic anemia, bone marrow infiltrate and drugs
2. Increased destruction: ITP, allo-immune and hypersplenism.
3. Splenic sequestration.

What are the common clinical findings in this case?

1. Spontaneous purpura and ecchymosis.
2. Bleeding from mucous membranes.
3. Internal hemorrhage in severe cases.

What are the appropriate treatments for this condition?

First-line treatment is steroids. Second-line treatment includes intravenous IgG, anti-Rh, splenectomy, or rituximab (anti-CD20), immunosuppressive therapy and platelet transfusion.

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, chloramiphenicol, 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):

- ***Allergic or (Henoch- schonlein purpura).***
- ***Thrombasthenia (platelet function disorders):***
  - Disorders of adhesion.
  - Disorders of platelet secretion (release reaction).
  - Storage pool deficiency.
  - Disorders of aggregation.

Idiopathic Thrombocytopenic Purpura (ITP)

Definition: It's a syndrome characterized by thrombocytopenia, shortened platelet survival, presence of platelet autoantibodies 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

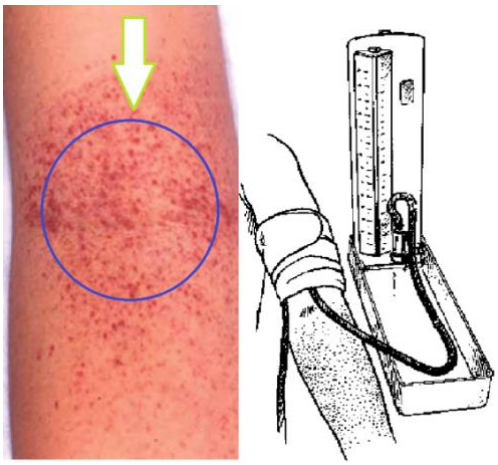
ITP is an autoimmune disease in which IgG antibodies are responsible for thrombocytopenia. Most ITP patients have an increased level of IgG on the platelet surface.

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 / cmm.
4. Bone Marrow examination: Increase megakaryocytes count with decrease productive capacity (weakly productive or sterile).



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.
- Persistant of purpura more than 3 months.
- Extensive purpura involving all body with ecchymosis.
- Recurrent purpura.

1- Corticosteriod therapy:

- Prednisone 2mg/kg/day for three weeks.
- ***Mechanism of action***
  - Decrease antibody formation.
  - Bone marrow stimulant.
  - Increase stability of blood vessels.

2- IV 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 reticuloendothelial 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 of action:

- Block Fc receptors of reticulo-endothelial system.
- Anti-viral activity.
- Protect platelet destruction by antibodies.
- Decrease antibody formation.

4- Thrombopiotein receptor agonists (TPO-RA):

- TPO-RA (e.g., eltrombopag and romiplostim), are platelet growth factors, that have recently been approved for pediatric use in persistent ITP.
  - ***Romiplostim*** given subcutaneously weekly at doses of 1-10 μg/kg
  - ***Eltrombopag*** orally administered at starting dose of 50 mg/day with dose modifications of 25mg increment for age > 6 years, while the starting dose for children </=5 years is 25 mg.

5- Splenectomy for:

- Chronic thrombocytopenia more than one year.
- Severe cases not responding to corticosteroids, IV anti-D, and IVIG.
- Girls near menarche.

- Precautions before splenectomy:

- Age >5 years.
- Preoperative vaccination by pneumoccocal and hemophilus influenza vaccines.
- Platelet transfusion during operation.
- Post-operative long-acting penicillin.

6- Immunosuppressive drugs:

- Vincristine, cyclophosphamide, azathioprine.

7- Monoclonal antibody therapy: Anti-CD20 (Rituximab)

- Mechanism of action: Eliminate auto reactive B cells**.**

- Dose: 375mg/ m2 IV weekly for 4 weeks.

8- Plasmapharesis.

9- 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.

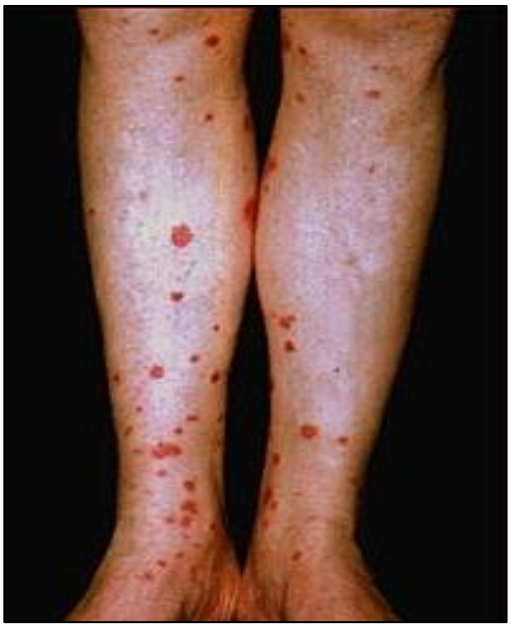
Henoch–Schoenlein Purpura

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.

Subarachinoid or cerebral hemorrhage may occur.

4. **Renal manifestation:**

Hematuria, renal colic, nephritis or nephrotic syndrome.

5. **Joint manifestation:** Arthalgia and arthritis

Investigations:

- Platelet count: normal.
- Renal function testes 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 **and indicated if**
    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.

II. Childhood Leukemias and Lymphomas

Case 7

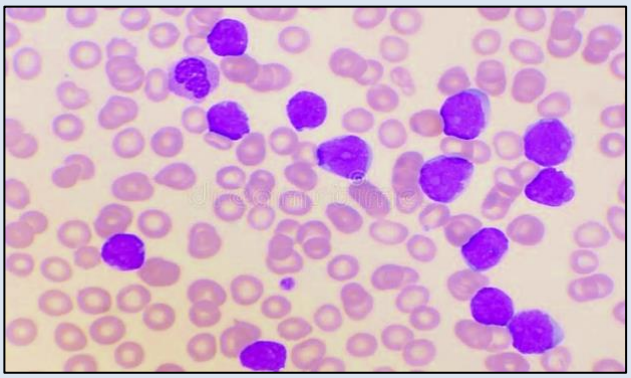
A 6-year-old boy who has Down syndrome presents with a 2-day history of fever (temperature to 39.0°C) and a painful limp and favoring of his right leg. During the past 2 weeks, he has had decreased appetite, increased pallor, and increased bruises on his upper and lower extremities. Physical examination reveals pallor and multiple ecchymoses on his arms, legs, and trunk. Bilateral cervical and supraclavicular lymph nodes are palpable; the nodes are firm, nontender, and 1 to 2 cm in size. The liver is palpable 3 cm below the right costal margin, and the spleen is palpable 2 cm below the left costal margin. Tenderness is elicited over the right distal femur. Radiographs of the right distal femur reveal osteopenia plus a small lytic lesion. A chest radiograph shows normal results with no mediastinal mass or pulmonary infiltrate. Relevant laboratory findings include the following:

Hemoglobin: 6.5 g/dL

White blood cell (WBC) count: 50,000/mm^3

Platelet count: 39,000/mm^3

Peripheral smear: Many immature white cells with condensed chromatin, absent nucleoli, and scant agranular cytoplasm.



What is the most likely diagnosis?

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. It accounts for 25% of all childhood cancers and 75% of childhood leukemias. The Peak onset of ALL occurs between 2-10 years and 10% occur in infants less than 1 year.

What is the differential diagnosis of this case?

All of the following conditions feature anemia, low platelet count, and/or symptoms similar to this patient's:

-Aplastic anemia

-Small round cell tumors as neuroblastoma or retinoblastoma.

-Some infectious diseases may mimic ALL because of the presence of fever, lymphadenopathy, hepatosplenomegaly, blood cytopenia and atypical lymphocytes.

-Osteomyelitis and rheumatologic disease when ALL presents with bone-ache and arthralgia.

However, the markedly elevated WBC and blood smear in this patient make a form of leukemia, in this case ALL, the most likely diagnosis.

What are the laboratory investigations of ALL?

*Complete blood picture: normocytic normochromic anemia, thrombocytopenia. WBCs may show leucocytosis, leucopenia or hyperleucocytosis and blast cell may be present.

-Bone marrow examination: bone marrow contains ≥ 25% blast cells.

*CSF Examination: CSF analysis and cytology. Cell count > 5 per HPF, with blast cells, are diagnostic of CNS infiltration.

*Biochemical analysis: increased serum uric acid, hypercalcemia ,hyperphosphatemia, serum LDH is increased ,blood urea and serum creatinine may be increased.

*Radiography: radiograph of the chest, plain x ray for long bones, abdominal ultrasound.

What are the complications of ALL?

1-Hyperleukocytosis:

2-Leukopenia: predisposes the patient to opportunistic infections.

3-Coagulopathy: due to thrombocytopenia, consumption of coagulation factors.

4-Organ infiltration.

5-Cerebro vascular accidents: due to hyperleukocytosis, coagulopathy, or drugs induced.

6-Psychological disturbances:

7-Metabolic disturbances: as tumor lysis syndrome.

8- Secondary neoplasm: CNS tumors are the most common then leukemia and lymphomas.

9- Late effects of treatment.

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:

A. 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).

B. 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 are associated with ALL.*

a. 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

b. 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.

c. 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.

d. 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.

e. 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 present 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 hyporflexia.
- 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 ovarien involvement.

8. Cardiac infiltration:

Symptomatic heart disease occurs in < 5% of cases with leukemic infiltrate and hemorrhage of myopericardium.

9. Lung involvement:

Lung may be involved with leukemic infiltrates, hemorrhage, pleural effusion or anterior mediastinal mass.

Laboratory investigations:

1. 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.

2. Bone marrow examination:

Although blast cells in BM is normally less 5%, diagnosis is confirmed only when bone marrow contains ≥ 25% blast cells. Definitive diagnosis of type of leukemia is made by:

1. Morphologic assessment: French American British (FAB) classification divides ALL into L_1, L_2 and L_3 while Egyptian modification of FAB (FAB-E) divides ALL into:L_1 / L_2 with morphological features in between L_1 and L_2, L_2 / L_3 with features in between L_2 and L_3 and leukemic phase of lymphoma, which is a separate group with its own features
2. Immunophenotyping: Determination of cell of origin of leukemia which may be:
   - B cell ALL (85%): Classified according to the degree of maturation into early pre-B, pre B- and mature B-ALL.
   - T cell ALL (15%): Classified into early, intermediate and late stages T-cell ALL.
3. Cytogenetic study.

3. 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.

4. 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.

5. Radiographic investigation:

- Radiograph of the chest may show lung infiltration, infection, or anterior mediastinal mass.

- Plain x ray for long bones may show lytic areas, periosteal elevation, and diffuse osteoporosis.

- Abdominal 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:

1. 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.

2. Thrombocytopenia: Is corrected by platelets transfusion to raise platelet count above 20.000/mm^3.

3. Anemia: Is corrected with packed RBCs transfusion.

4. Neutropenia: Is treated using empiric use of antibiotics and hematopoietic growth factors as G.CSF and G.M.CSF.

5. Hyperleukocytosis: Therapy is directed towards prevention of tumor lysis syndrome by:

- Hydration therapy with 3 L/m^2/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/m^2/day.
- Leukapharesis 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 extramedullry disease. It includes corticosteroids, vincristine, asparginase and anthracycline for 6 weeks. Failure of induction therapy occurs in < 5% of patients treated with current regimens. Mortality rate during induction is ≤ 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 ± 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:

Age: Prognosis is poor when age is < 2 years and > 10 years at diagnosis and worst prognosis is found in infant < 1 year.

Sex: Higher relapse rate is evident in boys than girls

Race: Black children have lower remission and higher relapse rates due to higher incidence of high initial WBC count, mediastinal mass, L_2 morphology and lower socioeconomic status.

Onset of leukemia: The more slowly the onset, the more durable the remission that follow institution of therapy.

Leukemic cell burden: Which can be assessed by evaluation of extramedullary disease as the degree of hepatosplenomegaly and lymphadenopathy.

CNS involvement: CNS infiltration is associated with lower rate of remission induction, a higher risk of relapse and a shorter survival.

Nutritional status: Malnourished children may have less tolerance and receive sub-optimal doses of chemotherapy.

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.

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.

Platelet counts: Patients with low platelet counts below 20.000/m^3 have shorter duration of

remission. Leukemia associated with petechial hemorrhages may predispose patients to testicular and CNS relapses.

Lactate dehydrogenase enzyme (LDH): Higher LDH levels are associated with shorter remission.

Blast morphology: L_1 is associated with more favorable prognosis, than L_2 morphology, which has poor prognosis. L_3 have the worst prognosis.

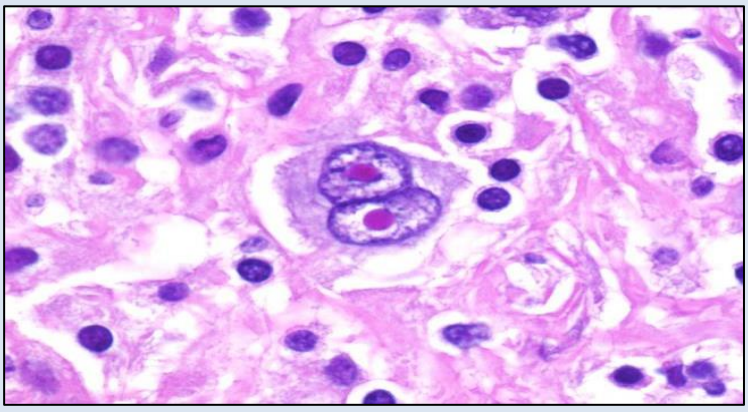
Immunophenotyping:

- 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 week independent predictor of treatment outcome.
- Mature T-cell have poorer outcome than early T.

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.

Case 8

A five year old male child presented to primary care physician with chief complaints of neck swelling (right) since 4 months. The mother explained that he has been having fever and night sweats for the past 4 months. Additionally, he has been feeling increasingly tired and itchy over his body. On physical examination, the patient has lost 3 kg since his last visit and has 3 enlarged non matted, painless, hard lymph nodes in his right anterior cervical chain largest measuring 2.5 cm. No organomegaly noted. The hemogram, liver function tests and renal function tests were found normal. Cervical lymph excision was done and sent for histopathological examination.



What is the most likely diagnosis?

Hodgkin lymphoma. Most patients present with nontender asymptomatic palpable lymphadenopathy, often in the neck and supraclavicular area. Alternatively, many patients will present with a fairly large asymptomatic mediastinal mass on routine x-ray of the chest.

Approximately one-third of patients experience fever, night sweats, weight loss, fatigue, and pruritus. There are five main classes of Hodgkin lymphoma.
What type of cell is characteristic for odgkin lymphoma? The classic Reed-Sternberg cell, characterized by large size, bilobed nucleus, and nucleolar inclusion bodies ("owl's eyes"). Classically, these cells, formed from germinal B cell centers, also display a common set of markers, including CD15+ and CD30+.
What are B symptoms? Classic B symptoms are unexplained weight loss, persistent or recurrent fevers, and night sweats. These symptoms generally correlate with an advanced stage of disease and tumor burden and a slightly worse prognosis independent of stage.
What is the appropriate treatment for this condition? More than 90% of patients with early-stage localized disease are cured with excision and localized radiotherapy. Patients with more advanced disease typically undergo the ABVD chemotherapy regimen consisting of doxorubicin (adriamycin), bleomycin, vinblastine, and dacarbazine. Cure rates are very high, even with advanced, stage 4 disease.

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 enlargment 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 > 38^0C.

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 non-specific 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 nerve 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 extralymphatic 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 extralymphatic 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.

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 T-cell 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, Vinblstine and Decarbazine).

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 asparginase 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.

Practice Questions (Choose one correct answer)

1- Which of the following may be a cause of normocytic anemia?

a) Iron deficiency anemia.
b) G6PD deficiency.
c) Thalassemia.
d) B 12 deficiency.

2- The only curative treatment of ß-thalassemia major is:

a) Folic acid tablets.
b) Bone marrow transplantation.
c) Hydroxyurea.
d) Repeated regular packed RBCs transfusion with regular iron chelation medications.

3- The hyperhemolytic crisis in sickle cell anemia may be caused by:

a) Sickling of the red cells.
b) Parvovirus B19 infection.
c) Pyruvate kinase enzyme deficiency.
d) Associated G6PD deficiency.

4- Which one of the following is correct as regard hemophilia A:

a) Severe hemophilia A is factor level activity <1%
b) Mild hemophilia A is factor level activity > 10 %
c) Prolonged PT
d) Normal PTT

5- In hemophilia B, the coagulation factor deficiency is:

a) Factor I
b) Factor VII
c) Factor VIII
d) Factor IX

6- ***Reed-Sternberg cells are diagnostic of:***

a) Hodgkin lymphoma
b) Non-Hodgkin lymphoma
c) Acute Myeloid leukemia
d) Acute lymphoblastic leukemia

7- ***In acute lymphoblastic leukemia, blast cells in the bone marrow are:***

a) Less than 5%
b) 5 – 25%
c) More than 25%
d) More than 10%

8- The first line of treatment of immune thrombocytopenic purpura is:

a) Intravenous immunoglobulin
b) Intravenous anti-D
c) Corticosteroids
d) Splenectomy

Chapter 15

Nephrology and Urology

Learning Objectives:

By the end of this chapter, students should be able to:

1. Identify the clinical features and laboratory diagnosis of different glomerular disorders.
2. Know the causes and risk factors of urinary tract infection and identify its clinical features and laboratory diagnosis
3. Formulate the management plan for different renal disorders

Contents:

1. Nephrotic Syndrome
2. Acute Post streptococcal Glomerulonephritis
3. Urinary Tract Infections

NEPHROTIC SYNDROME (NS)

Case 1

Male child aged 7 years old was brought to pediatrician by his mother. She noticed that the child has buffy eyes at morning and improved at evening 10 days ago. Then he starts to gain weight. The child looks well, conscious, but he has generalized edema. Blood pressure is normal. Urine analysis showing Albumin +++, RBCs 5 C/ HPF and hyaline casts.

What is the most likely diagnosis? How to confirm?

-Minimal change nephrotic syndrome.

-Diagnosis is confirmed by estimating 24h urinary proteins > 40 mg/m2/h or urinary protein/creatinine ratio > 2 mg/mg, low serum albumin levels and high serum cholesterol levels.

What is the mechanism of edema in this child?

Edema: It is the increase in the interstitial component of the extracellular fluid volume. It results from the hypoalbuminemia and the decrease in the oncotic pressure of the blood.

What is the differential diagnosis of this condition?

Nephrotic syndrome must be differentiated from:

I- causes of generalized edema.

- Nutritional as kwashiorkor.
- Cardiac edema as in cases of congestive heart failure.
- Hepatic edema. In cases of chronic liver cell failure.
- Allergic edema as in angioneurotic edema.

Il - Other causes of renal edema as renal failure and acute post-streptococcal GN

What is the specific treatment for this condition?

Prednisone is given in a dose of 2 mg/kg/day or 60 mg /m2/day divided into 1 - 2 doses for 4 consecutive weeks. Then we shift 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.

Definition:

The nephrotic syndrome is a clinical complex characterized by:

1. Heavy proteinuria (Predominantly albuminuria).
2. Hypoproteinemia (Predominantly hypoalbuminemia).
3. Generalized massive edema.
4. Hyperlipidemia.
5. Recurrent relapses.

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

Primary (Idiopathic) nephrotic syndrome

It is the most prevalent glomerular injury in childhood. It forms 90% of cases of nephrotic syndrome in childhood. The categories of primary N.S are:

- Minimal change disease (MCD) **85%**.
- Focal segmental glomerulosclerosis (FSGS) **10%**.
- Mesangial proliferative nephropathy (MPN) **5%**.

Secondary nephrotic syndromes

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).
   - Lymphoma, Hodgkin's.
   - Juvenile diabetes mellitus.
3. **Infections:**
   - Hepatitis B virus.
   - Infective endocarditis.
   - Malaria.
   - Bilharziasis.
   - Syphilis.

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. 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:** The glomeruli appear normal with no immune deposits by immunofluorescence.

3. **Electron microscope:** Fusion of the foot processes of the epithelia cells lining the glomerulus, and some irregularity of the thickness of the basement membrane. These changes are reversible.

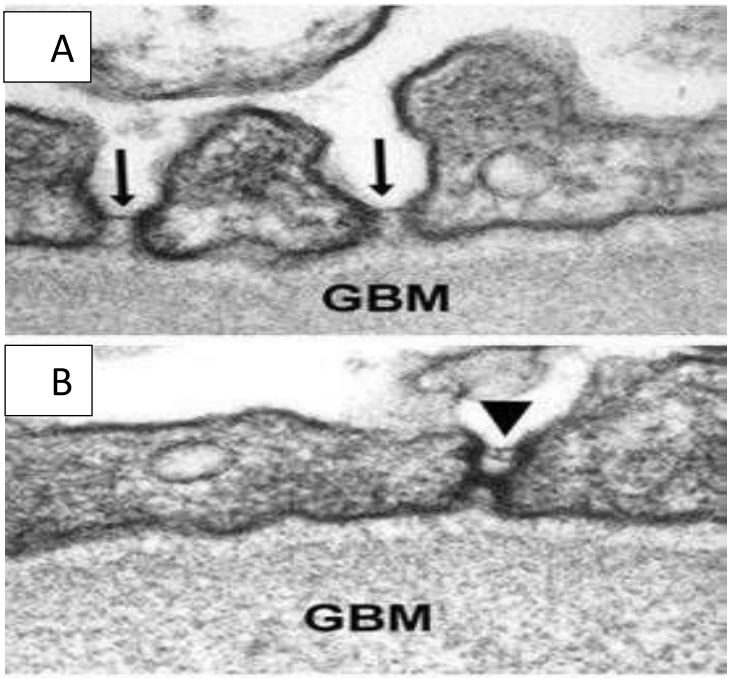


Figure 1: (A) EM picture of the normal glomerular filtration barrier, the arrows show the glomerular slit diaphragm between foot processes of podocytes. **(B)** EM of the glomerular filtration barrier in MCD, The arrow shows fusion of the foot processes and collapsing of slit diaphragm (**GBM,** glomerular basement membrane)

Pathogenesis: The glomerular leakage of serum proteins mainly albumin results in:

1. ***Hypoalbuminemia***.
2. ***Edema****:* It is the increase in the interstitial component of the extracellular fluid volume. It results from:
    - The hypoalbuminemia and the decrease in the oncotic pressure of the blood (underfill theory).
    - Decrease in plasma volume leads to the activation of the renin angiotensin- aldosterone axis with salt and water retension (overfill theory).
3. ***Hyperlipidemia:***
    - It is mainly due to increase in serum cholesterol and triglycerides.
    - 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 due to:
    - Decrease in serum immunoglobulins and complement, which are lost in urine.
    - Edema fluid acts as good bacterial culture media.
    - Protein deficiency and decreased bactericidal activity of leukocytes.
    - iv. Defective opsonization of bacteria due to Loss of properdin factor B in urine

5. ***Hypercoagulability:***
    - Due to increase plasma levels of certain coagulation factors such as V, Vll, fibrinogen decreased plasma level of antithrombin, platelet aggregation and increased blood viscosity.
    - So, there is tendency for thrombosis, but this is less common in children.

Clinical Picture: The onset gradual usually in a child of 2-5 years of age often following influenza like syndrome.

1. Edema:

- It may be slight 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

I - Clinical presentations.

II- Laboratory investigations:

1 - Urine

a - Proteinuria:

- Normally urine contains very minute amount of protein up to 4 mg/m^2 /hour.
- Significant proteinuria is the presence of > 4 and less than 40 mg/m^2 /hour.
- Heavy proteinuria or proteinuria of nephrotic range is the presence of ≥ 40 mg/m^2 /hour or the presence of 1 g/ m^2 /day or more.
- So, for the diagnosis, the urine must contain proteinuria of nephrotic range.

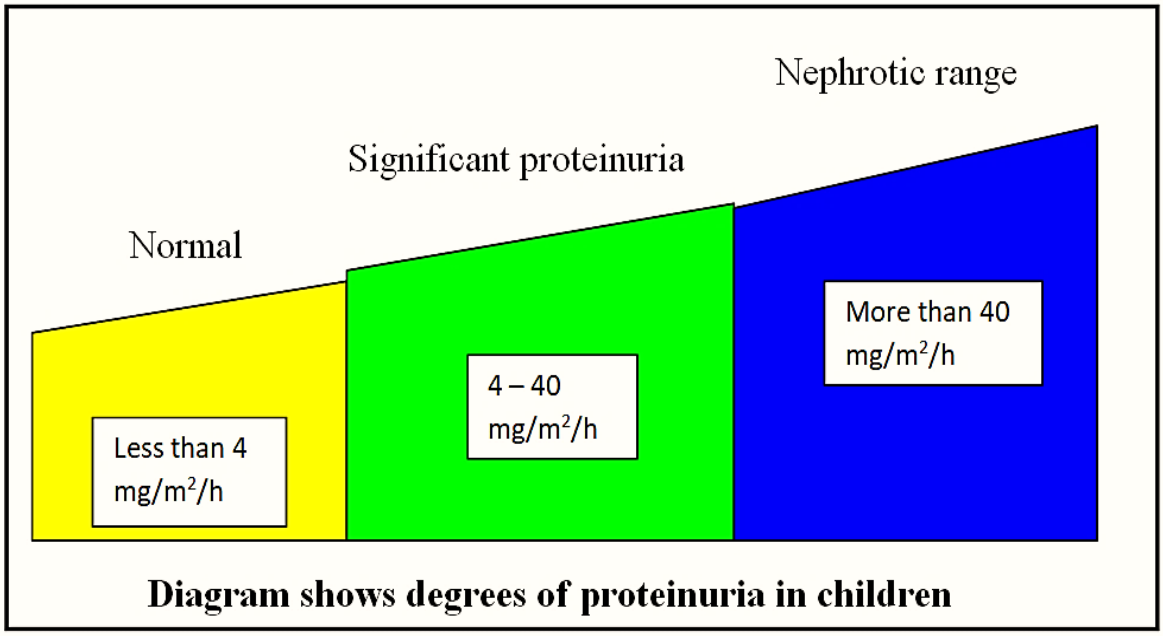


Diagram shows degrees of proteinuria in children

b - The urine contains number of cellular granular hyaline and lipoid casts. Microscopic hematuria may be present.

2 - Blood:

1) Decreased serum proteins, mainly serum albumin. Edema usually starts when serum albumin is ≤ 2.5 g/ l dL.
2) Increase in serum cholesterol (> 250 mg/dL) and triglycerides.
3) Total serum Ca level is diminished owing to the decrease in albumin- bound fraction.
4) The serum complements 3 (C_3) level is normal.
5) Increased E.S.R and anemia is usually present.
6) Renal function tests are normal in MCD.

3 - Renal biopsy: To study the underlying pathology of the disease. It is indicated in:

1) Age of less than one year and more than 10 years in the first presentation
2) Presence of hypocomplementinemia.
3) Raised BUN and serum creatinine not responding to volume and albumin correction.
4) Steroid resistant, steroid dependent and multiple relapses.
5) Presence of persistent hypertension and hematuria.

Complications of nephrotic syndrome

1 – Infection:

- Bacterial and viral infections are common due to increased liability of nephrotic patient 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 common.
- Steroid therapy reduces the clinical signs of infection, so we must treat infection before starting the 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 I dL.
- Its manifestations occur according to the site of thrombosis as intestinal obstruction (mesenteric B.V), skin gangrene (Cutaneous B.V) hemiplegia (Central nervous B.V.) or severe hematuria (renal B.V.).

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.
- 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 Renal 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- *Causes of generalized edema.*

- Nutritional as kwashiorkor.
- Cardiac edema as in cases of congestive heart failure.
- Hepatic edema as in cases of chronic liver cell failure.
- Allergic edema as in angioneurotic edema.

Il- *Other causes of renal edema* as renal failure and acute post streptococcal glomerulonephritis.

Treatment:

1 - *Hospitalization:* No indication for hospitalization except:

- First time for teaching the mother and to observe child's response to steroid therapy.
- Presence of severe infection, electrolyte disturbance or hypertension.
- Severe cases with anasarca.
- Acute renal failure.

2 - *Activity:*

- Encourage normal activity except in the presence of respiratory distress, anasarca, hypertension, shock & impaired renal function.

3 *- Diet:*

- Well-balanced diet with daily recommended allowance of protein. Salt poor diet (1 to 2 g / day). Restriction of fluid 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 or 60 mg/m^2/day in 1 or 2 divided doses:
  - In initial episode: 4 consecutive weeks
  - In case of relapse: till urine becomes free of protein and remains 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.

- Daily administration of potassium as KC1 in dose of 2 - 4 g day as long as there is adequate urine output.

- ***Steroid responder***: when urine becomes protein free within 4 wks of steroid therapy.

- ***Steroid resistant***: persistent proteinuria after six weeks of steroid therapy.

-***Steroid dependent***: when proteinuria reappears after shifting to alternate day therapy or within 15 days of stopping the alternate day therapy.

c - Other immunosuppressive drugs: Used alone or with steroid therapy in cases with Steroid resistant, Steroid dependent, Frequent relapses and in case of ccurrence of toxic complications of steroid therapy (osteoporosis, fits, papilledema and hypertension).

- **Cyclophosphamide**: in dose of 2 - 3 mg/kg/day for 8 - 12 weeks,
- **Chlorambucil**: 0.1 - 0.15 mg/kg/ day for 12 weeks, and
- **Cyclosporin**: 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 IV.

Prognosis:

- ✓ Most 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

Case 2

Female child aged 6 years old presented with her parents. The mother noticed that her daughter had dark red urine one day ago. There was history of sore throat 10 days ago. On examination there was puffy eye and Blood pressure was 130/90mmHg.Urine analysis showing albumin++, RBCs >100 c/HPF, WBCs 30 c/ HPF and RBCs casts.

What is the most likely diagnosis? How to prove?

-Acute post streptococcal glomerulonephritis.

-To prove the diagnosis we should perform :

- Serum C3 & C4 level,: low C3 and normal C4 indicate alternate complement pathway activity which occurs in APSGN

-Evidence of sterprococcal infection by:

- Antistreptolysin o titre (ASOT), anti deoxyribonuclease B (ADNA ase-B)
- Throat culture

What is the pathogenesis of hypertention in this disease?

-salt and water retention and circulatory overload (circulatory congestion), in addition renal ischemia and activation of rennin angiotensin system.

What is the differential diagnosis of this condition?

I - Other glomerular diseases: as Nephrotic syndrome, Post-infectious acute glomerulonephritis following pneumococcal, gram - ve bacteria or viral infections, Anaphylactoid purpura, SLE, IgA nephropathy.

II - Other causes of red urine

- Drugs as rifampicin
- Foods as root beets
- Bilirubin as obstructive jaundice and acute hepatitis
- Hemoglobinuria as in acute hemolytic anemia
- Other cases of hematuria as Trauma. Blunt trauma and urinary stones & crystaluria
- Infection: Urinary tract infection, Renal T.B, and Urinary Bilharziasis.

What is the appropriate treatment for this condition?

- Hospitalization, rest, salt and water restriction
- A 10 - days course of penicillin

- 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.

Acute Poststreptococcal Glomerulonephritis (APSGN)

It is the most common form of nephritis in childhood, **Characterized by:**

- Hematuria.
- Significant proteinuria.
- Mild to moderate edema.
- Circulatory congestion.
- Hypertension.
- Variable degrees of impaired renal function.

Etiology:

- APSGN follows infection of the upper respiratory tact (Pharyngitis, nasopharyngitis, or otitis media). or skin infection (impetigo, acne, or erysipelas) with certain nephritogenic strains of group A beta - hemolytic sterptococci.
- 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:

- 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 renal failure.

Clinical presentation

Age 3 - 10 years, 2/3 of the cases between 3-7 ys, more common in males, male to female ratio 2:1.

Asymptomatic cases: The disease may be so mild to be passed unnoticed.

Symptomatic cases may have:

1 - *General manifestations:* anorexia, nausea, fever (usually low grade) and abdominal pain (loin pain).

2 - *Urinary manifestations*

Hematuria:

- Occurs in 100% of cases.
- Ranges from microscopical hematuria 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 I - 14 days.

Decreased urine volume and oliguria in cases of acute renal failure (ARF).

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 H.F. 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

1. *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.
2. *Hypertensive* encephalopathy: The child gets severe headache, nausea, vomiting, drowsiness, papilledema, and convulsions may occur.
3. *Acute renal failure:* The child develops progressive oliguria and even anuria with increasing edema, with nausea, vomiting, drowsiness and convulsions may occur.

Investigations

I – Urine

- Decreased volume or even oliguria.
  - Normal urine output is 1.5 to 3.5 cc/kg/hour.
  - Reduced urine volume (0.8 – 1.5 cc/kg/h) is normal variation occurs in dehydration, starvation & hot weather.
  - Oliguria is urine output less than 0.8 cc/Kg/hour and anuria is severe oliguria with 24-hour urine volume less than 25 cc in children.
  - Increased urine volume ;(3.5 – 5 cc/kg/h), is normal variant occurs in cold weather, recovery from edema & excessive drinking.
  - Polyuria (5 or more cc/kg/h).
- Specific gravity increases to 1020 or more.
- Gross hematuria or microscopical hematuria.
- RBCs are dysmorphic.

- RBCs cast.
- Some WBCs & granular casts.
- Significant proteinuria (>4 mg/m^2/hr and less than 4 mg /rn^2/ hr).

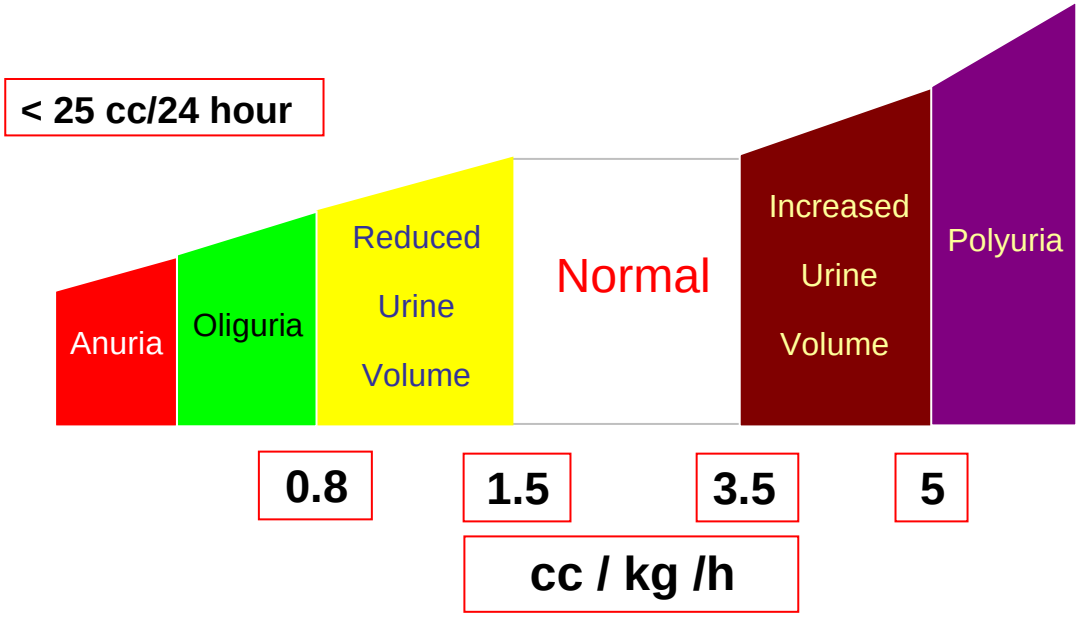


Diagram shows normal and abnormal urine volumes in children

II - 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 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.

III - Positive throat culture for streptococci.

IV - Chest X-ray:

- Pulmonary congestion, cardiomegaly and pulmonary edema in severe cases.

V – Renal biopsy indicated in:

- Acute renal failure
- Rapidly progressive glomerulonephritis (RPGN)
- Secondary nephrotic syndrome
- Persistent hypocomplementemia
- Recurrent gross hematuria
- Persistent hematuria and proteinuria

Differential Diagnosis

I - Other glomerular diseases

- Nephrotic syndrome.
- Post-infectious acute GN following pneumococcal, gram -ve bacteria or viral infections.
- Anaphylactoid purpura.
- SLE.
- IgA nephropathy.

II - Other causes of hematuria

- Congenital polycystic kidney.
- Trauma. Blunt trauma and urinary stones & crystaluria (oxaluria).
- Infection: Urinary tract infection, Renal T.B, and Urinary Bilharziasis.
- Blood diseases: Coagulation defects (Hemophilia), ITP, and Sickle cell anemia
- Malignancy: Leukemia, and Renal tumors (Wilm's tumor).
- Drugs: Anticoagulants (Heparin), and Sulfonamides.

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:

I- 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/m2/day.
- Water: equal to insensible water loss (400 cc/m + urinary output of previous day - the planned weight loss). So, getting negative fluid balance. This helps reduction of hypertension and edema.

II- Specific treatment

1- Ten days course of ***penicillin*** is given to the patient and any culture - positive family members, to eradicate streptococcal infection.

2- ***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.

3- ***Anti hypertensive drugs:*** Indicated if blood pressure is 140/90 or more and 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 µg/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 / 6 hr.

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.

III- Treatment of complications:

1- Hypertensive heart failure:

- Reduction of high blood pressure especially with diuretics.
- In the absence of organic myocardial disease digitalization will offer no beneficial effects.

2- Hypertensive encephalopathy:

- Reduction of high blood pressure.
- Control of convulsions by diazepam 0.3 mg/kg/dose. I.V. and phenobarbitone sodium in dose of 3-5 mg/kg/day to prevent convulsions.

URINARY TRACT INFECTION (UTI)

Case 4

A 9 ys old female child came to our clinic complaining of urinary frequency, enuresis and dysuria. Her mother said that she had these symptoms two times before and she has history of chronic constipation. Urine analysis showed RBC's:30- 40c /HPF, protein: +, pus cells: 80-90 c/ HPF and leukocyte esterase positive.

What is the diagnosis?

- Recurrent urinary tract infection (cystitis)

How to confirm this diagnosis

Bacteriological examination of urine (Colony count):

In mid-stream urine sample: The finding of 100 $x10^3$ organisms per ml of single organism is indicative of active U.T.I. Less than 100 x 10^3 organisms/ml or if two or more different organisms are cultured, indicate contamination.

What are the risk factors for recurrence?

- Sex: female - Chronic constipation

What is the most common organism for this disease?

The causative organisms in 80% of cases is Escherichia coli (E. coli), and the rest 20% by streptococcal fecalis, proteus, klebsiella and pseudomonas

Urinary tract infections are common infections 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 organisms in 80% of cases is Escherichia coli (E. coli), and the rest 20% by streptococcal fecalis, proteus, klebsiella 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, U.T.I. 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 U.T.I. as in stricture ureters, stones or neurogenic bladder.

3- Malnutrition: P.E.M. and vitamin A deficiency favor U.T.I.

4- Poor perineal hygiene: wiping from back to front in females, Pinworm infestation.

6 - Frequent instrumentation of urinary tract

7- Constipation

8- Uncircumcised males

9- 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

There are three routes.

1- Hematogenous: Hematgenous 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 U.T.I

1- In newborns:

- Picture of septicemia as high fever or hypothermia, vomiting, diarrhea, poor feeding, jaundice, convulsions, and failure to thrive

2- In infants and preschool age:

- Diarrhea - Vomiting - Fever - Irritability
- Failure to thrive - Dysuria - Strong smelling or bad smelling urine

3- In school aged children:

- Fever & Vomiting
- Abdominal pain, loin pain or suprapubic pain.
- Strong smelling or bad smelling urine
- Frequency, Urgency & dribbling
- Nocturnal enuresis.
- Asymptomatic bacteriuria occurs usually in school children.

B – Complications of recurrent or chronic U.T.I:

1- Failure to thrive.

2- Renal scaring 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 (WBCs) per high power field of centrifuged urine sediment.
- Minimal significant proteinuria.
- Leukocyte casts in cases of pyelonephritis.
- Few RBCs (minimal hematuria) without RBCs 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 $x10^3$ organisms per ml of single organism is indicative of active U.T.I. Less than 100 x 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 (I.V.P) and voiding cystourethrogram (VCUG) are indicated to exclude reflux nephropathy (RN). Also, renal scanning to detect any functional changes.

Treatment

- While awaiting the result of urine culture. We must start with one of the sulfa drugs or ampicillins.
- 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 U. T. I in children:

1) Ampicillin 100 mg/ kg / day orally.
2) Amoxicillin 50-100 mg/ kg/day orally.
3) Trimethoprim 5 mg/kg/day orally.
4) Nalidixic acid 25-50 mg/kg/day orally.
5) Gentamicin 5-7 mg/kg/day IM.
6) Cefaclor 25 mg/kg/day orally.

Prophylaxis in recurrent cases:

- Nitrofurantion 1- 2 mg/kg/d or Trimethoprim 1-2 mg/kg/d for 6 months .

Practice Questions (Choose one correct answer)

1- ***The following are causes of pediatric hematuria:***

b) Acute post-streptococcal glomerulonephritis
c) Renal stones
d) Renal trauma
e) All of the above

2- ***The main presentation of acute post-streptococcal glomerulonephritis (APSGN) in children is:***

a) Hematuria
b) Massive edema
c) Proteinuria
d) Renal failure

3- ***The most common cause of nephrotic syndrome is:***

a) Primary nephrotic syndrome
b) Focal segmental glomerulosclerosis
c) Congenital nephrotic syndrome
d) Secondary nephrotic syndrome

4- ***Nephrotic syndrome is characterized by:***

a) Edema
b) Heavy proteinuria
c) Hyper cholestrolemia
d) Hypo albuminemia
e) All of the above

Chapter 16

Pediatric Emergencies

Learning Objectives:

By the end of this chapter, students should be able to:

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. Pediatrics resuscitation.
2. Acute poisoning.
3. Respiratory failure.
4. Shock.
5. Altered states of consciousness and coma.

Cardiopulmonary Resuscitation (CPR)

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.

Resuscitation team 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: It consists of 3 successive stages: basic life support (BLS), advanced life support (ALS), and prolonged life support (PLS).

1. 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:

A. 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 centralized in sniffing position by placing a folded towel under the occiput.
- Oral airway placement may improve airway status.

B. 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.

C. 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 finger-breadths above the xiphoid.

2. Advanced life support (ALS): aims to restore spontaneous circulation by supporting circulation and treatment of the life-threatening arrhythmias.

A. 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.

B. 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

3. 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.

A. Recognition and treatment of the cause: such as hypothermia, tension pneumothorax, cardiac tamponade, hypovolemia, metabolic imbalance, toxin ingestion or closed head injury.

B. 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).

C. 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).

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:

* **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.

* **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:

1) Lung diseases:

A] Airway obstruction: (central or peripheral) : Tracheomalacia, subglottic stenosis, epiglotitis, croup, vocal cord paralysis , FB aspiration, Bronchiolitis, and bronchial asthma .

B] Pulmonary diseases: Aspirations, pneumonia, ARDS, pulmonary edema , pulmonary hemorrhage or embolism, and massive lung collapse.

2) Neuromuscular diseases: Guillain-Barre syndrome, botulism, birth trauma, werdnig 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 hypercapneia 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 oxymetry 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:

1] Oxygen therapy.

2] Ventilatory support; mechanical ventilation objective is to provide adequate gas exchange.

3] Treatment of the underlying disease.

4] Extracorporeal membrane oxygenation (ECMO)

5] Inhaled nitric oxide.

SHOCK

Definition: A clinical state of 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	• **Venous:** - Pneumothorax - Pulmonary embolus: clot, fat or air - Cardiac tamponade. • **Arterial:** - Critical aortic stenosis. - Critical aortic coarctation - Critical pulmonary stenosis.	- Fulminant sepsis without localization - Secondary to focal infection

Pathophysiology:

A. 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°C).
   - Slow capillary refill time over finger nails (> 5 seconds).
   - Skin mottling and peripheral cyanosis.

B. 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. **Then**, 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).

C. 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.

D. Irreversible (refractory) shock:

- Clinically, **myocardial ischemia** (serious arrhythmias) and **brain ischemia** (deep coma)
- **Metabolic acidosis** is severe or profound and is refractory to therapy.

Treatment:

1. ABC's,
2. Cardiovascular system support,
3. Other systems support,
4. Specific treatment,
5. 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 mI/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 I - 2 hours should suggest cardiogenic shock or obstructive shock.

3. Contractility augmentation:

Drugs	Dose (µg/kg/min)	Effects
Dopamine	Low (0.5 – 4) Medium (5-10) High (11 – 20)	Renal vasodilator Inotropic 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 (µg/kg/min)	Effects
Nitroprusside	0.5 – 10	Arterial dilatation (+++) Venous dilatation (+)
Nitroglycerin	1 – 20	Venous dilatation (+++) Arterial dilatation (+)
Amrinone	1 – 20	Vasodilator lnotropic

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 tachyrrhythmias 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 mI / 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 heparnization 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).
- 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: 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:

a. Aware of himself and environment.

b. Capable of responding correctly to verbal and mechanical stimuli.

c. 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:

1. RAS**:** a small lesion is sufficient to produce coma.
2. Cerebral cortex: an extensive lesion is necessary to produce coma.

Assessment of the state of consciousness:

This can be assessed by ***Glasgow coma scale*** which 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 bedside and does not need any investigations.

Glasgow Coma Scale (GCS)

ACTIVITY	BEST RESPONSE		
	Adults/Older Children	**Infants (modified GCS)**	**Score**
Eye Opening	▪ Spontaneous ▪ To speech ▪ To pain ▪ None	▪ Spontaneous ▪ To speech ▪ To pain ▪ None	**4** **3** **2** **1**
Verbal	▪ Appropriate speech ▪ Confused speech ▪ Inappropriate words ▪ Incomprehensible or none specific sounds ▪ None	▪ Coos, babbles ▪ Irritable, cries ▪ Cries to pain ▪ Moans to pain ▪ None	**5** **4** **3** **2** **1**
Motor	▪ Obeys commands ▪ Localizes pain ▪ Withdraws to touch ▪ Decorticate to pain ▪ Decerebrate to pain ▪ None	▪ Normal spontaneous movement ▪ Withdraws to touch ▪ Withdraws to pain ▪ Decorticate to pain ▪ Decerebrate to pain ▪ None	**6** **5** **4** **3** **2** **1**

Significance of Glasgow coma scores:

(1) 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.

(2) Follow – up of comatose children: Glasgow coma scores helps in follow-up of patients and in assessment of response to therapy.

(3) 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:

A. Head trauma may produce:

- Cerebral concussion.
- Cerebral contusion.
- Cerebral laceration.
- Brain edema.
- Extra and subdural hematoma.

B. Vascular: Hemorrhage, thrombosis, and embolism.

C. Epilepsy (Post-convulsion coma).

D. Central nervous system infections:

- Meningitis.
- Encephalitis.
- Brain abscess.
- Cerebral malaria.

F. Brain tumors.

II. Systemic causes:

A. 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.
- Hypernatremia and hyponatremia.

B. Renal failure.

C. Hepatic failure.

D. Severe systemic sepsis .

E. Heat stroke and hypothermia.

F. 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. • Organophosphrus poisoning • Rubbing alcohol sponging

IV. Psycho - neurological problems: Hysteria or functional coma: rare, recognized by exclusion.

Diagnostic Approach of a Child with Alerted Consciousness:

1. 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).

2. Mode of onset:

- **Acute onset**: 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.

3. Family history: Family history of neonatal deaths, may suggest inherited metabolic disorders.

4. Clinical examination: Clinical examination of a comatose child aims at:

- **Assessment of depth of coma:** through GCS as mentioned before.
- **Detection of causes of coma:** e.g. head trauma, hepatomegaly, heart lesion, otitis media, etc…
- **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:

1. 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.

2. 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.

3. Urine: In addition to toxic screen, urine must be examined for characteristic odor, reducing substances, specific gravity, pH, ketones, glucose, RBCs, casts, and albumin.

4. C.S.F. examination: bloody in subarachnoid hemorrhage, purulent in bacterial meningitis. The lumber puncture is contraindicated if there are signs of increased intracranial pressure or if the patient is shocked.

5. Gastric lavage: examination of gastric aspirate is indicated if there is a possibility of poisoning.

6. Radiological investigation:

- Plain x- ray: Skull, spine, chest and heart.
- Brain imaging. (CT and MRI).

7. Electro-encephalogram: indicated in cases with unexplained stupor or coma.

8. **Electro-cardiogram & 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 residua.

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- 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.

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