BABY NELSON

Pediatrics



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MD Pediatrics

Baby Nelson

In

Illustrated Pediatrics

Editor

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جميع حقوق الطبع و النشر محفوظة للمؤلف

غير مسموح بطبع أونشر او استغلال اى جزء من الكتاب باى صورة إلا بإذن كتابي من المؤلف فقط و من يفعل ذلك فسوف يعرض نفسه للمسائلة القانونية

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Dedication

I dedicate this novel edition

*To **my Mother and my Father** who always believed in me more than I have ever believed in myself*

*To the soul of my father in law **Dr. Ahmad Hamdy Elwelily** who was always filling me with faith, encouragement and love in my entire career*

To all my professors and colleagues in pediatric department , Zagazig university faculty of medicine

*To my wife , **Dr Saly** , and my son , **Mazen** , my beloved inspirational companions for whom I drag myself out of bed each morning and the reason I rush home each night*

*To my brother **Dr Ashraf El Komy** who did for me much more than I can ever do for myself*

*To my family kids : **Mena , Omar , Hosam, Ahmad, Zyad, Khalid, Abd rahman, and Saif***

*To my friends **Mr Ahmad Talaat** ;the pioneer teacher of physics and the smart pediatrician **Dr. Tark***

List of abbreviations

1. 25 (OH)2 D3	: One, twenty five dihydroxy cholecalciferol.
25 (OH) D3	: Twenty five hydroxy cholecalciferol.
ACTH	: Adreno corticotropine hormone.
Acute H AN	: Acute hemolytic anemia.
ADH	: Antidiuretic hormone.
ALK phos	: Alkaline phosphatase.
ALT	: Alanine amino transferase
ARF	: Acute renal failure
AST	: Aspartate amino transferase
C/S	: Culture & sensitivity
Ca	: Calcium.
CBC	: Complete blood count Congenital heart disease.
CHD	: Carbohydrate
CHV	: Cytomegalo virus.
DIC	: Disseminated intra vascular coagulation.
DM	: Diabetes Mellitus.
Fe	: Iron
G-CSF	: Granulocyte colony stimulating factor
GE	: Gastroenteritis.
GERD	: Gastroesphageal reflux disease
H.F.	: Heart failure
HBV	: Hepatitis B virus.
HIE	: Hypoxic ischaemic Encephalopathy.
HIV	: Human immunodeficiency virus.
ICT	: Intracranial tension.
IUGR	: Intrauterine growth retardation
LCPUFA	: Long chain poly unsaturated fatty acids.
LFTs	: Liver function tests.
MR	: Mental retardation.
Ph	: Phosphate.
PTH	: Parathyroid hormone.
RFTs	: Renal function tests.
SIDS	: Sudden infant death syndrome
TPN	: Total parenteral nutrition.
UOP	: Urine out put.
URTI	: Upper respiratory tract infection
UTI	: Urinary tract infections.

Growth And Development

Definitions

* **Growth** is increase in size of organism due to increase size and / or increase number of its constituent cells.
* **Development** is maturation of functions & acquisition of skills.

Stages of Growth & Development

1- Intrauterine stage

Embryonic period 1st trimester (1st 12 weeks of gestation) ⇓	**Early fetal period** 2nd trimester (12-28 weeks) ⇓	**Late fetal period** 3rd trimester (28-40 weeks) ⇓
• Devoted for organogenesis • By end of this phase the embryo weight is **9 gm** and **5 cm** length • Teratogenic agents in this period may lead to: abortion or congenital anomalies.	Rapid growth mainly in length • Fetus is pre viable • At end of this period: - Length is **35** cm, - Weight is **1** kg • Teratogenic agents in fetal period may lead to fetal death, stillbirth, premature delivery **or** IUGR.	Rapid growth mainly in weight • Fetus is viable

2- Extra uterine stage

Neonatal	**Infancy**	**Childhood**	**Adolescence**
1st 4 weeks of life	- Early infancy up to one year - Late infancy during the 2nd year.	- Early childhood (2-5 years) - Late childhood (6 - 12 years).	From (12-15 years)

Factors affecting growth

1- Factors before conception:

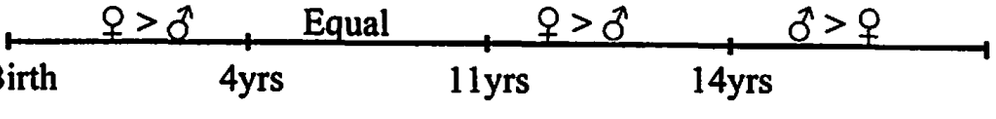
a. Racial b. Familial c. Constitutional

2- Maternal factors (during conception): including maternal diseases, medications & nutritional status.

3- After birth:

a. Age → growth rate is more during infancy and adolescence.

b. Sex →



c. Status → nutritional & psychological.

4- Hormonal role: growth is controlled by hormones depending on the stage.

Intrauterine	Infancy & childhood	Adolescence
1. Chorionic gonadotropines	1. Thyroxin	Sex hormones
2. Placental lactogen	2. Growth hormone	(estrogen & androgen)
3. Insulin		
4. Thyroxin (skeletal growth)		

Pattern of growth

- General → growth of bones, muscles & soft tissues
- Genital → growth of genital organs
- Nervous → growth of CNS
- Lymphatic → growth of lymphatics

Assessment of growth

I- Anthropometric measures

1- Weight

* At birth → 3 - 3.5 kg
* During the 1st year:
  - 1st 4 months → Weight ↑ by ¾ kg per month.
    (so, at 4 months → weight= 6 kg ⇒ double birth weight)
  - Next 4 months → Weight ↑ by ½ kg per month
  - Last 4 months → Weight ↑ by ¼ kg per month
* Beyond the 1st year → Weight is calculated as: **weight = age (in years) × 2 + 8**

N.B: During the 1st 3-4 days of life, baby lose ≈ 10% of baby weight due to scanty milk flow, passage of meconium & urine (physiologic weight loss) → this weight loss is regained by the 10th day.

2- Length

* At birth → 50 cm
* At 6 months → 68 cm
* At 1 year → 75 cm
* At 2 years → 87 cm
* After the 2nd year → Length is calculated as: **Length = age in years × 5 + 80**
  So; at 4 years the baby is 100 cm (double the birth length)

N.B: ✧ Under 2 years length is measured in supine position.
✧ Over 2 years height is measured in standing position.
✧ Height is 0.5 cm less than length due to joints compression on standing.

3- Head circumference

* At birth → 35 cm. (33-35 cm).
* At 6 month → 42 cm
* At 1 year → 45 cm
* At 2 years → 47.5 cm
* At 12 years → 52 cm

N.B: Maximum rate of increase in H.C is during the 1st year (especially in 1st 6 months) due to brain growth.

4- Head circumference(HC) & chest circumference (C.C) ratio

* At birth → H.C > C.C ⇒ H.C/C.C ratio > 1
* At 6 months → H.C equals C.C ⇒ H.C/C.C ratio = 1
* After 6 months → C.C exceeds H.C ⇒ H.C/C.C ratio < 1

✧ Value: Beyond 6 months, if H.C/C.C > 1 ⇒ should suggest malnutrition or hydrocephalus.

5- Mid arm circumference (MAC)

* In a baby 1- 4 years → MAC is > 14 cm
* In subclinical malnutrition → MAC is 12 – 14 cm
* In clinical malnutrition → MAC is < 12 cm

✧ Value: Early indicator of malnutrition ; measure the muscle bulk and is not affected by edema.

6- Skin fold thickness

Body fat can be estimated by measuring skin fold thickness in left triceps or left subscapular regions by skin fold calipers.

7- Proportions of upper segment & lower segment

* Upper segment (US) is measured from crown to symphysis pubis.
* Lower segment (LS) is measured from symphysis pubis to the floor.
* Proportions of US/LS:
  - At birth → 1.7
  - At 3 years → 1.3
  - After 7 years → 1

✧ Value: Help evaluation of short stature;
- Short stature with normal proportions for age → proportionate.
- Short stature with abnormal proportions for age → disproportionate.

8- The Arm span - Height relationship:

* Span is shorter than height by 3 cm at 1-7 years.
* Span equals height at 8-12 years.
* Span exceed height by 4 cm (in male), and 1 cm (in females) at 14 years.

II- Teething

Primary = Deciduous or milky teeth		Secondary (permanent) teeth	
Tooth	**Age (months)**	**Tooth**	**Age (years)**
- Central incisor	6 - 8	- Central incisor	7
- Lateral incisor	8 - 11	- Lateral incisor	8
- Canine	16 - 20	- Canine	10
- 1st molar	10 - 16	- 1st premolar	11
- 2nd molar	20 - 30	- 2nd premolar	12
		- 1st molar	6
		- 2nd molar	13
		- Wisdom tooth	22
* Count : 20 teeth * Teething start at 6 months and completed at 24 months. * The lower jaw incisors precedes the upper jaw by one month		* Count : 32 teeth * Teething start at the 6th years and completed at 22nd years. * Eruption follow exfoliation immediate or may lag 4-5 months	

Teething problems

1. Delayed teething : no eruption beyond 13 months age.

   Causes :

   i. Local: e.g. supernumerary tooth, cysts, over retained primary teeth

   ii. Generalized : - Mongolism
   - Achondroplasia
   - Cretinism
   - Rickets
   - Osteogenesis imperfecta
   - Hypopituitarism , hypoparathyriodism

   iii. Idiopathic : the commonest cause

2. Diarrhea, drooling or fever have doubtful real correlation with teething.
3. Teething pains : treated by paracetamol, teething gel , and rubber toys
4. Congenital missing teeth: frequently maxillary lateral incisor
5. Congenital extra teeth: frequently extra molar teeth
6. Early exfoliation : may be due to histiocytosis X , cyclic neutropenia , trauma
7. Premature teething is seen is:
   - Natal teeth (should be extracted to avoid aspiration).
   - Ellis Van Creveled syndrome: micromelic short stature, polydactyly, and atrial septal defect.
   - Congenital syphilis.

III- Fontanels

There are 6 fontanels present at birth (2 anterolateral, 2 posterolateral, 1 anterior & 1 posterior) but only 2 (the anterior & posterior fontanelles) are usually palpable on physical examination.

Posterior fontanel:

- Normally: Closed at birth or opened < 0.5 cm and closes within 2 months
- Abnormally: Opened > 1 cm or Not closed within 4 months



Causes :

- Prematurity
- Increased intra cranial tension (e.g. hydrocephalus)
- Mongolism
- Cretinism

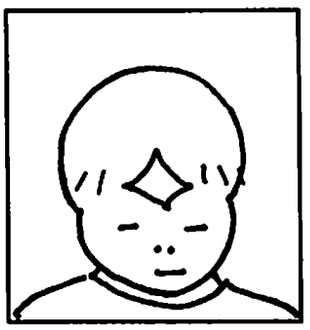
Anterior fontanel: Clinical value

1- **Assessment of growth**

- At birth → 3 fingers (≈ 3- 4 cm).
- At 6 months → 2 fingers.
- At 12 months → 1 finger.
- At 18 months → closed.

2- **Size**

A- Large fontanel (delayed closure) in: (MACRO HIP)



- Mongolism
- Achondroplasia
- Cretinism
- Rickets
- Osteogenesis imperfecta
- Hypopituitarism
- Increased intra cranial tension
- Premature

B- Small fontanel (premature closure; before 6 months) in:

- Craniosynostosis
- Microcephaly
- Congenital hyperthyroidism
- Hypercalcemia

3- **Surface** : normally smooth & continuous with skull bones.

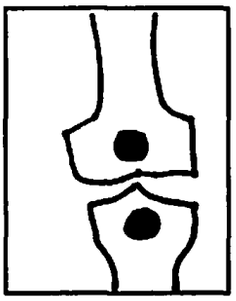
A- Bulging : in increased intra cranial tension e.g.

- CNS infections ; meningitis, encephalitis
- Hydrocephalus
- Intra cranial hemorrhage.

B- Depressed : in dehydration & shock.

4- **If absent at birth** : there may be skull bones over molding or caput succedaneum.

IV- Osseous Growth



✧ Normally, there's 5 secondary ossific centers at birth in:
- Lower end of femur.
- Upper end of tibia.
- Calcaneus, talus & cuboid.

✧ Carpal bones start ossification after birth as follow:
- The 1st carpal bone → at 2 months.
- The 2nd carpal bone → by the end of first year.
- Later on, one carpal bone ossifies each year till the 6th year (= 7 bones). the 8th bone ossifies at 12 years.

✧ Bone age is determined by:
1- At birth → by x-ray knee.
2- Later on → by x-ray wrist.(bone age = count of carpal bones-1)
3- In late childhood → from fusion of epiphysis & skull sutures.

Causes of delayed bone age	Causes of advanced bone age
1- Growth hormone deficiency	1- Growth hormone excess
2- Hypothyroidism.	2- Thyrotoxicosis.
3- Hypogonadism.	3- Androgen excess (e.g. precocious puberty)
4- Delayed puberty.	4- Simple obesity.
6- Cushing syndrome	
5- Chronic illness / under nutrition	

V- Growth Charts (Curves)

Definition: Graphic method for assessment of physical growth of a child

Value
1- Demonstrate the normal growth variations among children of the same age.
2- Earlier diagnosis of abnormal growth.
3- Made for different aspects of growth, e.g. weight, height & skull circumference.

Types:

1. Percentile growth curves

Each chart is composed of 7 percentile curves
- 97th percentile → Highest normal.
- 90th percentile → High normal.
- 75th percentile → Above average.
- 50th percentile → Average.
- 25th percentile → Below average.
- 10th percentile → Low normal.
- 3rd percentile → Lowest normal.

Normal child on percentile curves

1- Should lie between the 3rd and the 97th percentile curves. So on single measurement, values below 3rd or above 97th are abnormal.

2- Should follow the same percentile level throughout the growth period. So on serial measurement deviation of the child from his own percentile curve is abnormal.

3- Not all the child growth parameters necessarily fall into the same percentile.

2. Distance curves

✧ Demonstrate length, weight, head circumference attained at every year and plotted against the age.

Value: in cases of protein energy malnutrition (PEM):

- Decrease of weight / age and normal length / age indicate recent nutritional deficiency.
- Decrease of length/ age and normal weight/age indicates nutritional deficiency in the past.
- Decrease of both length and weight/age indicates both recent and old nutritional deficiency.

3. Velocity curves

✧ Demonstrate height velocity in cm per year.

✧ There are four periods of growth velocities:

- In the first 2 years → rapid increase in length.
- From 2 years to pre adolescence → slow growth period.
- From puberty to 15-16 years → rapid growth period.
- Growth normally cease at 15 years in females and 16 years in males.

4. Standard deviation curves

These curves show the degree of dispersion of observations around the mean for each sex at various ages. Abnormal measure is 2 standard deviations below or above the mean.

Morley's chart:

- Applied for children 3-5 years old of both sexes.
- Contain 2 curves
- Record feeding, vaccination and illnesses so, useful in follow up.
- Help early detection of malnutrition.
- Help monitoring success of treatment of malnutrition.
- A good method for education of mothers.

Assessment Of Development

1- Motor milestones : (Locomotor development)

A. Gross motor

At
- 3 months → Head support (no head lag)
- 5 months → Sit with support
- 6 months → Sit without support
- 9 months → Crawling
- 10 months → Stand supported
- 12 months → Walking alone
- 16 months → Run
- 1.5 year → Ascend stairs in child manner
- 2 years → Descend stairs in child manner
- 3 years → Ride a tricycle

B. Fine motor

At
- 3 months → Grasp rattle
- 4 months → Reach for objects
- 5 months → Transfer objects
- 2 years → Copies a vertical line
- 3 year → Copies a circle
- 4 years → Copies a cross and square /Draws man with three parts
- 5 years → Copies a triangle/ Draws man with six parts

2- Mental milestones :

- Disappearance of neonatal reflexes (for relevant dates ; see neonatology).

A. Social adaptation

At
- 1 month → Angle smile
- 2 months → Social smile
- 4 months → Mother recognition
- 6 months → Imitates
- 9 months → Father recognition , respond to his name, waves bye bye
- 15 months → Drinks from a cup
- 18 months → Points to 3 parts of body

B. Speech development

At
- 1 year → Says 3 words
- 2 years → Says 3 word sentence (phrases).
- 3 years → Says his name & age
- 5 years → Says clear speech

C. School achievement.

3- Special sense development

A. Hearing

At
- Birth → Hearing is impaired due to amniotic fluid in middle ear
- 2 weeks → Good hearing → baby can respond to noise by Moro reflex
- 3 – 4 months → Respond to sound by cessation of movement
- 5 – 6 months → Turns his head to the sound

B. Vision

At
- 1 month → Macula not yet developed → no fixation
- 2 months → Fix on steady objects
- 3 months → Fix on slowly moving object
- 7 months → Follow rapidly moving object

4- Sphincters control

Occur from 1 – 4 years depending on :
- Maturation of pyramidal tracts
- Training
- Psychological status.

Normal vital data

Heart rate: (Beat/minute)
- Birth → 120
- 2nd year → 100
- 4th year → 90.
- 6th years → 80.

Blood pressure:
- At birth → 70/50 mmHg, (systole ↑ 10 and diastole ↑ 5 every 3 years)

So at
- 3 years → 80/55
- 6 years → 90/60
- 9 years → 100/65
- 12 years → 110/70

Respiratory rate:
- During the first year → 35-45/min.
- During the second year → 25-35/min.
- During the 8th year → 20/min.

Infant Feeding

Patterns of Infant Feeding:

1. Breast feeding from:
   - Mother
   - Wet nurse (healthy, has a child 2-5 months).
   - Breast milk banks → not allowed in Egypt.

2- Artificial feeding:
   - Fresh fluid animal milk.
   - Evaporated & condensed milk.
   - Dried powdered milk.

3- Mixed feeding:
   - Complementary feeding.
   - Supplementary feeding.

Breast Feeding

Control of milk production

1- Maternal Reflexes

1. Prolactin (Production) reflex

⇓

Suckling of nipple

↓

+ + vagus nerve

↓

+ + hypothalamus

↓

+ + anterior prtuitary

↓

↑↑ prolactin

↓

+ + milk secretion

2. Milk ejection (let down) reflex

⇓

Suckling of nipple

↓

+ + vagus nerve

↓

+ + hypothalamus

↓

+ + posterior pituitary

↓

↑↑ oxytocin

↓

+ + milk ejection.

N.B: Maternal anxiety, stress and fatigue inhibits ejection reflex.

2- Infant Reflexes

a- Rooting reflex

The infant turn his head to the side in which the nipple is felt → then the nipple is settled in the mouth then in the oropharynx by action of buccal muscles.

b- Suckling reflex → rhythmic movements of the mandible applying pressure on the lacteals → expression of breast milk.

c- Swallowing reflex

N.B: Coordinated suckling and swallowing occur in babies born after 34 weeks

Stages of milk production

A- Breast preparation during pregnancy:

- Estrogen → stimulate duct system.
- Progesterone → stimulate gland system.

B- Initiation of milk flow:

After delivery → placental sex hormones drop → release of pituitary gland from inhibition → ↑ prolactin → ↑ milk secretion.

C- Maintenance of milk flow by:

1. Mechanical factors: The chief stimulus which is achieved by:
   - Suckling : the more regular & vigorous suckling, the more the milk flow.
   - Complete and regular evacuation of the breast.
2. Good maternal nutrition with plenty of :
   - Sugary fluids
   - Vitamins B complex
   - Lactagogues: e.g. Helba.
3. Good maternal psychological state and family support.
4. Hormonal balance:
   - Prolactin: lactogenic hormone.
   - Growth hormone: anabolic hormone
   - Thyroxin: stimulate cell metabolism.
   - Sex hormone.
5. Rooming in (keeping the baby in mothers room).
6. Demand feeding (feeding according to the infant desire)
7. Avoidance of bottle supplements

Disadvantages of breast milk

1- Breast milk protein Allergy → very rare.

2- Breast milk jaundice → may occur due to pregnandiol secreted in breast milk.

3- Deficient Content of :

* Vitamin K→ bleeding tendency ; prevented by giving vitamin K at birth
* Vitamin D→ risk of rickets .
* Iron→ risk of iron deficiency anemia

  Both rickets & iron deficiency anemia can be avoided by supplementing breast fed infant with iron and vitamin D from the 4th –6th months onwards.

4- Some Drugs are secreted in breast milk e.g.

- Anti cancer agents, anti thyroid, lithium, recreational drugs
- Antibiotics: chloramphenicol , tetracycline, sulphonamides.
- Metronidazole
- Anthraquinone laxatives
- Babiturates ,opiate , atropine, bromide, salcylates

5- Some viruses are Excreted in breast milk e.g CMV, HIV, HBV.

Breast Milk Composition

✧ Colostrum → from birth to the 5th day of life.
✧ Transient milk → from the 5th day to 21th day.
✧ Mature milk → after the 21th day.

	Colostrum	Mature milk
Amount	40-60 ml	1 liter
Reaction	Slightly alkaline	Neutral
Color	Lemon yellow	Whitch
Consistency	Thick	Thin
Caloric value	57 cal/dl	67 cal/dl
Specific gravity	1040 – 1060	1030 – 1035
Protein	7 gm%	0.9-1.2 gm%
Fat	3 gm%	4 gm%
Carbohydrates	4 gm%	7 gm %
Ashes	high	0.25 %
Colostrum corpuscles	Large endothelial cells from breast acini or fat laden leucocytes	Absent → if present, it means deteriorating breast milk secretion
Value	1. Nutritive (↑ protein) 2. Protective → ↑↑ Ig A & ↑ PMNLs & monocytes 3. Initiate gastrocolic reflex → mild laxative	See later

Advantages Of Breast Feeding

I. To the mother

1- Help involution of the birth canal and reduce risk of post partum hemorrhage.
2- Natural method of contraception.
3- Reduce the incidence of cancer breast.
4- Always available without cost.
5- Construct strong psychological bond between the mother & the infant.

II. To the infant

A- General values of breast milk

- Sterile
- Soothing on the gastrointestinal tract.
- Adequate quantity & quality
- Allergy is extremely rare.
- Constant temperature.
- Colostrum is protective, nutritive and mild laxative.

B- Adequate composition than animal milk

Composition of breast milk	
✧ Water	88 gm/dl.
✧ Protein	1.2 gm/dl
✧ Fat	4 gm/dl.
✧ Carbohydrate	7 gm/dl.
✧ Minerals	0.25 gm/dl.
✧ Vitamins A , B	sufficient.
✧ Vitamin D	12- 60 IU/L
✧ Vitamin C	3.8 mg/dl
✧ Calcium	30 mg/dl
✧ Phosphate	15 mg/dl.
✧ Iron	0.15 mg/dl.
✧ Copper	6 μ mol/ L
✧ Zinc	45 μ mol/ L
✧ Calories	67 cal/dl

Cow, Buffalo, Goat & Ass milks

⇓

Have

✧ Higher content of
- Proteins
- Minerals.
- Calcium & phosphate (inadequate ratio)

✧ Sufficient content of
- Vitamin A & B complex.

✧ Lower content of
- Carbohydrates
- Vitamin D & C
- Iron ,Copper & Zinc

✧ Variable content of fat (higher in goat's & lower in cow's milk)

C-Qualitative differences between human and cow's milk

	Human milk	Cow's milk
1- Protein		
a. Dietetic protein	- 60% (α-lactalbumin)	- 20% (β lactglobulin)
- Soluble (whey)	- 40% (casein)	- 80% (casein)
- Insoluble (curd)	Small amount; fine and thin so easily digested	Large amount; tough & thick So hardly digested.
- Soluble /Insoluble ratio	- 3:2	- 1:4
b.Non dietetic protein		
- Lactoferrin	- ↑↑ → bacteriostatic to E.coli → ↑ absorption of iron	- Traces
- Immunoglobulins	- ↑↑ →specific to human pathogens	- Traces → specific to animal pathogens.
- Lysozymes	- ↑↑ → bactericidal	- Traces.
- Essential amino acids	- ↑↑ → e.g. glutamic, taurine essential for brain development	- Traces.

	Human milk	Cow's milk
2- Fat		
- Fat globules	- Small	- Large → hard digestion
- Diurnal variation	- Present → high concentration at the evening & end of feed	- Fixed concentration
- Lipase enzyme	- High → help digestion	- Low level
- Essential fatty acids	- Higher (11%) especially Leinoleic and oleic acids.	- Smaller < 2%
- Volatile fatty acids.	- Small amount → less GIT upsets	- High → frequent GIT upsets→ regurgitation & distention
3- Carbohydrate	- β lactose → no fermentation (no gases nor vomiting) - Some is converted to lactic acid: → ↑↑ calcium absorption. → Bacteriostatic	- α lactose → high incidence of fermentation → excess gases, vomiting.
4- Minerals		
- Amount	- Low → avoid hyperosmolality & renal overload.	- High.
- Calcium/Phosphate ratio	- 2/1 so better absorption → rickets is rare	- 4/3 so less absorption → high risk of rickets
- Sodium content	- Low so ↓ renal solute load	- High
- Iron	- Low with good absorption sufficient for 4 – 6 months	- Very low with bad absorption (less bioavailable)
5- Bacterial content	- Sterile	- High, unless well boiled

N.B Fat content in breast milk (unlike protein & lactose) varies with maternal nutrition.

D- Anti-infective properties of breast milk

1- Breast milk contain Antibodies (humoral immunity) against:

1- Viruses: e.g. Poliomyelitis, mumpes, rota virus, influenza, measels

2- Bacteria: e.g. E.coli, cholera, salmonella, shigella.

Functions:- IgA → inhibit attachment of viruses and bacteria to gut and respiratory mucosa .

- IgG & IgM → passive humoral immunity.

Criteria : - High level of secretory Ig A compensate for the lower levels in infant in the 1st year of life.

- Ig G & Ig M level is lower than Ig A as they are rapidly formed by the infant after birth.

2- Anti staph factor: Thought to be a polyunsaturated fatty acid.

3- Anti protozoal:

Lipase enzyme stimulated by infant bile salts → can kill Entameoba histolytica & Giardia Lamblia.

4- Receptor Analogues:

As oligosaccharides, mucins & glycolipids which act as receptor analogues → inhibit binding of enteric & respiratory microbes.

5- Other Antimicrobial agents:

- Fibronectin → act as opsonin.
- Activated C3 & C4 act as opsonins & chemotactic factors.
- Lactoperoxidases → inhibit E.coli, cholera, salmonella, shigella.

6- Anti-inflammatory agents:

✧ Value : During enteric & respiratory infections - in breast fed infant - there's less inflammatory response → less damage to mucosa.

✧ Due to: - ↓ Mediators of inflammation in breast milk.
- ↑ Anti-inflammatory agents e.g. Antioxidants, α_1 anti trypsin.

7- Bifidus factor:

✧ Nature: Amino sugar

✧ Role: stimulate growth of lactobacillus bifidus which is a normal bacteria flora in the intestine → interference with pathogenic bacteria as E. coli & vibrio cholera.

8- Binding proteins:

✧ Nature: - Folic acid binding protein.
- B_{12} binding protein.
- Lactoferrin; Iron binding protein.

✧ Role : Folic acid, B_{12}, and iron are essential for growth of pathogenic bacteria ; binding proteins deprive pathogenic bacteria from these growth factors with subsequent bacteriostasis.

9- Low buffering effect:

Breast milk has neutral or slightly alkaline pH. So, preserve gastric acidity which acts as a barrier against infection.

10- Cellular immunity:

Breast milk contains polymorphnuclear leucocytes and macrophages which can secrete lysozymes, complement, and lactoferrin.

11- Interferon: Acts as broad spectrum antiviral.

12- Immuno modulating agents:

- IL-6 and transforming growth factor β→ increase Ig A antibodies production.
- Interferon α → increases expression of secretory component of Ig A.
- IL-1 β → increases T-cell production.
- IL-8 → attracts polymorphnuclear leucocytes & CD8 – T cells.
- IL-10 → decreases pro inflammatory cytokines.

E- Recent beneficial effects of breast milk

1. Convenient composition for premature:

1. Protein is higher by **20%** with higher immunoglobulins and lactoferrin.
2. Fat is higher by **50%** with higher content of long chain polyunsaturated fatty acids which are essential for brain and retinal growth.
3. Vitamins → higher content of vitamins A & E.
4. Carbohydrate → lower lactose content.
5. Contain platelet activating factor acetyle hydrolase & IL-10 which protect against NEC.

2. High content of oleic acid : Reduced risk of coronary heart disease in later life.

3. Growth factors & hormones

Criteria:

- Higher concentration in breast milk than maternal blood.
- Modified to avoid digestion.

Types : - Progesterone.
- Thyrotropin releasing hormone.
- Compounds essential for brain growth & retina which can't be formed by baby: - Carnitine.
  - Taurine.
  - Long chain poly unsaturated fatty acids (LCPUFA).

4. Enzymes:

1. Digestive → lipase, amylase.
2. Transport → xanthine oxidase for iron.
   → glutathione peroxidase for selenium.
3. Protective

5. Bioactivity of breast milk:

Despite some nutrients are present in low concentrations but have better absorption e.g. : - Calcium and phosphate (optimal ratio)
- Iron (due to lactoferrin)
- Zinc (high bioavailability)

Program of Breast Feeding

I- Maternal instructions

- Nipple care to avoid retracted nipples.
- Suckling should be initiated as soon as possible.
- No extra fluids except for cooled boiled tap water in 1st 4months.

II- Technique of nursing:

- Mother sit comfortable.
- Nipples & hands are cleaned.
- Baby held semi sitting.
- Breast held with nipple fitting in baby mouth.
- Both breasts are given.
- After nursing → eructate the baby.
- Baby left sleep on the back (*back to sleep*)

III- Intervals between feeds

Ideally 3 hours intervals (= gastric emptying time)

2 hourly feeding for

- ✧ 1st 2 weeks of life.
- ✧ Premature (weak sucker)
- ✧ Scanty milk flow.

4 hourly feeding for

- ✧ After the 4th month.
- ✧ Overweight and strong suckers.
- ✧ Liberal milk flow.

IV- Adequacy of breast feeding

Adequate feeding	Under feeding	Over feeding
- Adequate weight gain - Satisfied after feeding ⇓ Sleep 2-4 hours in-between feedings - Normal bowel habit - Normal urine flow	- Poor weight gain - Lack of satisfaction after feed ⇓ - Excessive crying, irritable & sucking fingers due to hunger - Constipation - Oliguria ± dehydration	- Excessive weight gain - Lack of satisfaction ⇓ - Excessive crying & irritable due to colics. - Bulky stool (may be diarrhea) - May be sore buttocks.
Management		
➢Evidence of adequate feeding 1- Marked filling of breasts between feeds 2- Test feed : weigh the baby before & after feeding with unchanged clothes 6 times a day → calculate amount of the feed for 3 days → take the average .	• Search for causes of difficult feeding in the infant and the mother • If no cause : give milk supplementation.	- Allow feeding every 4 hours. -No suckling > 20 min / feed. - Remove excess breast milk by pump after feeding.

Difficulties In Breast Feeding

I- Maternal causes of difficult feeding

1. Scanty milk supply

Due to : - Maternal malnutrition, disease psychic troubles or poor suckling

Treatment : - Treat the cause
- Increase milk flow by frequent nursing, short course of chlorpromazine and /or electric breast pump.
- Complementary feeds with dried powdered milk

2. Milk engorgement

Due to : - Incomplete evacuation of breasts → accumulation of milk and overdistention of alveoli .

C/P : - Tender edematous breast
- Fever and malaise in severe cases

Treatment : - Proper emptying of breasts either manually or by a pump after sucking.
- Cold compresses to suppress breast congestion.
- Severe cases: antibiotic and temporary stoppage of milk with estrogen

3. Retracted nipples

Due to : - Non projectile nipples due to lack of antenatal care.

Treatment : - Daily manual breast pump traction during latter weeks of pregnancy
- Truly inverted nipples may be helped by use of milk cups, starting as early as the 3rd month of pregnancy.

4. Painful nipples

Types : - Sore nipples (erosive type; occur in the first week)
- Fissured nipples (occur after the first week).

Treatment: - Expose nipples to air
- Keep nipples dry between feeds: apply absorbent pads to absorb any leaked milk
- Avoid soap and alcohol
- In severe cases:
  * Manual expression of milk from the fissured side
  * Paint the nipple with gentian violet or panthenol (about 24 hrs).
  * Nipple shields may be helpful
  * For severe bilateral fissuring :temporary stoppage of breast feeding

5. Acute mastitis & breast abscess

Risk factors : - Milk engorgement & fissured nipples

Organism : - Mainly staph aureus

Treatment : - In mastitis : stop lactation from affected side ,evacuation& antibiotics.
- In abscess : stop lactation from both sides , incision & antibiotics.

6. Large pendulous breast

To guard against infant suffocation the mother must support the breast in feeding and never allow lactation from sleeping mother.

7. **Work and lactation**

Worker mothers are advised to feed their infants just before leaving for work and just after returning and if work time is more than 4 hours → supplementary feed.

8. **Contraception and lactation**

Estrogen containing contraceptive pills decrease milk flow, so, progesterone pills and intrauterine device are more suitable.

9. **Pregnancy and lactation**

No harm of lactation during pregnancy with adequate maternal nutrition but after the 24th week of gestation milk changes to colostrums and most mothers prefer to wean.

10- **Twins and lactation**

- Must be followed by weight for age chart.
- If there is no adequate weight gain supplementation is advised.

N.B: Expressed breast milk :

Can be stored in freezer for up to 1 month and in refrigerator for 24 hours

Can be used for feeding of:
- Premature
- Sick hospitalized infants
- Infants with poor suckling
- Infants of working mothers

II- Infant Causes of difficult feeding

1- Congenital anomalies

- Bilateral cleft lip / cleft palate
- Trachoesophageal fistula
- Macroglossia or micrognathia (e.g. Pierre-Robin syndrome)

2- Painful mouth

- Stomatitis
- Oral ulcers
- Moniliasis

3- Weak suckling

- Prematurity (< 32 weeks)
- Sepsis (especially in the neonatal period).
- Sleepy infant e.g. Hypothyroidism
- Neurologic insult (e.g intracranial hemorrhage, facial palsy, mental retardation.)

4- Nasal obstruction

- Bilateral choanal atresia
- Nasal allergy
- Adenoids

5- Dyspneic conditions

- Pulmonary e.g. pneumonia
- Cardiac e.g congenital heart diseases with increased pulmonary blood flow.

Contraindications of breast feeding

I. Maternal causes

Temporary	Permanent
1. Bilateral nipple fissuring.	1. Debilitating chronic diseases e.g.
2. Bilateral acute mastitis & abscess	- uncontrolled diabetes mellitus
3. Acute maternal disease e.g typhoid	- decompansated rheumatic heart disease
4. Post-partum illness e.g. eclampsia.	2. Malignancy
5. Herpes simplex of nipples	3. Active maternal CMV infection
6. Mothers receiving some drugs	4. Local breast causes e.g cancer breast & T.B

N.B. The mother can lactate with precaution in the following conditions:

A- Syphilitic mother : her baby is always syphilitic so, allow feeding and give a course of penicillin for 2 weeks.

B- Tuberculous mother :

1- The mother receives anti T.B drugs

2- The mother uses mask during feeding.

3- The baby receives prophylactic INH 10 mg/kg/d.

4- Perform tuberculin test at **3 months**

If

Negative	Positive	Positive
Vaccinate the baby with INH resistant BCG and INH can be stopped	Without physical or radiologic evidence of T.B → continue INH till 9 months	With physical or radiologic evidence of T.B → treated as T.B case

C- Maternal viral hepatitis B :

i. Infant born to HbsAg positive mothers: give HBV vaccine and immunogloblin immediate after birth (within the 1st 24 hours)

ii. If mother catches infection during nursing: give accelerated protocol of immunization (0,1,2)

D- Maternal HIV infection :

WHO recommends:

i. In developed counties: stop breast feeding

ii. In developing counties: continue breast feeding unless safe formula is available.

E- Mother with psychosis or mania :

Mother can lactate under supervision.

II- Infant Causes

1. Temporary

1. Breast milk jaundice (withhold breast milk for 24-48 hours).
2. Respiratory distress (to avoid aspiration).
3. Very low birth weight (< 1.5kg or < 32 weeks); but can be fed with expressed breast milk with nasogastric tube

2. Permanent

1- Milk protein allergy : extremely rare.

C/P - Colic ,vomiting, diarrhea
- May be bloody stool or occult blood in stool.

Treatment - Hypoallergenic milk

2- Lactose intolerance :

Due to - Lactase deficiency ; primary or secondary to gastroenteritis

C/P - Accumulated lactose in intestine leads to:
* Fermentation → abdominal distension ,colic &vomiting
* Osmotic diarrhea → reducing substance in stool.
* Change to lactic acid → acidic motions → perianal soreness → stool pH < 5

Treatment - Lactose free formula

3- Galactosemia: Autosomal recessive disorder

Normally : Lactose $\xrightarrow[\text{enzyme}]{\text{Lactase}}$ glucose + galactose -1-Phosphate.

Galactose –1-Ph $\xrightarrow[\text{Uridyle transferase}]{\text{Galactose 1 phosphate}}$ glucose.

In galactosemia : Defective last enzyme → accumulated galactose –1-Ph. leads to:
- Hypoglycemia → neonatal convulsions
- Chronic active hepatitis & cirrhosis
- Mental retardation
- Cataract

Diagnosis : Reducing substance in urine (galactose) **and** enzyme assay.

Treatment : Lactose free milk.

4- Phenyleketonuria: Autosomal recessive disorder

Normally : Phenylalanine $\xrightarrow[\text{hydroxylase}]{\text{Phenylalanine}}$ tyrosine & tryptophan .

In phenylketonuria : Defective phenylalanine hydroxylase enzyme leads to:
- Fair skin , hair and blue eyes
- Cerebral palsy
- Mental retardation.

Diagnosis : - Screening tests: Guthrie test and ferric chloride test
- Confirmatory test: elevated blood phenylalanine (> 20 mg/dl)

Treatment : Phenylalanine free milk (contain tyrosine).

Artificial Feeding

Indications

1- Complementary feeding (Breast feeds are completed by bottle feeds)
- Indicated when breast milk is not enough (scanty breast milk secretion)
- Precautions:
  - Breast milk should be given first, then the feed is completed by bottle.
  - The prescribed milk should be one of humanized milk formulas.

2- Supplementary feeding (some breast feeds are replaced by bottle feeds) for:.
- Working mother.
- Twin delivery (breast and bottle given to each baby alternatively)

3- Substitutive feeding (all breast feeds are replaced by bottle feeds)
- Absent breast milk secretion
- Maternal illness: making the mother unfit to feed her baby
- Infant illness: permanent contraindications (see before)

1. Fresh fluid animal milks

Types :
* Cow's milk → most commonly used worldwide.
* Buffalo's milk → most commonly in Egypt.
* Goat's milk
* Ass milk → near in composition to human milk.

Composition : see before

Disadvantages :

i. General: - Liable to contamination.
- Lack quantitative & qualitative balance of breast milk.

ii. Specific:

A. Drawbacks of Goat's milk:
1. low caloric value
2. low folic acid →↑ incidence of megalobalstic anaemia
3. high risk of brucellosis.

B. Drawbacks of cow milks:-
1. Higher incidence of diarrheal disorders due to milk-borne infections.
2. Allergies eg. atopic eczema & asthma.
3. Otitis media & respiratory infections.
4. High risk of iron deficiency anemia due to:
   - Low iron content.
   - Only 10% content of iron is absorbed (75% in breast milk).
   - Low lactoferrin content.
   - Occult blood loss due to heat labile protein.
   - Cow milk protein allergy.
5. High protein content in developmental period may cause:-
   - ↓ intellectual outcome.
   - ↑ incidence of diabetes.
   - Possible defect in renal functions.

Advantages: Goat's milk has: - More digested proteins → hypoallergenic
- More essential fatty acids

Sterilization of animal milks

By - boiling → modify protein but destroy vitamin C.
- pasteurization → modify protein & preserve vitamin C.
- autoclaving → only during milk borne epidemics.

Humanization of animal milks

Definition: Bringing animal milk as near as possible to human milk by:

1. Addition of boiled water according to age

Age	Boiled milk	Boiled water
0-2 months	1	1
2-4 months	2	1
4-6 months	3	1

2. Boiling of milk (modify proteins & fat).
3. Few drops of vitamin C.
4. Add 5 grams of sugar to each 100 ml.

* Homogenization: milk is passed under pressure from fine holes → break large fat globules
* Peptonization: partial predigestion of proteins.

2. Evaporated & condensed milks

Definition

* Evaporated milk :Water is partially removed. So diluted 1:1 with water before use.
* Condensed milk: is evaporated milk to which sugar is added in high concentration, it is not suitable for infant feeding.

Advantages

1- Remain sterile in its can for months without refrigeration.
2- Casein curds & lactalbumin are smaller and softer so less allergenic than fresh milk
3- Can be fed in higher concentrations than usual.
4- The caloric value of each ounce is 40 calories.
5- Vitamin D is usually added.

3. Dried powdered milks

* Based on cow milk in most cases
* Reconstituted by dissolving them in water in a ratio of 1:7

Advantages

1- Can be modified according to the infant needs.
2- Fortified with vitamins & minerals.
3- Easier to digest due to fine curd.
4- Kept for a long time in its can
5- Can be used where fresh milk is not available.

Types

Formulas for healthy infants	Formulas for diseased infant
✧ Humanized milks ✧ Half cream milks ✧ Full cream milks	✧ Predigested formulas ✧ Lactose free milks ✧ Hypoallergenic milk ✧ Premature formula ✧ Phenylalanine free formula ✧ Low salt milks ✧ Acidified milks ✧ Protein milks

1- Humanized milks

Modifications : Modified to be very similar to breast milk :
- Protein and electrolyte content are reduced
- Carbohydrate content is increased .
- Fat is replaced by vegetable oils increasing poly unsaturated fat
- Vitamins (especially vitamin D & C) are added
- Calcium: phosphate content reduced and ratio adjusted
- Trace minerals are added particularly Iron , copper and zinc.

Indications : - Healthy infants during the first 6 months of life.
- Mild degrees of malnutrition.

Examples : - Lactogen ,Bebelac1, Nan, Enfamil ⇒ 1 spoonful(4gm) for each 30 ml water.
- Similac , S26 , S26 Gold ⇒ 1spoonful (8gm) for each 60 ml water.

2- Half cream milks

Modifications : - Half of the fat content is removed.
- Sweetened → for good taste.

Indications : - Feeding the babies who refuse humanized milk.

Example : - Bebelac Z 12.

3- Full cream milks

Modifications : - Unmodified whole milk

Indication : - Healthy infants above age of 6 months & older children

Example : - Nido.

4- Predigested formula

Modifications : - Proteins in the form of protein hydrolysates.
- Fat in the form of medium chain triglycerides.

Indications : - Persistent diarrhea. - Malabsorption

5- Lactose free milk

Modification : - Lactose is replaced by other sugar (sucrose or glucose)
Indications : - Lactose intolerance.
- Galactosemia
Examples : - Bebelac FL, Isomil , Nursoy

6- Hypoallergenic milk

Types : - Soy protein based formula(also lactose free).
- Casein hydrolysate based formula.
- Evaporated goat's milk.
Indications : - Cow or breast milk protein allergy.
- Some cases of malabsorption

7- Preterm infant formula

Modification : - Higher protein ; Whey to casein ratio is 60:40.
- Lower lactose (pre term have less lactase enzyme in their GIT), instead they contain glucose polymers.
- Medium chain triglycerides as 40-50% of their fat.
- More calories: 80 calories /100 ml
- Extra vitamins as vitamin E, and minerals are added.
Indications : - Preterm infant until approaches term
Examples : - S26 low birth weight formula , Enfalac premature formula.

8- Phenylalanine free milk

Indications : - Phenyleketonuria
Example : - Phenolac

9- Low salt milk

Indications : - Nephritis , heart failure , nephrogenic diabetes inspidus
Example : - SMA

10- Acidified milk

Modifications : - Addition of lactic acid or lactic acid producing lactobacillus
Value : - GIT disinfection & enhance calcium absorption
Drawbacks : - Acidosis - Bad taste - Constipation

11- Protein milk

Modifications : - High protein content (4 gm%)
Indications : - Used as additive to formula for: - Malnutrition
- Healthy infants above 6 months.
Drawbacks : - Excess urea production - Hard digestion - Expensive
Example : - Sustagen

Program of Artificial Feeding

1. Decide type of milk:

- Dried powdered milk (e.g. humanized type for healthy infant)
- Fresh fluid animal milk(not preferred).

2. Determine the amount of milk needed by :

a- Age method :

- Valid only for healthy full term .
- Amount of milk (ml/feed) = Age in days × 10
  Age in weeks × 10 + 70
  Age in months × 10 + 100

b- Caloric(weight) method :

- Valid for both the healthy and diseased
- More accurate than age method
- Calculation:
  - ⌖ Infant normal needs 110 cal/kg/d.
  - ⌖ Milk contain 67 cal/per 100 ml.
  - ⌖ So total daily need of milk = $\frac{100}{67}$ × (110 × body weight).
  - ⌖ This amount is divided into feeds.

3. Number of feeds per day :

According to age;

- ☞ 0-4 months → every 2-3 hours (≈ 6 feeds).
- ☞ 5- 8 months → every 4 hours (≈ 5 feeds).
- ☞ 9-12 months → every 5 hours (≈ 4 feeds).

4. Formula (concentration of milk).

i- Formula of dried powdered milks:

- ⌖ One measure of 4 gm diluted by 30 mL boiled water e.g. Bebelac, Nan.
- ⌖ One measure of 8 gm diluted by 60 mL boiled water e.g. Similac, S 26.

ii- Formula of fresh fluid animal milk depend on age:

See the 4 steps of humanization of fresh fluid animal milk (see page 23)

Weaning

Definition:

- Introduction of semisolid and solid foods besides breast milk or formula.
- The term complementary feeding is preferred to weaning.

Values

1. Increase energy, vitamin and mineral density of the diet to match infant needs that can not be fulfilled by breast milk alone.
2. Train the gastrointestinal tract and train the baby to use cup and spoon.
3. Increase social interaction with carers
4. Encourage tongue and jaw movements in preparation for speech

Guidelines of WHO & American academy of pediatrics for weaning:

1. Exclusive breast feeding for the 1st 6 months of life
2. Introduce complementary foods from 6 months while continuing breast feeding.
   Rational: beyond 6 months there is :
   - Maturation of digestive enzymes for starchy foods occur
   - Decline of minerals and vitamin stores (e.g. Iron , zinc, vit D)
   - Caloric value of breast milk become inadequate.
3. Continue frequent on demand breast feeding until 12 – 24 months of age.
4. Safe foods:
   - Serve foods immediate after preparation
   - Use clean spoons ,cups & utensils
   - Avoid bottle feeding
5. Amount:
   - Foods are introduced once at a time at weekly intervals before new food is given
   - Stepwise weaning ; small amount of one food is started and increased gradually.
6. Food consistency:
   - Start with pureed, mashed and semisolid foods
   - Gradually increase consistency as the child get older
   - By 12 months most children can eat family foods
7. Feeding manner:
   - Feed slowly, do not force; many trials may be needed as spitting can occur.
   - If feeding refused , try different food combinations, tastes & attractive presentation.
8. Frequency: Start with 2-3 times per day at 6-8 months then increase gradually
9. Feeding during illness:
   - Increase fluid intake (frequent breast feeding)
   - Give soft , appetizing , favorite foods
   - Increase food intake after the illness.

Weaning program

Rules:

- ⊕ Meat , fish, poultry or eggs should be eaten as often as possible.
- ⊕ Supplement with vitamins A , D , C.
- ⊕ Supplement with minerals: iron , zinc and calcium

How to start:

- ✧ Cereals , pureed rice given first
- ✧ Vegetables soups and fruits next
- ✧ Followed by stained meats, fish
- ✧ Finally egg yolk
- ✧ Whole cow milk should not be given below 1 year while milk products as cheese and yogurt may be used from 6 months onwards.

Limit :

- Puddings and desserts
- Phytate (to enhance mineral absorption)
- The amount of offered juice(no more than 240 ml per day)

Avoid:

- Canned foods
- Salt and spices
- Use of whole cow milk below 1 year
- Use of skimmed milk below 2 years
- Excess sugary drinks
- Chocking foods(e.g. nuts, grapes, raw carrots)
- Allergenic foods e.g. Egg white

Problems with weaning

1- Allergies → may follow some new foods e.g eggs, ...

2- PCM → sudden weaning on starchy foods → Kwashiorkor (KWO).

3- Colics → especially with → excess sugary fluids.
→ early aggressive weaning.

4- Diarrheal disorders → gastroenteritis due to contaminated foods.

5- Dental caries: associated with excess carbohydrates and bottle feeding.

6- Delayed weaning may predispose to: - Marasmus
- Iron deficiency anemia.
- Rickets.

7- Some Diseases may manifest during period of weaning :e.g. - Favism.

Nutrition

Normal Nutritional Requirements

i. Caloric requirements for different ages:

Age in years	Calories/kg /day
Below 6 mo	115
6 mo-1 year	105
1-3	100
4-6	90
7-9	80
10-12	70

N.B: Beyond one year ; caloric requirements ↓ by 10 cal / kg every 3 years

ii. Protein requirements for different ages

Age in years	gm/kg /day
Below 1 year	2.5 gm/kg/day
1- 5	2.0 gm
6- 10	1.5 gm
11-14	1.0 gm

iii. Water requirement:

Age in years	ml/kg /day
Below 1 year	150
1- 3	125
4- 6	100
7- 12	75

iv. Carbohydrate (CHO) requirements:

- 10 gm/kg/day.

N.B :

* Each 1gm fat gives 9 calories
* Each 1gm protein gives 4 calories
* Each 1gm carbohydrate gives 4 calories.

Abnormal Nutrition:

1- Undernutrition: Chronic caloric deficiency e.g marasmus.

2- Overnutrition : Caloric excess e.g obesity.

3- Malnutrition : Deficiency of one or more elements with normal or even increase total caloric intake e.g protein deficiency & vitamin deficiency.

Protein Caloric Malnutrition (PCM)

[Protein Energy Maluntrition (PEM)]

Classifications

1- Wellcome classification : Depends on weight for age & presence of edema.

Actual wt / normal wt for age	Symmetrical Oedema	Diagnosis
> 80%	+ +	Nutritional oedema or KWO
60-80%	- -	Simple underweight
60-80%	+ +	Kwashiorkor (KWO)
< 60%	- -	Marasmus
< 60%	+ +	Marasmic KWO

Other forms of protein energy malnutrition:

1- Incomplete KWO (pre KWO).

2- Nutritional dwarfism

2- Waterlow classification : Depends on growth charts in reference to 50th centile.

Definition	Diagnosis
Weight for height/length %	
89-80	Mild wasting
79-70	Moderate wasting
< 70	Severe wasting
Height/length for age %	
94-90	Mild Stunting
89-85	Moderate Stunting
< 85	Severe Stunting

Kwashiorkor (KWO)

(Edematous PCM, Red Baby)

Definition: Type of malnutrition in which there's:

1. Acute protein deficiency.
2. Normal or even high caloric intake.

Kwashiorkor means: - Deposed child, who no longer suckled.
- A disease the older child catches when a younger baby is born

Causes

1- Primary (dietetic) KWO:

Occur more frequently with poor, ignorant mothers due to:

- Faulty weaning on starchy, carbohydrate diet.
- Depressed child → KWO occur in the 1st baby when a 2nd is born due to:
  - Sudden weaning on starchy (sugary) food.
  - Maternal deprivation.

2- Secondary KWO

The following are predisposing factors rather than actual causes:

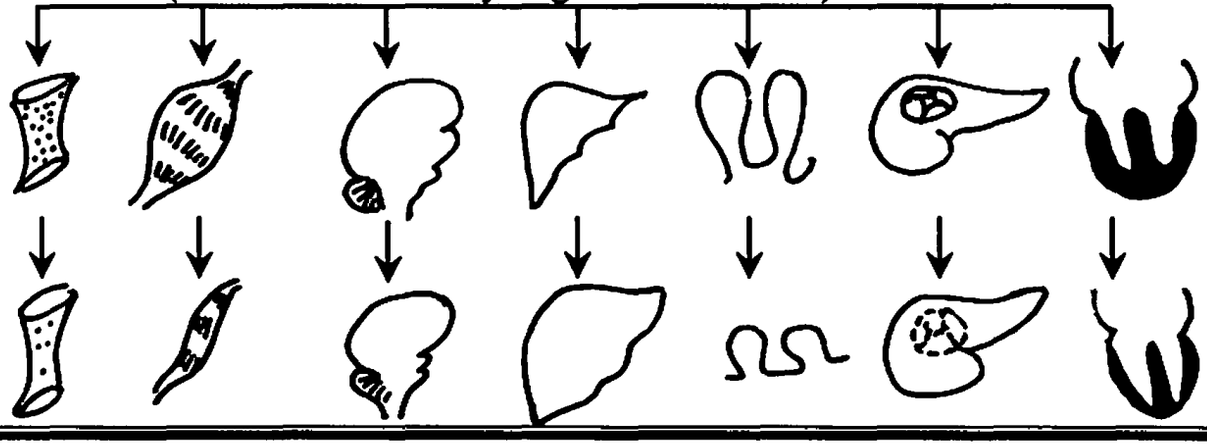
- Pertussis → due to recurrent vomiting.
- Chronic diarrhea → due to protein loss in stool.
- Measles → due to complicating enterocolitis.
- Parasitic infestation e.g. Giardia lamblia.

} Along with associated anorexia & faulty food restriction

Pathology

Acute protein deficiency leads to:

1- Decreased plasma proteins.
2- Brain → slow atrophy (but reversible with treatment).
3- Delayed bone growth, with a reduction of total bone mass and osteoporosis
4- Skeletal muscles → degenerative changes to compensate for ↓ plasma proteins.
5- Liver → fatty infiltration (steatosis) but usually no necrosis nor cirrhosis.
6- Gastrointestinal tract → atrophy of villi → ↓ digestive & absorptive enzymes.
7- Pancreas → atrophy of acini → ↓ digestive enzymes → steatorrhea.
8- Heart → degenerative changes in cardiac muscles → weakness
(heart is small in early stages → dilated late)



Clinical picture

Target age : 6 months - 2 years

I. Constant features of KWO

1.Edema

- Starts in dorsa of hands & feet → gradually increases to involve face, arms & thighs.
- Facial edema produce prominent cheeks → moon face appearance.
- Edema is bilateral, pitting & painless.
- Usually there is no ascites nor pleural effusion.

Due to:

- Hypoalbuminemia → reduced plasma osmotic pressure
- Salt & water retention due to decreased inactivation of aldosterone by the fatty liver
- Increased activity of ADH → water retention
- Weak capillary support → increased permeability.

Recently edema is attributed partially to extensive membrane dysfunction due to lipid peroxidation due to: - Increase pro-oxidants (e.g. free iron).
- Decrease antioxidants (↓ vit E, vit A, glutathion).

2. Mentality changes

- The baby looks apathetic, miserable, disinterested in his surroundings with marked anorexia

Due to: - Reduced aromatic amino acids (phenylalanine, tyrosine & tryptophan).

↓

reduced serotonine, nicotinic acid & adrenergic neurotransmitters

- Maternal deprivation.

3. Growth retardation

- Failure to gain weight followed by weight loss → loss of 20 - 40% of body weight

-Weight loss may be masked by: - Oedema.
- Preserved subcutaneous fat (due to intact calories).

- Length is much less affected as KWO is acute disease.

4. Muscle wasting

Due to: Protein deficiency

Detected by:

- Decreased mid arm circumference → 12-14 cm in subclinical KWO
  → < 12 cm in clinical KWO.
- Decreased chest circumference.
- Palpation of biceps & deltoid → muscles are thin, atrophic & weak ; however it is not as severe as in marasmus.

II. Variable Features of KWO

1. Hair changes

- Characters: - Hair is dry, brittle, sparse, easily epilated
- Color changes: - Progressive lightening of hair
  (black → brown → orange → yellow)
- Flag sign: - Alternating bands of light color & normal color
  - Occurs in long haired with multiple relapses.
- Due to: - Sulphur containing amino acids (e.g tyrosine) deficiency
  - Copper deficiency due to decreased ceruloplasmin.
  (Both are essential for melanin synthesis).

2. Skin changes

- Starts as dry scaling of the skin → erythema → hyperpigmentation & desquamation
  (Giving picture of flaking paint dermatosis or cobblestone appearance).
- There may be fissuring & ulcerations.
- Skin infection is common due to: - Oedema fluid → favours infection.
  - Fissuring → provides portal for organisms.
- Sites : Pressure areas (back, buttock, knees , ankle)and irritated areas (groin & perineum).
- Due to: - Vitamin A deficiency
  - Essential fatty acids deficiency.
  - Zinc deficiency
  - May be suprarenal gland dysfunction.

3. GIT manifestations

i- Hepatomegaly

- The liver may be palpable; soft to firm, smooth, rounded border.
- Size may increases at the start of treatment if high caloric diet is used due to accumulation of glycogen before disposing fat.
- Hepatomegaly is reversible with treatment.
- Usually there is no cirrhosis as it is acute disease and no hepatocyte necrosis.
- Hepatomegaly is due to fatty infiltration due to:
  - Decreased lipotropic factors.
  - Increased fat synthesis due to high carbohydrate diet .

ii- Diarrhea: may be due to:

- Infectious: due to gastroenteritis
- Non infectious : due to malabsorption e.g. with lactose intolerance.

iii- Abdominal distension may be due to:

- Hypokalemia.
- Malabsorption.
- Toxic ileus (with infections).

4. **Anemia:** May be due to: - Iron deficiency → hypochromic microcytic.
   - Protein deficiency → normochromic normocytic
   - Folic acid & B_{12} deficiency → megaloblastic.
   - Prothrombin deficiency → hemorrhagic anemia

5. **Vitamin deficiency :**

1. Vitamin A deficiency: (very common) manifested by:
   - Eyes : xerosis, Bitot spots, keratomalacia & corneal ulcers.
   - Mouth : stomatitis.
   - Weak epithelium ; respiratory & gastrointestinal → more susceptible to infection.
2. Vitamin B_2 deficiency → cheilosis, angular stomatitis.
3. Vitamin D deficiency :usually it is not manifest due to arrested growth but there may be atrophic rickets in which manifestations of osteoid overgrowth are absent.
4. Vitamin K deficiency → bleeding tendency.

Complications

1- Dehydration: Due to gastro enteritis & anorexia.

2- Intercurrent infection:

Due to : - Defective immune system with resultant 2ry immunodeficiency

Pattern : - Gastro enteritis ;bacterial, viral or giardiasis
- Pulmonary infections particularly tuberculosis & bronchopneumona
- Skin infections
- Oral moniliasis : Painful mouth interferes further with dietary intake.

3- Septic shock

4- Electrolyte disturbances:
- Dilutional hyponatremia
- Hypokalemia due to loss in diarrhea , reduced intake & aldosterone effect
- Hypocalcemia & hypomagnesemia ⇒ may lead to tetany.

5- Blindness :due to keratomalacia secondary to severe vitamin A deficiency

6- Hypothermia (temperature<35.5 °C) due to:
- Serious systemic infection
- Hypoglycemia
- Edema favors heat loss.

7- Hypoglycemia(blood glucose <50mg/dl):
- Commonly associated with serious systemic infection.
- Manifestations: - lethargy, convulsions , hypothermia, even death

8- Heart failure due to:
- Severe anemia.
- Volume overload.
- Weak myocardium ⇒ dilated cardiomyopathy.

9- Hemorrhage (bleeding tendency) due to:

- Vitamin K deficiency.
- Disseminated intravascular coagulation (DIC).

Differential diagnosis :From

1- Other causes of generalized oedema ⇒ Cardiac, Renal, Hepatic & Angioneuritic

2- Other skin lesions:

- ✧ Acrodermatitis enteropathica due to Zinc deficiency
- ✧ Pellagra
- ✧ Napkin dermatitis due to → soiling, monilia, contact or acidic motions.
- ✧ Addison disease (adreno cortical insufficiency) → triade of:
  - Hypotension & hypoglycaemia (↓ cortisol).
  - Diarrhea & polyuria (↓ aldosterone).
  - Hyperpigmentation in flexural areas (↑ ACTH).

Investigations

i. Laboratory data of kwashiorkor:

1- Confirm diagnosis :

1- Plasma proteins:

- Decreased total plasma proteins (normal 6-8 gm/dl).
- Decreased albumin < 2.5 gm / dl (normal 3.5 – 5 gm/dl).
- Decreased α & β globulin (γ globulins may increase due to infections).
- Decreased carrier proteins e.g ceruloplasmin, transferrin & haptoglobin
- Decreased enzymes e.g amylase, lipase, alkaline phosphatase.

2- Non essential / essential amino acids **> 3**

3- Low urinary urea & hydroxyproline to creatinine ratio.

2- For effect :

1. On fat metabolism:
   - Increased free fatty acids (due to excess carbohydrate intake)
   - Decreased cholesterol (due to decreased fat mobilization)
2. On CHO metabolism:
   - Fasting hypoglycemia.
3. Mineral metabolism : Copper and zinc deficiencies are frequent
4. Tissue effects:
   - Diminished pancreatic enzymes activity but reversible with treatment
   - Delayed bone growth, with reduced total bone mass and osteoporosis

3- For complication :

- CBC for anemias.
- Sepsis workup in suspected cases including tests for tuberculosis, increased ESR & leucocytosis.
- Electrolytes: Na, K, Ca, Mg.

ii - Diagnosis of early subclinical cases:

- Decreased serum albumin between 3-2.5 gm / dl.
- Non essential / essential amino acids between 2-3 (normally ≤ 2)
- Decreased serum prealbumin , retinol binding protein & transferrin ⇒ all have shorter half life, so rapidly changes with nutritional disorders.

N.B

⊕ Other causes of hypoproteinaemia to be excluded:

- Hepatic edema → check liver function tests.
- Nephrotic syndrome → check 24 hours urine protein.
- Protein losing enteropathy → check elevated α_1 antitrypsin in stool.

⊕ KWO may predispose to pleural effusion due to associated immunodeficiency → pneumonia with effusion (esp. tuberculosis)

⊕ Ascites may rarely occur in kwashiorkor with:

- Septic peritonitis.
- Nutritional recovery syndrome(see later).

Incomplete KWO (pre KWO):

The patients shows all constant features of KWO except oedema & all variable features except skin changes.

Phenomena which may occur during treating KWO

i- Hypokalemia :

Hypokalemia is already present ⇒ aggravated by glucose infusion used in treating hypoglycemia.

ii- Circulatory overload:

There's already salt & water retention ⇒ with infusion of large doses of blood or plasma →↑ plasma osmotic pressure → shift of fluid from interstitial compartment to intravascular compartment → volume overload and even heart failure.

iii- Initial weight loss :

May occur at the start of treatment due to absorption of edema fluid.

iv- Nutritional recovery syndrome may rarely occur due to either:

A- Excess caloric intake → excess glycogen deposition in the liver before getting rid of excess fat → hepatomegaly may increase at the start of treatment ,then regress gradually.

B- Excess protein intake > 6 gm/kg/d → liver is exhausted by protein metabolism ⇒ excess ammonia load on the liver leads to:

1. Hepatic encephalopathy with lethargy, convulsions & coma.
2. Hepatocyte necrosis → liver cell failure with hepatomegaly, jaundice, ascites and even liver cirrhosis later on.

Marasmus

(Infantile atrophy or failure to thrive or non oedmatous PCM)

Definition: Chronic under nutrition in which there's deficiency of both proteins & calories.

Predisposing factors to marsmus

1- Ignorance regarding nutritional requirements , proper feeding and food hygiene.

2- Maternal malnutrition .

3- Low socio-economic status : As in rural areas .

4- Infections : e.g. measles and whooping cough .

5- Twins and preterms.

6- Order among siblings :Marasmus usually affects:

- The earlier (due to lack of knowledge) or
- The late order infant (due to lack of interest).

Causes

I- **Primary (Dietetic, Exogenous)** ⇒ target age: 6 months – 2 years
⇒ usually in low socioeconomic classes.
⇒ inadequate food intake due to

Low quantity	Poor quality
- Scanty breast milk in breast fed infants	- Prolonged breast feeding without supplementation
- Small amounts or number of feeds in artificially fed	- Diluted formula in artificially fed

II- **Secondary (Non dietetic; Endogenous)**

✧ Target age: may occur in older children

1. **Infant unable to feed:** due to e.g.:
   - Premature or debilitated infant(Sick)
   - Serious intra cranial damage.
   - Mental retardation(e.g.cerebral palSy).
   - Facial palSy.
   - Sleepy infant.
   - Severe problems of the nipple or breast.
2. **Gastrointestinal causes:**
   - Recurrent gastro enteritis / Chronic diarrhea .
   - Malabsorption syndrome due to e.g Cystic fibrosis, cholestasis , giardiasis
3. **Chronic infections**
   - Due to e.g Tuberculosis , empyema, chronic pyelonephritis,....
   - Mechanism:- Anorexia , parenteral diarrhea ,& hypercatabolic state

4. **Preterms and twins:** are more prone to maramsus due to :
   - Higher rate of growth
   - Susceptibility to infection .
   - Less fat stores
   - Weak suckling power
   - Limited capacity for digestion and absorption
5. **Congenital anomalies & malformations**
   - Neurologic : e.g. Cerebral palsy , mental retardation, floppy infant
   - Congenital heart diseases
   - Gastrointestinal e.g.: - Bilateral cleft palate
     - Gastroeosphageal reflux disease.
     - Congenital pyloric stenosis.
     - Herschsprung disease.
   - Renal anomalies (due to associated urinary tract infections & acidosis).
6. **Metabolic disorders e.g**
   - Lactose intolerance.
   - Galactosaemia.
7. **Psychological:** due to maternal neglect (child abuse)
8. **Endocrinal** e.g.:
   - Hyperthyroidism (due to hypercatabolism & diarrhea).
   - Hypothyroidism (due to poor feeding).
   - Diabetes mellitus.
   - Addison disease (due to chronic diarrhea & polyuria).
9. **Malignancies :** due to anorexia, hypercatabolic state & chemotherapy.
   e.g. - leukemias
   - Wilms.

Pathophysiology of marasmus

- **Basal metabolic rate (BMR)** = The calories needed to maintain life at complete physical and mental rest (necessary for life).
- In infants the daily caloric intake is consumed as follows: BMR
  - BMR 50 % ⇒ unavoidable
  - Physical activity 25 %
  - Growth 12 %
  - Loss and others 13 % ⇒ unavoidable.
- When there is caloric deficiency the first compensatory mechanism will be decrease physical activity and arrested growth. With advanced caloric deficiency the body utilizes his own tissues firstly fat then proteins to maintain BMR which results in marasmus.

Clinical picture

I- Symptoms: (4C)

1- Failure to gain weight followed by progressive weight loss(Cachexia)

2- Baby is usually hungry : irritable, Crying & sucking fingers.

3- Constipation is usually present but there may starvation diarrhea (greenish, scanty, offensive with mucus & debris)

4- May be features suggesting the Cause

II- Signs:

A- General examination: - weak slow pulse & hypotension,
- abdomen is scaphoid or distended

B- Protein deficiency manifestation:

1. **Body weight** is less 60% of normal for age without oedema.
   - Loss of 40% of body weight → 1st degree marasmus
   - Loss of 40-50% of body weight → 2nd degree marasmus
   - Loss of > 50% of body weight → 3rd degree marasmus
2. **Muscle wasting:** - muscle are sacrified to keep normal plasma proteins.
   - more severe than in KWO
   - detected by decreased MAC & chest circumference.

C- Caloric deficiency manifestation:

1. **Loss of subcutaneus fat**
   - Loss of fat from the Abdominal wall → 1st degree marasmus.
   - Loss of fat from the Buttocks & limbs → 2nd degree marasmus.
   - Loss of fat from the Cheeks (senile face) → 3rd degree marasmus (the buccal pad of fat is the last to be lost as it is unsaturated fat essential for suckling).

   Outcome:
   - Skin becomes thin, loose, wrinkled, thrown into folds especially on the medial aspect of the thighs.
   - Triceps skin fold thickness less than normal; (about 10 mm at 1 year)
2. **Hypothermia** due to
   - Loss of subcutaneous fat → excess heat loss.
   - Hypoglycemia → decreased heat production.
   - Septic shock.

D- Vitamin deficiency, anemia, hair & skin changes are less common than in KWO

N.B

- Loss of subcutaneous fat → prominent normal costochondral junctions → called false rosaries.
- Rickets is a disease of growing bones so, in PCM it is usually absent due to arrested growth. However, severe vitamin D deficiency in prolonged PCM may manifest as atrophic rickets.

Complications

i. As in kwashiorkor :

1- Dehydration
2- Intercurrent infections
3- Oral moniliasis : In severe cases, mouth gangrene (cancrurm oris) may occur.
4- Septic shock
5- Electrolyte disturbance especially hypokalemia
6- Blindness
7- Hypothermia
8- Anemic heart failure.
9- Hypoglycemia.
10- Hemorrhagic tendency

ii. Frequent in marasmus :

1- Atrophic ulcers occur over bony prominences .
2- Edema: may occur with development of marasmic kwashiorkor
3- Purpura due to:
   - Severe impairment of capillary permeability
   - Platelet deficiency
   - Disseminated intravascular coagulopathy due to dehydration, toxemia, acidosis
4- Muscle fibrosis in advanced cases which my cause ankylosis of the joint.
5- Secondary lactose intolerance due to atrophy of mucosa of small intestine with subsequent lactase deficiency in the.

iii. Death : May occurs in severe malnutrition due to:

- Hypoglycemia
- Shock of septicemia or dehydration.
- Heart failure.
- Hypothermia
- Hyponatremia

Investigations

Value ⇒ mainly for detection of the cause in secondry marasmus

1- Biochemical changes in marasmus

Blood : - Fasting hypoglycemia (due to reduced glycogen stores in the liver).
- Plasma proteins slightly reduced.(due to chronic degradation of muscles to keep plasma proteins)
- ↑ Gamma globulins with infections.

Urine: - Ketonuria (due to fat hypercatabolism).
- Increased creatinine (due to muscles hypercatabolism)

2- For complications ⇒ as in KWO

3- Search for the cause (if 2ry marasmus is suspected)

1- Stool analysis for:

- Parasites
- Stool cultures
- pH
- Reducing substances

2- Urine analysis :

- Culture for urinary tract infection
- Glucosuria in diabetes mellitus.

3- Abdominal sonography.

4- Organ function tests (renal & liver functions tests)

5- Others :

- Chest x-ray
- Tuberculin test : is commonly negative due to secondary immunodeficiency
- Echocardiography for suspected congenital heart diseases.
- Barium study & endoscopy for suspected GIT diseases
- Metabolic screen

Prognosis of PCM (which is more worse?)

Marasmus: prognosis is poor with :

1. Young age.
2. Poorly controlled secondary causes.
3. Advanced muscle fibrosis.
4. Disseminated intravascular coagulopathy

KWO: prognosis is poor with:

1. Young age
2. Marked anorexia.
3. Complications.

N.B: Marasmic KWO:

- Weight < 60% of expected for age with oedema.
- It occurs mainly in marasmic child fed on carbohydrate diet only without adequate protein → appearance of oedema → marasmic KWO

N.B: Failure to thrive :

♦ It is defined as either:

- A child growing below 3rd or 5th percentile **Or**
- A child with growth has crossed 2 major growth percentiles in short time.

♦ Etiology & management : Same as marasmus.

Management of PCM

A. Prevention

i- Family measures:

1- Encourage breast feeding.
2- If breast milk is unavailable; use cup and spoon feeding instead of bottle feeding to avoid contaminated feeding and repeated diarrhea.
3- Advice mothers about proper weaning (gradual from the age 4-6 months, contain all essential elements).
4- Advice against food suspension & starvation during diarrhea.
5- Regular monitoring of growth by growth curves to pick early malnutrition which appear as flatting of weight curve.
6- Vaccinate against tuberculosis, pertussis, measles.
7- Appropriate treatment of infections.

ii-Community measures:

1- Safe water supply
2- Safe sewage disposal system
3- Safe food supplies.

} All help prevent diarrhea which is a leading cause of PEM.

4- Use vegetable protein mixtures e.g. beans to compensate for animal protein.
5- Health education through mass media.
6- Upgrade standard of living.

B. Curative

Hospitalization : Phases of treatment include:

- ✧ The 1st week: Stabilization phase; include emergency treatment & slow feeding.
- ✧ From 2nd week to the 6th week :Rehabilitation phase ;include advancement of feeding and supportive treatment.
- ✧ From 7th week to 26th weeks : Follow up phase

I. Emergency treatment (In the 1st 24-48 hours) for:

Hypoglycemia: - Glucose l 0% 2 –5 ml/kg I.V. then 50 ml by nasogastric tube
- Antibiotics for serious infections.
- Frequent feeding every 2-3 hours day & night.

Dehydration:

1- Start with lactated ringer or half strength saline for severe dehydration.
2- Oral rehydration solution.(preferably ReSoMal)
3- Continue breast feeding or starter formula F-75

Anemia: blood transfusion

- Indications: if
  - Heamoglobin < 4 gm/dl or
  - Heamoglobin between 4-6 gm/dl with respiratory distress.

- Fresh whole blood transfusion for severe anemia: 20 ml/kg for marasmus and 10 ml/kg for KWO.
- Fresh packed RBCs for anemia with heart failure:10 ml/kg for marasmus and 5 ml/kg for KWO(doses are halved in KWO to avoid circulatory overload)

Hypothermia

- Keep dry and wrap with warmed blankets
- Radiant warmer.
- Treat hypoglycemia & serious systemic infections.

Electrolytes correction:

- Hypocalcemia → Ca gluconate 10% slow I.V.
- Hypomagnesemia → Mg sulphate I.M.
- Hypokalemia → add extra potassium 3-4 m mol/kg/day

Infections: - Cotrimoxazole or Ampicillin /Garamycin

II. Dietetic treatment

1- Route:

- Oral is preferable.
- Nasogastric tube for cases with severe anorexia ,severe stomatitis or vomiting

2- Amount:

- Calculated by caloric method
- Start with 80-100 cal./kg/day then
- Increase gradually up to 150-220 cal/Kg/day for severely malnourished

3- Protein intake:

- Start with 1 gm/kg/d increased gradually to reach 4 gm/kg/d.

4- Frequency:

- Small frequent feeds every 2-3 hours day and night increased gradually over 1-2 weeks in strength & amount as appetite improve.

5- Type of food:

Unweaned infant	Weaned infant or above 6 months
- Continue breast feeding - Humanized milks supplement can be used for early cases - If there's lactose intolerance give lactose free milk - Protein milk can be used as protein additive.	1. Formula diets: - F-75 (75 cal/100ml) for initial feeding. - F-100 (100 cal/100ml) is used later 2. Other high protein diets: - Animal protein → yogurt, cheese. eggs, chicken, meat, fish, - Plant protein → beans & lentils.

III. Supportive treatment:

1. Vitamins especially.
   - Vitamin A
   - Vitamin D : avoid development of rickets during period of rapid growth.
   - Vitamin B complex
2. Minerals especially.
   - Zinc and Copper
   - Iron (should be used after the first week of treatment).
3. Plasma or albumin for KWO.

IV. Treat of the cause in secondary marasmus

V. Emotional support

N.B

Values of fresh whole blood transfusion in PCM

- Red cells → correct anemia.
- Plasma proteins → correct hypoproteinemia.
- Platelets & coagulation factors → correct bleeding tendency.
- Plasma salts → correct shock.
- Contain immunocomptent cells.

Criteria of successful treatment of PCM

1- Improved appetite.
2- Initial weight loss in oedematous cases (Decline of oedema).
3- Gradual increase in body weight >10 gm /kg/day.

What is refeeding syndrome ?

- May occur during the 1st week of starting to reefed severely malnourished
- Serum phosphate declines to below 0.5 m mol/l due to intracellular shift
- Manifested by weakness, arrhythmias, rhabdomyolysis , lethargy , even death
- Prevention :monitor serum phosphate during refeeding and correct deficiency

Other forms of PCM

A. Nutritional dwarfism

- Due to inadequate balanced diet.
- Child is underweight & under sized but his muscles & subcutaneous fat are proportional to body size.
- Weight for age & length for age are retarded to the same extent
- No loss of subcutaneous fat (differentiate it from marasmus)

B. Simple underweight

- A form of PCM which is commonly missed.
- Diagnosed by regular monitoring of weight → flattening of weight curve is the earliest sign of subclinical PCM.

Childhood Obesity

☆ Obesity : an excess accumulation of body fat

☆ Measurements: The body mass index (BMI) is commonly used:

⊕ BMI = weight (kg) divided by the square of height (meters)

BMI percentile for age	Weight status
< 5th percentile	Under weight
5th – 84th percentile	Normal weight
85th – 94th percentile	At risk over weight
> 95th percentile	Over weight

⊕ Beyond 18 years:

➢ BMI > 30 → Obese.

➢ BMI >25 → Overweight

Etiology

A. Exogenous obesity (excessive high caloric intake) may be due to:

- Excessive food intake: psychological disturbances, hyperinsulinism.
- Leptin resistance: secreted hormone ,acts on adipocyte the hypothalamus suppressing food intakes.
- Genetic predisposition
- The chronic offering of a bottle for soothing a crying infant .
- Lack of exercise and eating during televsion watching

B. Endogenous obesity (endocrinal, metabolic, malformation syndromes) e.g.

- Alstrom syndrome
- Bardet biedle syndrome
- Cushing syndrome
- Muscle Dystrophy
- Prader Willi syndrome

Clinical picture

A. General features (the only features in exogenous obesity) :

1. Usually heavier and taller and bone age is advanced than peers.
2. Fine facial features.
3. Adipose mammary regions in boys.
4. Pendulous abdomen with white striae .
5. External genitalia of boys appear as if small
6. Puberty may occur early.
7. The extremities: - Genu valgum is common.
   - Small hands and tapering fingers.
8. Significant social and psychological stresses.

B. Specific features in endogenous obesity : may be

- Dysmorphic features
- Developmental delay
- Delayed bone age and short stature
- Delayed puberty

Comorbidities

Disorder	Testing
- Asthma	- Pulmonary function tests
- Bone disease	- Hip and knee x ray
- Gall bladder Calculi	- Ultrsound
- Diabetes mellitus	- Glucose profile , insulin level
- Dyslipidemia	- Lipid profile
- Elevated blood pressure (hypertension)	- Serial testing
- Fatty liver	- Ultrsound
- Obstructive sleep apnea	- Poly somnography
- Pseudo tumor cerebri	- CT , MRI

Prevention and treatment

1. Modification of diet and caloric content. Very low-calorie diets are inappropriate because they may impair growth
2. Appropriate exercise programs.
3. Behavior modification for the child.
4. Psychologic support.

Minerals Requirements

	Calcium	Iron	Magnesium	Phosphorus
Daily need	800mg	10-15 mg	100 mg	600 mg
Sources	- Milk, cheese - green vegetables	- Liver, meat - Vegetables, apple	- Milk, meat - cereals, legumes	- Milk, proteins, milk products
Functions	- Bone & teeth - Muscle contraction - Nerve transmission - Blood coagulation - Cardiac action	- Haemoglobin. - Myoglobin. - Oxidative enzymes as catalase & cytochrome oxidase	- Bone & teeth - Conversion of proparathormone to parathormone	- Bone & teeth - Structure of muscles - CHO and fat metabolism
Deficiency	- Rickets - Tetany - Delayed teething - Osteomalecia - Osteoporosis	- Iron deficiency anaemia	- Tetany; associated frequenctly with hypocalcemia and hypokalemia.	- Rickets

Copper:

- ⌖ Disturbed metabolism in Wilson and Menkes syndrome.
- ⌖ Deficiency leads to refractory anemia, osteoporosis, neutropenia, ataxia, depigmentation and increased serum cholesterol.
- ⌖ Excess leads to cirrhosis.

Fluorine :

- ⌖ Deficiency leads to dental caries.
- ⌖ Excess leads to fluorosis : mottling of teeth with intake of > 4-8 mg/day.

Iodine:

- Deficiency leads to simple goiter, endemic cretinism.
- Excess medicinally may cause goiter.

Selenium :

- ✧ Sources : Vegetables, meats.
- ✧ Deficiency leads to: - Muscle disease in animals
  - Kashan cardiomyopathy
  - Arthritis.

Zinc:

- ✧ Sources : meat, grain, nuts, cheese.
- ✧ Deficiency leads to: - Growth retardation (Dwarfism)
  - Iron deficiency anemia
  - Hepatosplenomegaly
  - Hyperpigmentation
  - Hypogonadism
  - Acrodermatitis enteropathica
  - Dysfunction of immune system
  - Poor wound healing.
- ✧ Excess leads to gastrointestinal upsets & copper excess

Vitamin Metabolism

Water soluble vitamins	Fat soluble vitamins
♦ B complex and C	♦ ADEK
♦ Not stored in the body so not toxic	♦ Stored in the body so may be toxic.

Water Soluble Vitamins

Vitamin B_1 (Thiamine)

Value - Essential for carbohydrate metabolism

Deficiency

1. Cardiac ⇒ Cardiomyopathy → congestive heart failure with generalized edema (wet Beri Beri).
2. Neurologic ⇒ Dry Beri Beri:
   - Peripheral neuritis
   - Deep sensory loss
   - Dysphonia (recurrent laryngeal nerve paralysis)
   - Late; confusion, ataxia, psychosis (Wernick's Korsakoff syndrome)

Diagnosis
- Low erythrocyte transketolase
- Therapeutic trial → dramatic response

Treatment
- B_1 10 mg daily (consider supplying other vitamin B complex)
- Diet with rich sources: milk, vegetables, cereals, eggs

Vitamin B_2 (Riboflavin)

Value - Essentital for growth and tissue respiration

Deficiency
- Cheilosis
- Angular stomatitis.
- Glossitis
- Keratitis and corneal vascularization → Photophobia.

Diagnosis - Low erythrocyte glutathione reductase

Treatment
- B_2 10 mg daily
- Diet with rich sources as for vitmain B_1

Vitamin B_3 (Nicotinic acid, Niacin)

Deficiency ⇒ pellagra *(pellis = skin, agra = rough)*

1. Dermatitis
   - In sun exposed areas (hands, feet, head & neck).
   - Erythema, scales, crusts & desquamation.
   - Sharply demarcated borders.
2. Diarrhea - With stomatitis, cheilosis & glossitis
3. Dementia - Apathy, anorexia, insomnia.

Diagnosis
- Low urinary N methyle nicotinamide
- Therapeutic trial

Treatment - Vitamin B_3 50-300 mg daily
- Rich sources → meat, eggs, poultry
- Avoid maise (poor in tryptophan).

Niacin toxicity Relatively non toxic, high doses is associated with:
- Coetaneous: Peripheral vasodilatation and skin itching
- Metabolic: Increased uric acid , glucose intolerance
- Hepatotoxicity

Vitamin B_6 (pyridoxine)

Deficiency

1. Infantile convulsions - Why ? B6 is essential for synthesis of inhibitory neurotransmitter; GABA.
   - Nature? Myoclonic type
2. Anemia - Why ? Failure of heme synthesis due to failure of iron utilization.
   - Nature? Microcytic hypochronic.
3. Peripheral neuropathy - In patients on INH therapy
4. Skin - Cheilosis and dermatitis

Diagnosis - Therapeutic trial with 100 mg IM in convulsions
- Erythrocytes transaminases level

Treatment - For pyridoxine dependent child 10-100 mg oral daily

Biotin deficiency

Causes - Ingestion of raw egg white.
- Prolonged antibiotics

Deficiency - Alopecia
- Glossitis
- Seborrheic dermatitis

Vitamin C (Ascorbic acid)

Value - Synthesis of collagen.
- Necessary for folic acid and iron absorption.

Deficiency

1- Generalized bone tenderness mainly in legs → pseudoparalysis.

2- Bleeding: subperiosteal hemorrhages, swollen bleeding gums & purpura.

3- Scorbutic rosaries: - At costo chondral junctions.
- Sharply angular, tender, irregular.
- With sternal depression.

4- Follicular hyperkeratosis

5- Poor wound healing

6- Anemia (hemorrhagic , folic acid deficiency , iron deficiency)

Diagnosis

1. X-ray on ends of long bones show:
   - White line at the metaphysis (Fraenkel line)
   - Zones of destruction.
   - Rarefaction.
2. Ascorbic acid assay.

Treatment : Citrus fruits & vitamin C tablets 100-200 mg daily.

Vitamin C toxicity

- Osmotic diarrhea and abdominal pain
- Oxaluria.
- Interferes with copper absorption
- Enhance iron absorption → hazardous in iron overload states

Carnitine deficiency

Causes

- Infants (especially premature) who are fed soy formulas or fed parenteral.
- Dialysis patients
- Inherited defects in carnitine synthesis
- Organic acidemia.

Deficiency

- Fatty liver
- Hypoglycemia
- Progressive muscle weakness
- Cardiomyopathy.

Treatment

- Oral or IV carnitine .

Toxicity

- None recognized.

Fat Soluble Vitamins

Vitamin E deficiency

Causes - Fat malabsorption, oxidant stresses, malnutrition & prematurety

Deficiency - Hemolytic anemia.
- Predispose to oxidant injury to retina & brain in premature.

Toxicity - High doses in premature infants is associated with necrotizing enterocolitis& hepatotoxicity

Vitamin K deficiency

Deficiency - See hemorrhagic disease of newborn.

Toxicity - Vitamin K_3 may produce hemolytic anemia & jaundice in preterms.

Vitamin A deficiency

Deficiency - Night blindness.
- Eyes → Bitot spots , xerosis, keratomalacia & corneal ulceration.
- Mouth → Stomatitis.
- Weak epithelium (respiratory GIT, urinary) → more susceptible to infection.
- Perifollicular hyperkeratosis & pruritus.

Diagnosis - Serum vitamin A level < 20 μ g /dL

Treatment - For latent deficeincy: 1500 μ g / day
- For xerophthalmia : 1500 μ g / day for 5 days then 7500 μ g IM till recovery

Toxicity

1. Acute: Due to ingestion of 100.000 μ g or more.
   - Nausea , vomiting, drowsiness
   - Increased intracranial pressure (vomiting, headache,bulging fontanels,...
2. Chronic: With doses > 6000 μ g per day for weeks to months.

Skin :
- Alopecia
- Pruritus.
- Carotenemia (yellow skin)
- Desquamaion of hands and feet
- Seborrheic skin lesions
- Fissuring of mouth corners

Bones :
- Cortical thickening of long bones
- Tender swelling of Bones
- Craniotabes

Others:
- Increased intracranial tension
- Abdominal pain & hepatomegaly.
- May be hypercalcemia and liver cirrhosis

Vitamin D

Daily requirement → Breast fed full term ⇒ 200 - 400 IU/d from the 2nd months.
→ Preterm ⇒ 1000 IU/d from the 2nd weeks

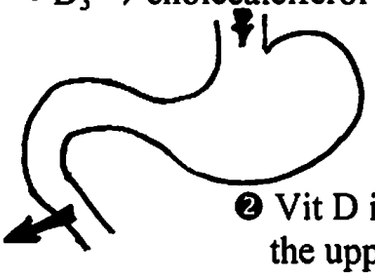
Metabolism

❸ Ultra violet rays convert



7- Dehydrocholesterol in the skin to vitamin D_3

❶ There's two forms of vitamin D
- D_2 → ergocalciferol ⇒ plant origin.
- D_3 → cholecalciferol ⇒ animal origin.



❷ Vit D is absorbed from the upper small intestine with aid of bile salts.

❹ Vitamin D is converted to 25 (OH) D_3 by the enzyme 25 hydroxylase. in the liver

If

- low serum calcium **or** phosphate
- high parathyroid hormone level

1 α hydroxylase enzyme is activated.

25 (OH) D_3 → 1, 25 $(OH)_2$ D_3

active form

⇓

Functions

Via synthesis of transport protein

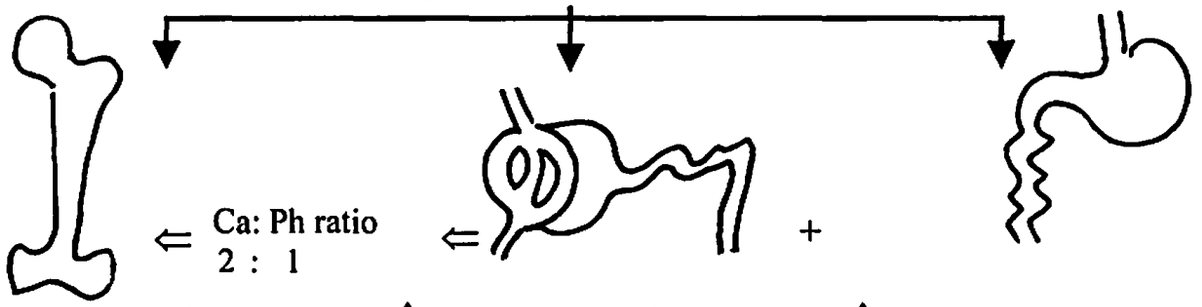
Normal **or** high serum calcium

24 hydroxylase enzyme is activated

25 (OH) D_3 → 24, 25 $(OH)_2$ D_3

↓

inactive form



⇐ Ca: Ph ratio 2 : 1

⇐ +

- Enhance Ca. phosphate deposition in bones.
- ↑ renal reabsorption of calcium & phosphate
- ↑intestinal absorption of calcium & phosphate

Disorders of Vitamin D Metabolism

Hypervitaminosis D

(Vitamin D intoxication)

Causes

- Excessive intake of vitamin D (the commonest cause).
- Ectopic production of 1, 25 $(OH)_2$ D_3 e.g by tumors , sarcoidosis.

Clinical picture

Manifestations are due to hypercalcemia:

1- Nausea, vomiting & constipation
2- Polyuria, polydipsia & dehydration
3- Hypotonia & hyporeflexia
4- Hypertension
5- Aortic valve stenosis.
6- In infants: marked irritability, poor feeding .
7- In severe cases calcium is deposited in various organs (metastatic calcification):
   - Nephrocalcinosis , renal stones , progressive azotemia
   - Acute abdominal pain due to pancreatitis or peptic ulcer .
   - Confusion, lethargy, coma (pseudotumor cerebri).

Prevention

Monitor serum calcium for cases treated with large doses of vitamin D;
if > 11 mg /dl; stop vitamin D.

Treatment

1. Stop	- Calcium & vitamin D intake and aviod sun exposure
2. Correct	- Dehydration
3. Enhance urinary calcium loss by	- Normal saline infusion at 1.5 times the maintenance - Furosemide 1-2 mg/kg when hydration is complete
4. Give	- Prednisone 1-2 mg/day → block action of 1.25 $(OH)_2$ D_3 → decrease calcium absorption
5. Shift calcium to bones by	- Calcitonin
6. Hemodialysis with low calcium dialysate for	- Severe hypercalcemia > 15 mg/dl

Important Notes

❶ Normal serum calcium (Ca) = 9 –11 mg/dl.
Normal serum phosphate (Ph.) = 4.5 – 5.5 mg/dl.
So, Ca: Ph. ratio in blood = 2:1 which is optimal for absorption & mineralization of bones

❷ Production of Ca × phosphate usually constant ≈ **40 – 50** this product is called Holland formula **or** solubility product.
* If serum phosphate increases → reciprocal decrease in serum Ca occur to keep the formula constant.
* If Holland formula > 80 ⇒ widespread deposition of ca phosphate occur in different tissues (metastatic calcifications) especially in the kidneys & heart.

❸ Serum Ca has 2 forms in balance:
* Non ionized form → inactive
* Inoized form → active form.

Ionized form

↑ ↑ in acidosis (pH < 7.35) ↓ ↓ in alkalosis (pH > 7.45)

❹ **Parathyroid (parathormone) hormone** (PTH) is secreted from the parathyroid glands, its main action is to keep serum calcium constant.
➢ ↓ serum Ca **or** ↑ serum phosphate stimulate parathyroids ⇒ ↑ parathormone.
⇒ Secondary hyperparathyroidism (**2^{ry} HPT**).

Actions

- ↑ Ca phosphate mobilization from bones
- ↑ Ca reabsorption & ↑Ph execretion in renal tubules
- ↑Ca & Ph absorption from the intestine

Tetany

Definition: A state of hyper excitability of the central & peripheral nervous system.

Causes:

1- Hypocalcemia

Due to - Decreased calcium intake
- Calcium malabsorption.
- Vitamin D deficiency & other causes of hypocalcemic rickets.
- Hyperphosphatemia
- Hypoparathyroidism.
- Magnesium (Mg) deficiency.

2- Alkalosis : Decreases ionized calcium

Due to: 1. Respiratory alkalosis: hyperventilation → Co_2 wash.

2. Metabolic alkalosis: due to e.g.
   - Loss of HCL due to repeated vomiting.
   - Excess alkali intake.
   - Barttar syndrome.

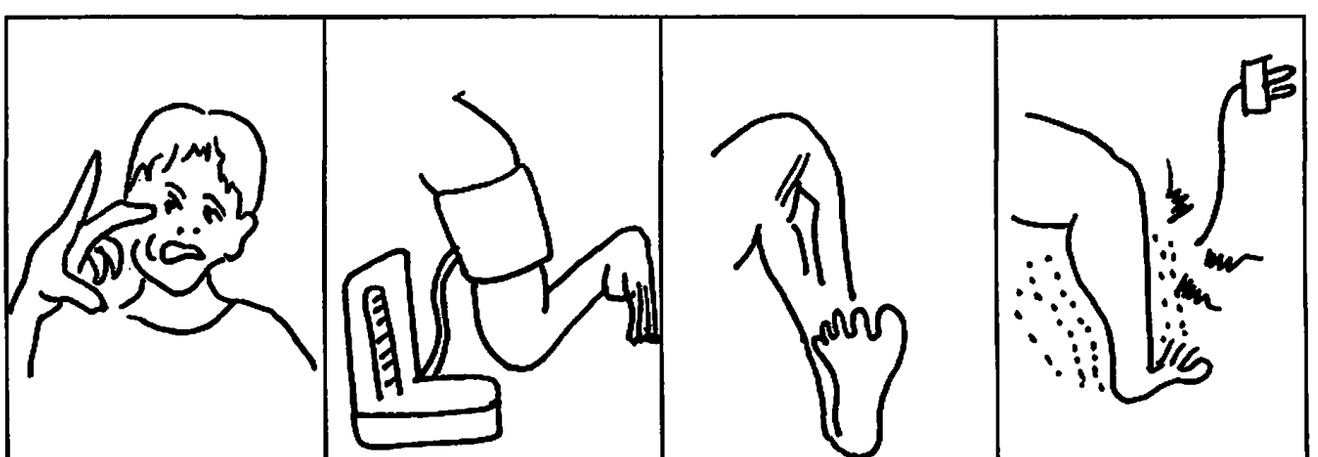
3- Hypomagnesemia (N = 1.6 – 2.6 mg/dl).

Clinical picture:

A . Latent tetany

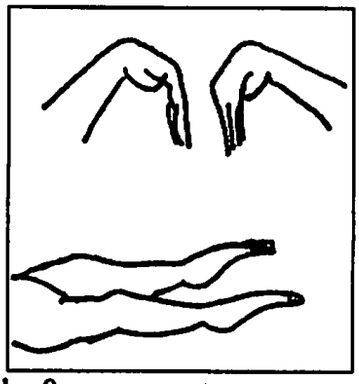
With serum calcium 7 – 9 mg/dl; detected by :

1. Chevostek sign : Tapping the facial nerve infront of the ear → twitch of the mouth
2. Trouseau sign : Inflation of sphygmomanometer cuff over the arm above systolic pressure for 3 min ⇒ carpal spasm.
3. Peroneal sign : Tapping of the peroneal nerve → dorsiflexion + abduction of the foot
4. Erb's sign : Motor nerve can be stimulated by low current (< 5 milliamperes).



Chevostek sign	Trouseau sign	Peroneal sign	Erb's sign

B. Manifest Tetany



With serum calcium < 7 mg/dl ; manifested by :

1. Carpo pedal spasm:
   - Flexion of the wrist & metacarpophalangeal joints
   - Extended interphalangeal joints
   - Flexed adducted thumb.
   - Plantar flexion & inversion of the feet
2. Laryngeal spasm (laryngismus stridulous): stridor is afebrile & recurrent.
3. Convulsions: generalized, recurrent,and baby is conscious between attacks
4. Paraesthesia: tingling & numbness in hands & feet.

Investigations

For hypocalcemia	For hypomagnesemia	For alkalosis
* Serum Ca (total & ionized) * Serum phosphate. * Serum parathyroid hormone.	* Serum magnesium	* Arterial blood gases

Treatment

1- Hypocalcemic tetany:

1. Acute attack:
   - Immediate relief of hypocalcemia by intravenous calcium
   - Dose: 100-200 mg/kg (1-2ml/kg) of calcium gluconate 10%
   - Slow infusion over 5-10 minutes with cardiac monitoring .
   - May repeat in 6-8 hrs until serum calcium level stabilizes.
   - Some requires continuous calcium drip to maintain normocalcemia.
2. Once symptoms of hypocalcemic tetany resolved :
   - Start oral calcium therapy (liquid or chewable tablets)
   - Dose: 50 mg /kg elemental calcium divided into 3-4 doses
   - Advice calcium rich diet
3. Vitamin D therapy :
   - Should not be started until the condition is controlled ;
   - For hypocalcemia with rickets → oral calcium & vitamin D till healing
   - For hypoparathyroidism → oral calcium & active vitamin D

2- For hypomagnesemia : Mg sulphate 50% (0.2 ml/kg); i.v, i.m or oral

3- For alkalosis : Re-breath into bag to ↑ $PaCo_2$

Rickets

Definition

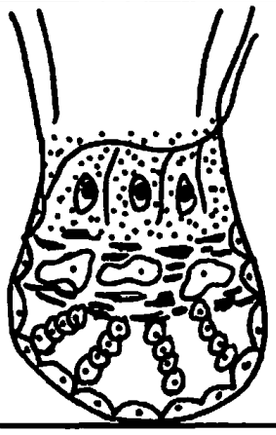
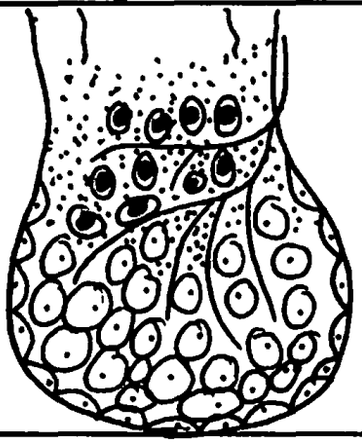
Metabolic bone disease due to failure of mineralization of osteoid tissue of the growing bones due to:

1- Defective intake or metabolism or function of vitamine D.
2- Inappropriate calcium / phosphate ratio (usually due to hypophosphatemia)

Pathology

Normally **there are** 2 types of ossification usually occur.

- Subperiosteal → increase bone thickness.
- Intracartilaginous → increase length of the bone.

Normal		Changes in Rickets
	♦The shaft ♦Zone of ossification ♦Degenerating cartilage ♦Proliferating cartilage. ♦Resting cartilage.	
1. Resting cartilage	- Single layer	• No change
2. Proliferating cartilage	- 4-6 layers regular - Avascular	• Very vascular → many layers → enlarged zone
3. Degenerating cartilage = zones of provisional calcification	- Swollen cells - Matrix impregnated with Ca → appear as sharp line at end of the shaft	• Very vascular. • Failure of cartilage cells degeneration. • No Ca deposition → lower end of the shaft frayed & irregular.
4. Zone of ossification	- ↑ capillaries → provide osteoblasts:→ lay osteoid → secrete alkaline phosphatase. - With normal Ca/Ph ratio → mineralization of the osteoid occur.	• Poor mineralization of the new osteoid → uncalcified osteoid (excessive & non rigid) → yield with pressure → cupping & broadening.
5. The shaft	Normal resorption & deposition of bone	-Resorption of bone → replaced by uncalcified osteoid → rarefaction -Bone become fragile → fractures & deformities.

Classification of rickets

		Serum Calcium
Non vitamin D deficiency rickets = Refractory (resistant) rickets	**Calcium deficiency with 2^{ry} hyperparathyroidism** A. Vitamin D disorders: 1. Nutritional vitamin D deficiency (infantile rickets) 2. Congenital vitamin D deficiency 3. Secondary vitamin D deficiency: - Vitamin D malabsorption (Celiac rickets). - Chronic hepatic disease. - Increased degradation with anti epileptic drugs. 4. Renal osteodystrophy (ROD). 5. Vitamin D dependent rickets type I 6. Vitamin D dependent rickets type II (End organ unresponsiveness to1, 25 $(OH)_2$ D_3) B. Calcium deficiency - Low intake - Premature infants - Malabsorption	Normal Or Low
	Phosphate deficiency without 2^{ry} hyperparathyroidism A. Phosphate deficiency - Decreased intake - Malabsorption. B. Renal phosphate losses 1. Familial hypophosphataemia. 2. Fanconi syndromes. 3. Renal tubular acidosis. 4. Oncogenous rickets	Normal
	Conditions resembling rickets 1. Hypophosphatasia 2. Metaphyseal dysplasia.	

(Nelson 2008)

Vitamin D Deficiency Rickets

(Infantile Rickets)

Incidence

Sex : - More in males (may be due to protective locus on x-chromosome)

Age : - From 3-4 months age → peak at 18 month.

Growth : - More in rapidly growing infants e.g twins & preterms.

- Less in infants with arrested growth e.g PCM & cretinism.

Etiology:

A. Decreased vitamin D intake due to:

1. Lack of rich sources of vitamin D as egg yolk, meat, fortified milks, fish liver oil.
2. Use of rachitogenic diet with:
   - Poor sources of vitamin D as unfortified animal milk and carbohydrates.
   - Poor sources of calcium as cereals ,and excessive leafy vegetables(contain excess phosphates ,oxalates and phytate that form insoluble calcium complexes).

B. Lack of access of ultra violet rays to the skin due to:

1. Glass windows, clouds(in winter) & dust.
2. Excessive wrappings of the infants.
3. Dark skinned infants.

N.B: Breast milk , in contrast to cow milk , is anti rachitogenic:

Provided :

- Adequate maternal vitamin D intake
- Adequate maternal sun exposure
- Proper weaning in proper time .

Benefits:

- Calcium: Phosphate ratio 2:1.
- Intestinal pH ideal for calcium absorption.
- Lactalbumin compound with vitamin D →↑ bioavalabibility.

Clinical picture

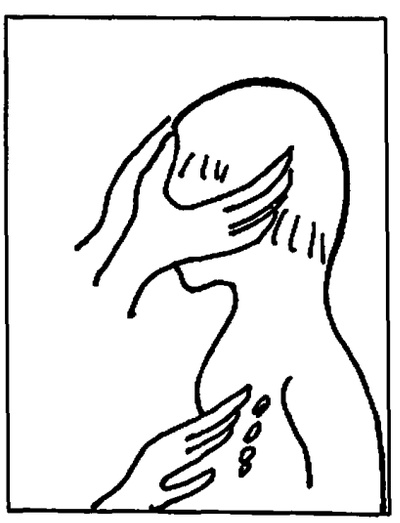
I- Early Rickets:

1- Anorexia, irritability, sweating of forehead

2- Craniotabes:

- Skull bones yield under pressure →
  Ping - pong or egg shell crackling sensation.
- Due to thinning of inner table of the skull
- Disappear by the end of 1st year.
- Detected by pressing over occipital or parietal bone.

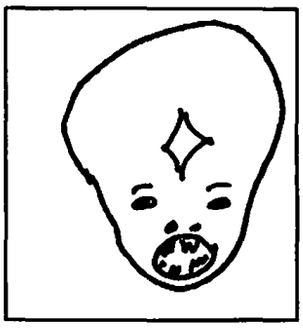
3- Racketic rosaries: palpable enlargement of costochondral junctions (due to excess osteoid)



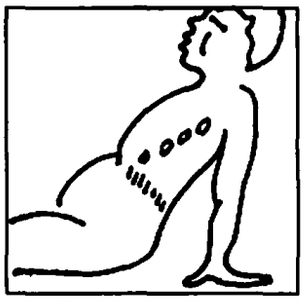
II- Advanced Rickets:

I. Skeletal Changes

1- Head



- Large head ;marked if rickets developed early in the 1st year.
- Large anterior fontanel (delayed closure).
- Asymmetric skull; may be box shaped
- Bossing of frontal & parietal bones due to excess osteoid
- Craniotabes disappear by the end of the 1st year
- Depressed nasal bridge due to frontal bossing.
- Delayed teething with caries of existing teeth.



2- Chest

a. Rachitic rosaries : - visible & palpable.
- rounded, regular, non tender

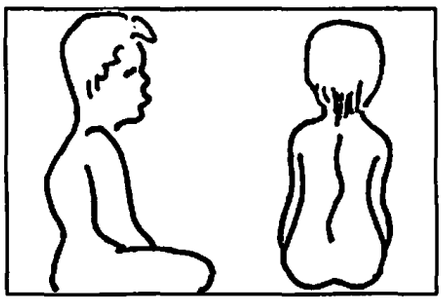
b. Longitudenal sulcus → lateral to the rosaries.

c. Harrison sulcus → transverse groove along the costal insertion of the diaphragm (due to pulling on the soft ribs).

d. Chest deformities:

* Pigeon chest → sternum & adjacent cartilages project forwards.
* Funnel chest → depression of the sternum & flaring out of the lower ribs.

3- Vertebral column : there may be



a. Kyphosis : in dorsolumbar region.
- smooth.
- apparent on sitting , disappear by lifting.
- with compensatory lumber lordosis.

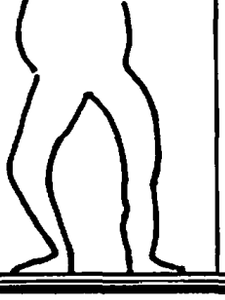
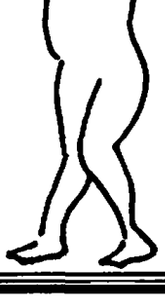
b. Scoliosis : lateral curvature of the spine

4- Extrmities

a. Broadening of epiphysis of long bones espicially at wrist & ankles.

b. Marfan sign: transverse groove over the medial maleolus due to unequal growth of the two ossific centers.

c. Deformities: due to weight bearing on the soft bones.

Bowing of forearm in crawling infants	Bow legs (Genu varus)	Knock knees (Genu valgum)	Overextended knees (Genu recurvatum)
			

5- Pelvis

a- Contracted inlet → due to forward projection of sacral promontory.

b- Contracted outlet → due to forward projection of cocxygeal tip

both may lead to obstructed labour in later life.

II. Non Skeletal Manifestations

Manifestations:

1- Delayed motor milestones.

2- Abdominal distension (pot belly abdomen) ; with or without umbilical hernia

3- Ptosis of the liver & the spleen (also due to chest deformities).

4- Constipation → due to intestinal hypotonia.

Etiology:

- Hypotonia of skeletal muscles (due to hypophosphatemia)
- Laxity of ligaments

Complications

1- Respiratory infections & atelectasis due to:

a- Limited chest expansion.

b- Hypotonia of respiratory muscles → weak cough reflex.

2- Gastroenteritis due to intestinal hypotonia → stasis → 2^{ry} bacterial overgrowth.

3- Tetany : may occur in rickets with hypocalcaemia; rare in vit D deficiency rickets (but may occur in 3 occasions ;see above).

4- Skeletal deformities: - Mild and early managed cases → reversible.

- Advanced and neglected cases → perminant.

5- Disproportionate short stature (Rachitic dwarfism)→ due to deformities of spine, pelvis & limbs

6- Iron deficiency anemia is a common association.

Investigations

I- Biochemical

* Serum calcium is normal, but may be low (normal = 9 – 11 mg/dl).
* Serum phosphate (Ph.) is low (normal value = 4.5 – 6.5 mg/dl).
* Serum alkaline phosphatase (Alk. Phos.):
  - High (normal value = 5-25 king Armstrong units or 50-150 unit/liter)
  - The most sensitive indicator of rachitic activity; due to osteoblastic activity
  - Return to normal after complete healing of rickets.
* Parathyroid hormone (PTH) → high.
* 25 (OH) D_3 → low
* 1.25 $(OH)_2$ D_3 → low in severe vitamin D deficiency.

Explanation: ↓ 1,25 $(OH)_2$ D_3 →↓ calcium absorption → serum calcium tend to be low → ↑ PTH → ↑ calcium & ph. mobilization from bones + ↑ ph. loss in urine → normalized serum calcium + ↓ serum ph.

However hypocalcemia (and may be tetany) may occur with:

1- Failure of 2^{ry} hyperparathyroidism to occur.
2- In advanced cases with depletion of bone calcium.
3- Shock therapy → ↑↑↑ deposition of calcium Ph. in bone on the expense of serum calcium which may fall below normal.

II- **Radiologic:** by X-ray at lower ends of long bones especially wrist due to easy access , rapid growth and soft tissue around is thin.

a- Active rickets

The lower ends show
- Broadening
- Cupping (concavity)
- Irregular epiphyseal line(fraying).
- Wide joint space



The shaft shows
- Rarefaction →↓ bone density
- Double periosteal lines (subperiosteal transluscent osteoid).
- May be green stick fracture.
- May be deformities.

b- Healing rickets

* Usually after 2 weeks of treatment
- The lower ends shows white concave continuous line at ZPC
- Less evident features of rickets



c- Healed rickets



* Usually after 4 weeks of treatment
- The lower ends show straight continuous line at ZPC.
- No features of active rickets.

Different diagnosis from other causes of :

1. Delayed motor milestones.
2. Large anterior fontanelle.
3. Craniotabes which may occur in: - Premature.
   - Hydrocephalus.
   - Osteogenesis imperfecta.
   - Congenital syphilis.
4. Rosary beads:
   a. Scorbutic rosaries: Due to deficient collagen (slipping of sternocostal junctions and subperiosteal hemorrhage)
      Criteria: - At costo chondral junctions.
      - Angular, tender, irregular.
      - With sternal depression.
      - Associated with other clinical and radiologic features of scurvy
   b. Chondrodystrophies
5. Pott's disease (T.B of spine): - Kyphosis is angular & persistent.
   - X-ray and CT spine is diagnostic.

Treatment

1- Prevention

a. Vitamin D supplement for:

- Breast or animal milk feeders; not for fortified formula feeders
- Dark skinned infants, protected from sunlight and those born in winter months

Dose: - For breast fed full term → 200 - 400 IU/day from the 2nd month.

- For prematures → 1000 IU/day from the 2nd week.

b. Advice parents for exposure to sunlight and vitamin D rich diet

2- Curative

a. Vitamin D_3:

* Shock or Stoss therapy :
  - Dose : 300.000 - 600.000 IU oral or intra muscular as 2- 4 doses over 24 hours
  - Indicated if compliance is questionable
* Oral : 2000 – 5000 IU/day for 4 - 6 weeks

b. Diet with adequate calcium and phosphorus (formula, milk , dairy products)

c. Advice parents to avoid weight bearing in infants during active rickets.

d. Treatment of complications:

* Tetany: calcium gluconate 100 mg /kg slow i.v , followed by oral calcium 1000 mg daily for 4-6 weeks , then kept on adequate dietary calcium
* Deformities: osteotomy and reconstruction if severe and persistent.

After 4- 6 weeks of treatment:

1. Adequate response by radiology & normal alkaline phosphatase
   Decision: Revert to normal daily requirement of vitamin D
2. Failure of response
   Decision: Suspect vitamin D resistant rickets

Rickets with calcium deficiency

- Classic picture of rickets that occur later than nutritional rickets
- Commonly occur after weaning from breast milk
- Due to poor intake of calcium or calcium malabsorption
- Treated by oral calcium 350 – 1000 mg daily ± vitamin D

Congenital rickets

- Due to severe maternal vitamin D during pregnancy
- Presentation: a newborn with :
  - a- Classic rachitic changes
  - b- Hypocalcemic tetany
  - c- Intra uterine growth retardation
- Prevented by adequate prenatal sun exposure and vitamin D supply

(Nelson 2008)

Vitamin D Resistant Rickets

Definition: Rickets resistant to the usual doses of vitamin D

1. Rickets with malabsorption	2. Rickets with chronic Liver diseases	3. Rickets with antiepileptics
Causes: malabsorption of vit D	• Biliary atresia → fat malabsoption (→ vit D malabsorption) • Hepatocellular disease → ↓ synthesis of 25 (OH) D_3	• Phenytoin & phenobarbitone are enzyme inducers → ↑ ↑ inactivation of 25 (oH) D_3 • ↓ Ca intake. • Epileptics kept indoors.
Clinical picture: General features of rickets **plus**		
• Features of malabsorption syndrome.	• Features of chronic liver disease e.g. (jaundice, hepatomegaly, bruises)	• History of antiepileptic treatment

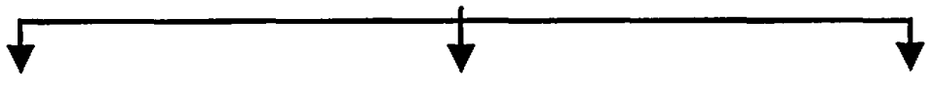
Investigations

Ca	Ph.	PTH	Alk. Phos.	25 (OH) D_3
Normal or ↓	↓	↑	↑	↓

Others • Steatorrhea	• Abnormal liver functions tests	
Treatment: • Treat the cause • Vit. D I.M (not oral)	• Treat the cause • 25 (OH) D3 2000 – 4000 iu / d	• Adequate Ca intake. • Adequate sun exposure. • Prophylaxis: extra dose of vit D 500 – 1000 iu /d • Curative: - 25 (OH) D3 2000 – 4000 iu / d

Renal Rickets

Definition: Vitamin D resistant rickets due to



Renal osteodystrophy (Renal glomerular rickets)	Vitamin D dependent Rickets type I	Renal tubular disorders

❶ Renal Osteodystrophy (ROD)

Definition: rickets occurring with chronic renal failure (CRF)

Pathogenesis

CRF

Phosphate retention

↓ 1 α hydroxylase

⇓

↓ 1.25 $(OH)_2$ D_3 synthesis

↓ serum calcium

⇓

secondary hyperparathyroidism (2ry HPT)

⇓

↑↑ bone resorption

(↑ Ca & phosphate mobilization)

⇓

more phosphate retention

(visious circle is settled)

Clinical picture:

a. Features of chronic renal failure.

b. General features of rickets but:

- Age usually > 2 years.
- Deformities & fractures are very common due to combined effect of rickets & secondary hyperparathyriodism.
- Tetany is rare → as metabolic acidosis ↑↑ ionized Ca
- Bone pain and muscle weakness in older children.

Investigations;

1- Biochemical:

Ca	Ph.	PTH	ALK phos.	25 $(OH)_2$ D_3	1.25 $(OH)_2$ D_3
↓	↑↑	↑↑	↑	Normal	↓

Others:

- Holland formula (Ca × ph) ⇒↑
- Impaired renal functions tests (↑urea & creatinine).

2- Radiologic:

*** General radiological features**

* May be with evidence of secondary hyperparathyriodism:

- Subperiosteal erosions of bones esp at: - distal & middle phalanges
  - distal clavicle
  - ends of long bones
- May be bone cysts ⇒ osteitis fibrosa cystica.

Management

A- Treatment of CRF → conservative treatment with or without dialysis.

B- Treatment of ROD in the following steps

1. Low phosphate diet (↓ proteins).
2. Oral phosphate binders → Calcium carbonate (calcimate)
   → Calcium acetate
   → Non calcium based binders (sevelamer; Renagel)
3. Calcium → 0.5 – 2 gm/day oral.
4. One alpha [1 α (OH) D_3] oral **or** calcitriol if:
   - Persistent low calcium despite phosphate fall below 6 mg/dL.
   - Increased PTH > 3 fold upper normal level
5. Partial parathyroidecomy for persistent hyperparathyroidism.

N.B.: Aluminum hydroxid [Al $(OH)_3$] should be avoided as it leads to aluminum intoxication in case of CRF→ further bone damage.

❷ Vitamin D Dependent Rickets Type I

- Autosomal recessive (AR) disorder
- Defect in 1 α hydroxylase enzyme →↓ 1.25 (OH) D_3
- Features of rickets develop early in life (at 3 – 6 months).
- Investigation:

Ca	Ph	PTH	ALK phos.	25 (OH) D_3	1.25 $(OH)_2$ D_3
↓	↓	↑	↑	Normal	↓

Treatment: 1.25 $(OH)_2$ D_3 0.25 - 2 μg/day till healing then maintain on 0.25μg/day

❸ Renal Tubular Rickets

♦ Rickets develop with renal tubular disorders due to either.
- Phosphaturia →↓ serum phosphate → serum Ca: Ph ratio become inappropriate for mineralization.
- Metabolic acidosis →↑ bone resorption.

♦ Types of renal tubular rickets:

1- Familial hypophosphatemia

2- Fanconi syndromes:
- ➢ Primary; sporadic
- ➢ Heriditary:
  - Cystinosis (Lignac syndrome)
  - Oculo-cerebro-renal (Lowe's syndrome)
  - Galactosemia.
  - Wilson disease.
- ➢ Drug induced:
  - Out dated tetracyclin
  - Cyclosporin A.
  - Heavy metals.

3- Renal tubular acidosis (Light Wood Syndrome)

4- Oncogenous rickets

1- Familial hypophosphatemia	2- Fanconi syndrome (Primary type)
Etiology: Sex linked dominant disorder (rarely AD) Characterized by decrease renal tubular reabsorption of phosphate → loss of phosphate in urine	Autosomal recessive disorder due to multiple defects in proximal renal tubules with ↓ urinary reabsorption of phosphate, bicarbonate & amino acids and may be potassium & glucose→ all are lost in urine
Clinical picture: - **Rickets** appear during the 2nd year of life especially bow legs with waddling gait and short stature. - Delayed teething and tooth abscesses - No evident rosaries , muscle weakness nor tetany	- **Rickets** - Vomiting (due to acidosis) - Polyuria and polydipsia. - Episodes of dehydration, fever - Muscle weakness and constipation - Growth retardation
Laboratory: • ↓ Ph. • Normal Calcium • No 2ry HPT • ↑ Alk. Phosphatase Others: Phosphaturia	• ↑ urinary Ph., bicarbonate & amino acids (may be potassium & glucose) • Metabolic acidosis
Treatment: 1- Oral phosphate 1 – 3 gm/day divided into 5 doses 2- Vitamin D: Value :- Complete bone healing - Offset 2ry HPT which usually accompany phosphate therapy. Types:- Vit. D_2 2000 IU/day was used but ; - More recently 1.25 $(OH)_2$ D_3 30 - 70 ng/kg/day are used. **N.B :** Large doses of vitamin D_2 (50.000 IU/day) is no longer used	
3- Growth hormone for short stature	3- Sodium bicarbonate tablets or sodium citrate and potassium citrate syrup for metabolic acidosis 4- Potassium chloride 2-3 mEq/kg/day for cases with hypokalemia

(Nelson, 2008)

3- Lignac syndrome (cystinosis):

- Autosomal recessive disorder: Characterized by deposits of cystine in lysosomes of liver, spleen, bone marrow, cornea & renal tutules → Fanconi like.
- C/P & investigations: As Fanconi plus: - Photophobia and hepatosplenomegaly.
  - Detect cystine crystals in cornea & WBCs
- Treatment: as Fanconi & cysteamine oral and eye drops.

4- Lowe's (oculo – cerebro – renal) syndrome:

- Sex linked recessive disorder of eyes, cerebral cortex & renal tubules → Fanconi like.
- C/P & investigations: as Fanconic Plus
  - Eye → cataract & congenital glaucoma (Buphthalmos).
  - CNS → mental retardation & hypotonia
- Treatment : as Fanconi & treat associations

5- Renal tubular acidosis (Light Wood Syndrome):

- Mainly proximal renal tubules defect → bicarbonaturia → Metabolic acidosis
- Clinical picture, investigation & treatment → as Fanconi

6- Oncogenous rickets :

- Associated with tumors of mesenchymal origin e.g. hemangiopericytoma
- Mechanism: Production of phosphatonins that induce phosphaturia and impair conversion of 25 (OH) D_3 to 1.25 $(OH)_2$ D_3
- Rickets may appear years before tumors are evident and resolve with its excision

Vitamin D dependent rickets type II

* End organ unresponsiveness to action of 1.25 $(OH)_2$ D_3 due to deficient receptors.
* Inheritance : Autosomal recessive disorder
* Associations : Short stature and alopecia.
* Investigations : Same as vit D dependent type I but level of 1.25 $(OH)_2$ D_3 is high.
* Treatment : 1.25 $(OH)_2$ D_3 [Calcitriol] 2 – 50 μg/d may improve some cases.

Conditions Resembling Rickets

1- Hypophosphatasia

* Due to : Decreased serum alkaline phosphatase enzyme
* Inheritance : Autosomal recessive disorders
* Forms :
  - Congenital lethal form
  - Severe infantile form
  - Mild childhood form
* There may be ↑ serum calcium
* Treatment : No specific treatment ; some cases may benefit from fresh plasma

2- Metaphyseal dysplasia

* Inheritance : - Autosomal dominant disorders
* Forms :
  - Jansen type
  - Schmidt type
* Clinical picture :
  - Short stature.
  - Bow legs with waddling gait.

Genetics

Basis of Genetics

Structure of the chromosome

- Each chromosome is composed of 2 chromatides
- The 2 chromatides are connected to each other at the centromere
- Each chromosome has 2 short arms (p) & 2 long arms (q)
- Each chromatide is composed of DNA in protein framework .

Chromosomal number

1. In somatic cells : 46 chromosomes (i.e. diploid number) ; 44 autosomes& 2 sex chromosomes; X X in females & X Y in males

2. In germ cells : 23 chromosomes (i.e. haploid number); 22 autosomes & One sex chromosome(X in ovum and X or Y in sperm)

Structure of the gene

Definition
- Part of DNA that code for synthesis of single polypeptide chain.
- Every trait (character or feature) is determined usually by 2 genes one from each parent.
- If both genes are similar → Homozygous (e.g. AA or aa)
- If both genes are different → Heterozygous (e.g. A a)

Dominant gene : Express itself whether in homozygous or heterozygous state

Recessive gene : Express itself only when homozygous

Genotype : Set of genes inside the cells

Phenotype : External appearance of the individual as determined by genotype & environment.

Composition of the genetic material

Each DNA is composed of:

a- Sugar (deoxyribose) & phosphate backbone.

b- Nitrogenous bases: - Pyrimidines ⇒ cytosine (C) & thymidine (T)
- Purines ⇒ adenine (A) & guanine (G).
  * A always pairs with T.
  * C always pairs with G.

Nucleotide is unit of one deoxyribose, one phosphate group & one base.

Types of DNA:

1- Non repetitive (unique) DNA → code for certain proteins.

2- Repetitive DNA → repeated DNA sequences → not code for genes.

3- Mitochondrial DNA(circular , maternally inherited ,double stranded DNA)

Functions of DNA:

1- DNA replication (duplication)

DNA can replicate itself.

* Aim? - To replace broken segments (i.e repair itself)
  - Formation of a complentary strand during cell division.
* How? DNA helix split → form two single strands → pairing of new complentary bases.

2- Protein synthesis:

1. Transcription: synthesis of mRNA strand with the same sequence of DNA strand.
2. mRNA leave the nucleus & attach to the ribosomes in the cytoplasm.
3. Translation:
   - Each 3 successive bases on DNA = 3 successive bases on mRNA is called codon which code for certain amino acid.
   - When the ribosomal RNA comes in contact with that codon the tRNA with specific anticodon complementary to it comes in place, leaving the specific amino acid carried on it.
   - The mRNA moves and brings another codon in contact with ribosome.
   - Another tRNA comes in place and its amino acid attach to the first amino acid.
   - The process will continue until the whole polypeptide chain is formed.

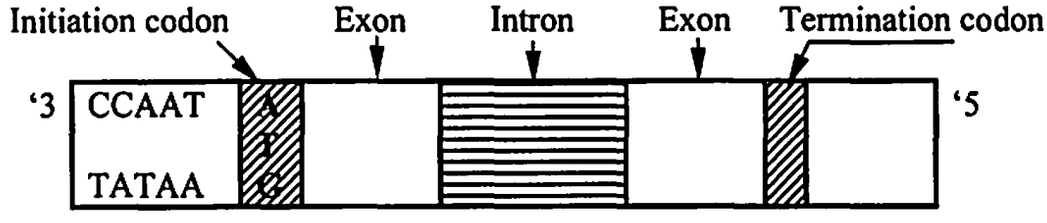
N.B: Differences between DNA and ribonucleic acid (RNA):

1- The sugar of RNA is ribose.
2- The chains are single, not double spirals.
3- RNA is present in both nucleus and cytoplasm, DNA is not present in the cytoplasm.
4- RNA has the pyrimidine base uracil (U) instead of thymine (T) in DNA.

Gene Expression

Human gene is composed of

* **Exons :** The functional portions of gene sequences coding for protein synthesis.
* **Introns :** Non coding DNA sequences of unknown function.
* **Initiation codon:** Specific sequence (ATG) which determines the initiation of protein synthesis.
* **Termination codon:** Specific sequences (TAA, TAG or TGA) which determine the end of transcription.
* **TATAA and CCAAT boxes :** Special sequences with unknown function, but may direct the enzymes for initiation sites.



Control of gene expression

* Each group of cells has special functions due to different expression of genes.
* This can be achieved by methylation theory which states that: Parts of the gene which is methylated tend to be non-functioning and non-methylated parts tend to be functioning.

Q: What is mutation? it is a change of bases sequence in the gene:

- Non sense mutation : addition or deletion of base → altered whole frame work.
- Misense mutation → substitution of single base → abnormal polypeptide.

Cell Division

Mitotic Division

Occur in all cells excepts CNS cells for → renewal of cells e.g epithelium
→ ↑number of cells e.g bone marrow cells

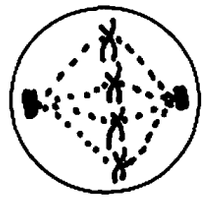
Pass in the following stages

1. Prophase



* Nuclear membrane disappear
* Centrioles duplicate & move to each pole of the cell
* Chromosomes condense & become visible by light microscope

2. Metaphase



* Chromosomes arranged along the equatorial plane
* Spindle protein fibers radiate from the centrioles to the centromeres

3. Anaphase



* Each chromosome divide longitudinally into 2 daughter chromatides.
* Each set of chromatids move to each pole of the cell by the spindle

4. Telophase



* Cytoplasm start to divide
* Nuclear membranes start to form.
* 2 daughter cells will form each contain 46 chromosomes (chromatids)

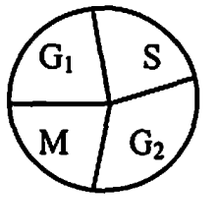
5. Interphase

G_1 phase
The 1st gap (5 hr)
All the DNA is unreplicated

S phase
Synthesis of DNA occur so, each chromosome now is composed of 2 chromatids

G_2 phase
The 2nd gap (5 hr)
from end of S phase till start of mitosis.

Mitosis



Meiotic Division

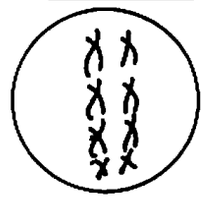
Occur only in gonads for production of gametes (ova & sperms)

1- **1st meiotic division** (reduction division)

Pass in the following stages:

1. Prophase

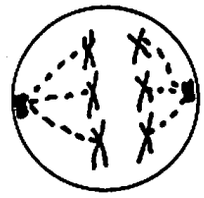
* Homologous chromosomes pair longitudinally.



* Crossing over may occur (recombination) between 2 homologous chromatides.

2. Metaphase

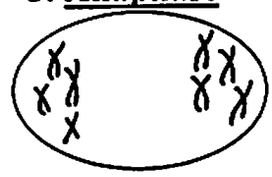
* Nuclear membrane disappear



* Spindle connect centeriols to the centromeres

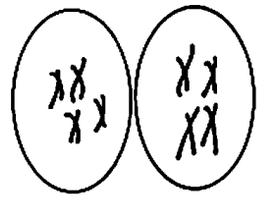
3. Anaphase

* Homologous chromosomes separate randomly to each pole of the cell



4. Telophase

* 2 cells are formed



* Each has haploid number of chromosomes

2- **2nd meiotic division**

Similar to mitosis

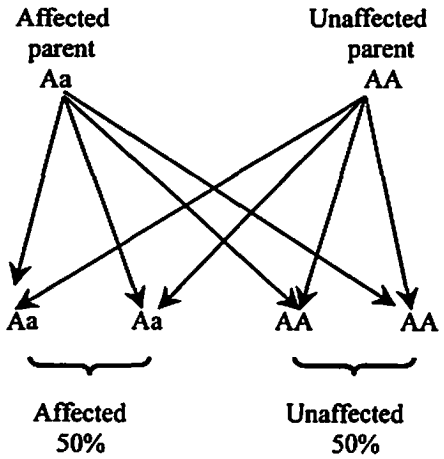
N.B : Gametes produced by meiotic division are very variable due to:

- Random migration of chromosomes.
- Crossing over.

Modes of Inheritance

Autosomal dominant (AD)

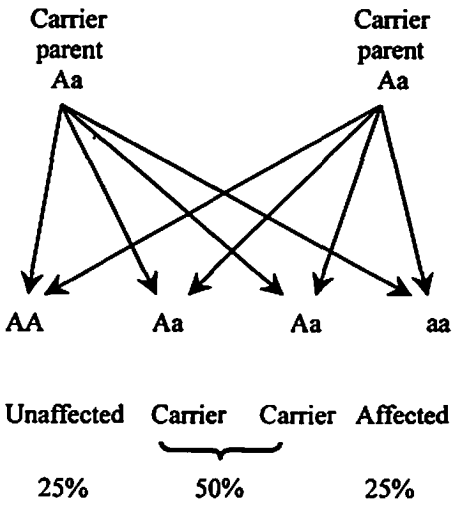
- The trait manifest whether in homozygos *or* heterozygous state.
- the disease appear in successive generations.
- *Affected person has an affected parent (vertical)*
- *New mutation is common*



e.g. - Spherocytosis
- Achondroplasia

Autosomal recessive (AR)

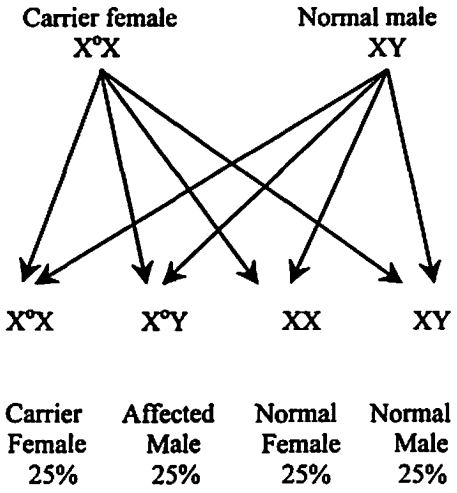
- The trait manifests only in homozygous state
- Both parents are carriers(horizontal)
- *Consanguious marriage increase the incidence*



e.g. - Thalassemia
- Phenyleketonuria.
- Albinism

Sex- linked recessive (XR)

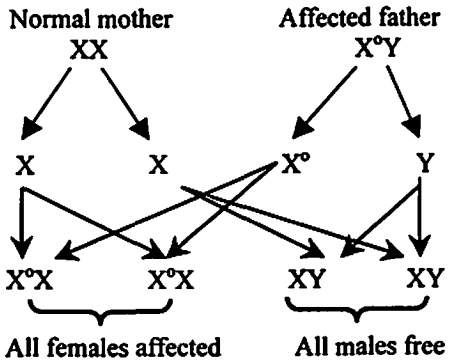
- Affect males
- Carrier females may be affected (due to Lyonisation)
- Sons of female carriers have a 50% chance of being affected
- Daughters of female carriers have 50% chance of being carriers
- There is no father son transmission.



e.g. - G6PD deficiency
- Heamophelia A

Sex linked dominant (XD)

- The trait manifest whether in homozygous (female) *or* heterozygous (male)
- Affected father transmit the trait to all daughters but never to this sons.
- Affected mother transmit the trait to ½ of her offspring.



e.g. Familial hypophosphataemia

N.B.: ABO blood groups is inhirted as dominant or codominant for A & B and recessive for O blood group.

Chromosomal Analysis

(Karyotyping)

Karyotyping: it is systematic arrangement of the chromosomes of a single prepared cell in pairs (according to the length) either by drawing or photography.

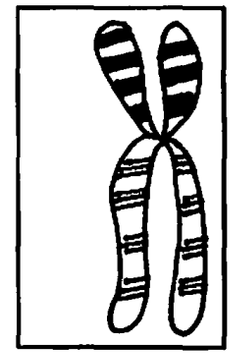
Preparation of study cells

Viable dividing cells can be obtained from:

1. Peripheral blood lymphocytes: Used for routine karyotyping.
2. Bone marrow: For rapid analysis and in leukemia.
3. Skin fibroblasts: In suspected mosaicism **or** if blood is not available (e.g post mortem).
4. Amniotic fluid cells: Diagnose chromosomal anomalies in the 2nd trimester.
5. Chorionic villous sampling (CVS): Diagnose chromosomal anomalies in the 1st trimester (at 10-12 weeks).

Techniques

1. G-banding:
   * Chromosomes are stained in metaphase using Trypsin/Giemsa stain → examined under light microscope
   * Chromosomes appear as dark bands alternating with light bands.



2- High resolution banding
   * As G-Banding but the chromosomes are studied in prophase or prometaphase.
   * Each band is subdivided into sub bands

3- Q-banding: using quinacrine stain and examined under fluorescence microscopy.

4- Other techniques: a lot of methods are used e.g. R- banding, C- banding.

Normal karyotyping

* Female : 46, XX
* Male : 46, XY

Indications of karyotyping

1. In neonate	- Confirm clinical diagnosis. - Dysmorphic features. - Ambiguous genitalia. - Major congenital malformations
2. In childhood	- Females with unexplained short stature or growth retardation. - Mental retardation of unknown origin. - Delayed puberty.
3. In adults	- Parents of child with chromosomal anomaly - Parents with 2 or more abortions of unknown cause. - Amniocentesis for mother with previous child with congenital anomalies and mothers > 35 years old.

Classification of Chromosomes

Chromosomes are classified regarding:

1- Size: short, medium sized, long.

2- Position of centromere:

* Metacentric → central centromere (p arm and q arm of almost equal size)
* Submetacentric → (p arm shorter than q arm).
* Acrocentric → centromere is close to one end (very short p, very long q)

Denver classification of chromosomes: (7 groups)

A 1, 2, 3 - Large - Metacentric 	**B** 4, 5 - Large - Submetacentric 	**C** 6 → 12 & X - Medium - Submetacentric 	
D 13, 14, 15 - Medium - Acrocentric 	**E** 16, 17, 18 - Short - Submetacentric 	**F** 19, 20 - Short. - Metacentric 	**G** 21, 22, Y - Short. - Acrocentric 

Chromosomal Anomalies

A. Abnormalities of chromosome structure

1. Translocation(t): Interchromosomal rearrangement of genetic material ; may be:

1. Balanced : The cell has a normal content of genetic material arranged in a structurally abnormal way; it is further divided into:
   a. Reciprocal→ exchange of genetic material between two homologous chromosomes.
   b. Robertsonian→ fusion of two acrocentric chromosomes.
2. Unbalanced : The cell has gained or lost genetic material as a result of chromosomal interchange.

2. Deletion(del)

* Part of the chromosome is broken & lost ⇒ gene loss.
* In most cases there is mental handicap and dysmorphism
* Example: Cri du chat syndrome (deletion chr. 5 p) which involve:
  - Mental retardation & miCrocephaly
  - Cry like cats
  - Congenital heart disease.

3. Duplication(dup)

* An extra copy of a chromosomal segment(in the same direction or reverse direction)
* Example: Cat Eye syndrome (duplication of chromosome 22ql1) which involve:
  - Iris coloboma
  - Anal or Ear anomalies.

4. **Isochromosome**(i)
   * Transverse division of the chromosome instead of longitudinal division
   * Resulting in 2 chromosomes with one consisting of 2q & the other of 2p.

5. **Inversion**(inv)
   * Two breaks occur in a chromosome with inversion of the intervening material & reconstruction of the chromosome ; It can be :
     - Paracentric : not involving the centromere or
     - Pericentric : involving the centromere

6. **Ring chromosome**(r)
   * Breaks at both ends of a chromosome with subsequent end to end rejoining
   * Often cause growth retardation and mental handicap.

7. **Fragile X chromosome**
   * Some cells when grown on specialized media (folate deficient) → chromosomes show elongation at one point (fragile site).
   * Example: Fragile X-syndrome; Male with:
     - Mental retardation and abnormal behavior
     - Large testes after puberty
     - Oblong face with prominent ears & jaw.
   * Diagnosis: DNA analysis for CGG repeats expansions

8. **Chromosomal fragility**
   * A group of autosomal recessive syndromes with DNA repair defects
   * There is excessive chromosomal breakages on exposure to certain chemicals , radiation and viruses
   * Carry high risk of malignancy
   * Examples:
     - Fanconi anemia
     - Ataxia telangiectasia
     - Bloom syndrome
     - Xeroderma pigmentosa

B. Abnormalities of chromosome number (Numerical anomalies)

1. Polyploidy = extra whole sets of chromosomes: e.g. triploidy 69, XXX; (lethal)
2. Aneuploidy = missing or extra individual chromosomes:
   a. Monosomy: only one copy of a particular chromosome (most are aborted).
   b. Trisomy: three copies of a particular chromosome.
3. Mosiacism= The presence of two or more different chromosome counts in different cells of the same individual

Kleinfelter Syndrome

Etiology: Extra X-chromosome in a male ⇒ (47, XXY) due to non disjunction.
may be many x-chromosomes e.g 48, XXXY, ...

Clinical picture

- Mental retardation(more severe with increased number of X chromosomes).
- Gyneacomastia ,diminished facial hair, feminine distribution of fat.
- Atrophic testis, azospermia ,sterility.
- Tall stature (enuchoid built).

Diagnosis

1. Buccal smear : chromatin (Barr) body +ve
2. Karyotyping: diagnostic (47, XXY)

Turner Syndrome

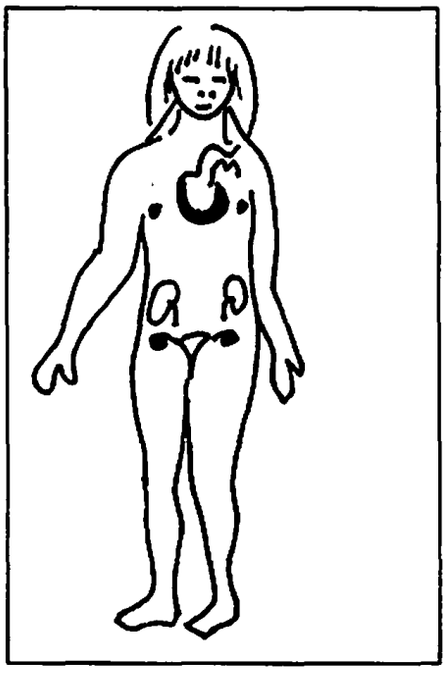
Etiology

a- Classic form (45, X0) ⇒ Monosomy X-chromosome
b- Deletion of short arm of one X-chromosome.
c- Turner mosaic: - 45 X0 / 46 X X.
- With isochromosome 45 X / 46 (X, i)
- With rings 45 X / 46 (X, r)

Incidence: 1 / 5000 (as most cases are aborted)

Clinical picture

At birth:
- Transient lymphoedema in dorsa of hands and feet.
- Low birth weight
- Loose skin at neck nape.



Later on:
- Ugly short stature female.
- Normal mentality
- Low post hair line
- Recurrent otitis media
- Webbing of the neck
- Congenital heart disease:
  * Aortic coarctation
  * Non stenotic bicuspid aortic valve
- Wide spaced underdeveloped nipples
- Cubitus valgus (wide carrying angle)
- Renal anomalies
- Ovarian dysgenesis (streak gonads)

N.B: Mosaic turner may have only short stature and amenorrhea without dysmorphism.

Diagnosis

1. Buccal smear → chromatin (Barr) body –ve
2. Karyotyping: Diagnostic (skin fibroblast karyotype can exclude mosaic Turner)

Treatment: a- Growth hormone b- Estrogen replacement at 14-15 years

Down Syndrome

Definition: Down syndrome is the commonest autosomal numerical disorder due to Trisomy 21 due to

- Non disjunction in 95% of cases (Called regular Mongol)
- Mosiacism in 1% of cases
- Translocation in 4% of cases

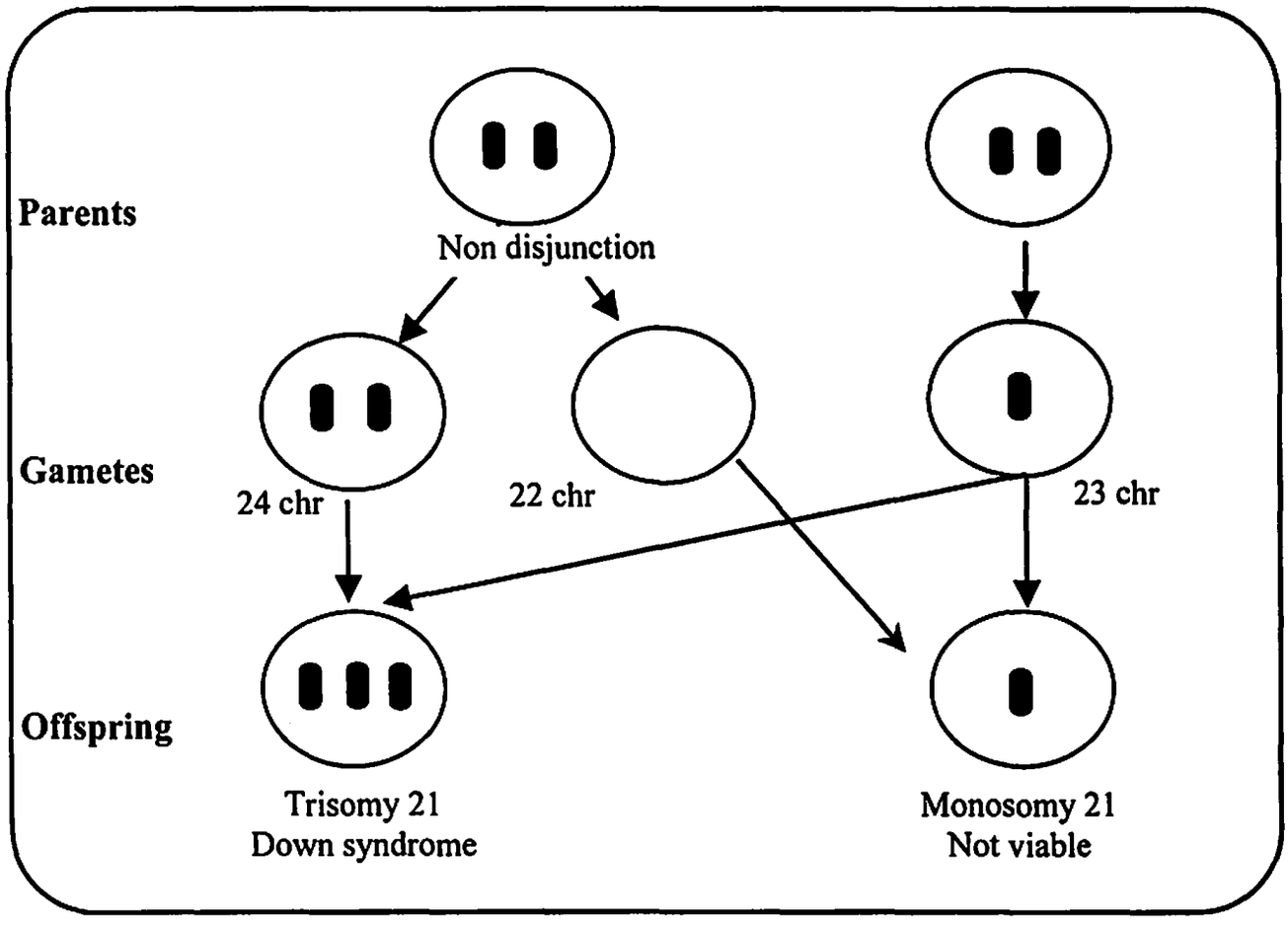
i. Non disjunction

Etiology: - Failure of the chromosomes to disjoin normally
- Occurring during gametogenesis (meiosis).

⇓

Production of a gamete with an extra chromosome 21

Source of extra chromosome: Maternal in 97% of cases (paternal in 3%).
Recurrence rate: Incidence increases with increasing maternal age.
(1/100 if age > 35 years.)
Chromosomal study: Baby karyotype is 47 XX (+ 21) or 47 XY (+ 21).



ii- Mosiac Down syndrome

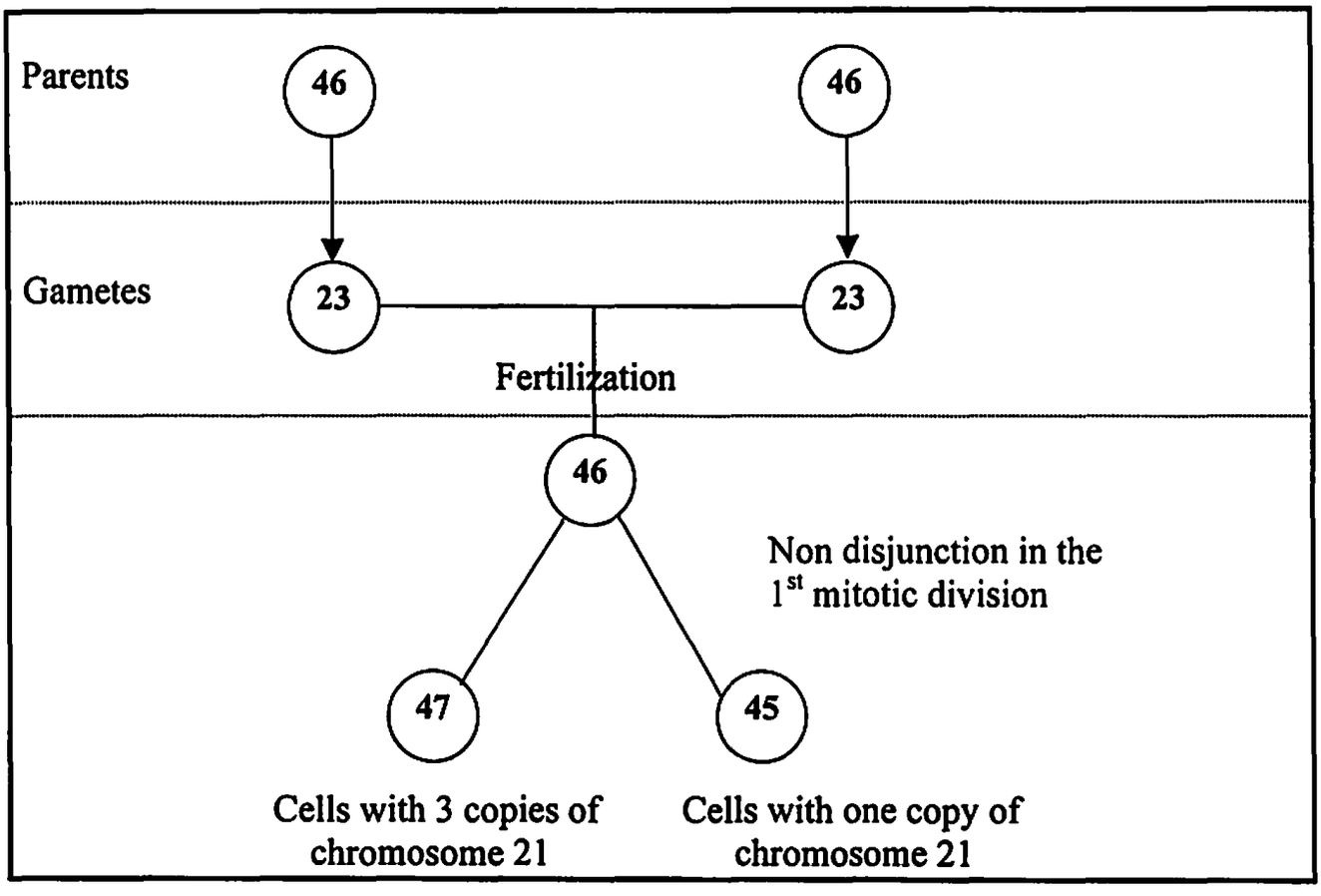
Etiology:

Non disjunction occurring post fertilization during the 1st or the 2nd mitotic divisions.

Chromosomal study:

Baby karyotype show either

* 2 cell lines → if non disjunction occurred in the 1st mitotic division
  e.g. Female Down mosaic : 47, XX, (+ 21) + 45, XX, (- 21)
* 3 cell lines → if non disjunction occurred in the 2nd mitotic division
  e.g. Female Down mosaic : 47 ,XX ,(+ 21) + 45,XX,(- 21) + 46,XX



iii- Translocation Down syndrome

Etiology: Chromosome 21 is translocated onto another chromosome it occurs only with another *acrocentric chromosome* i.e 14, 15, 21, 22.

How?

* The short arms of the acrocentric chromosomes contain no essential genetic material & being very short, they are easily lost→ The long arms of two acrocentric chromosomes may fuse together making one long chromosome without genetic loss.
* If translocation occur in a parent cells → he's a balanced translocation carrier.
* **In 25%** of translocation Down syndrome→ one parent is balanced translocation carrier
* **In 75%** of cases → translocation appears in a parent gametes as a mutation.

Recurrence rate:

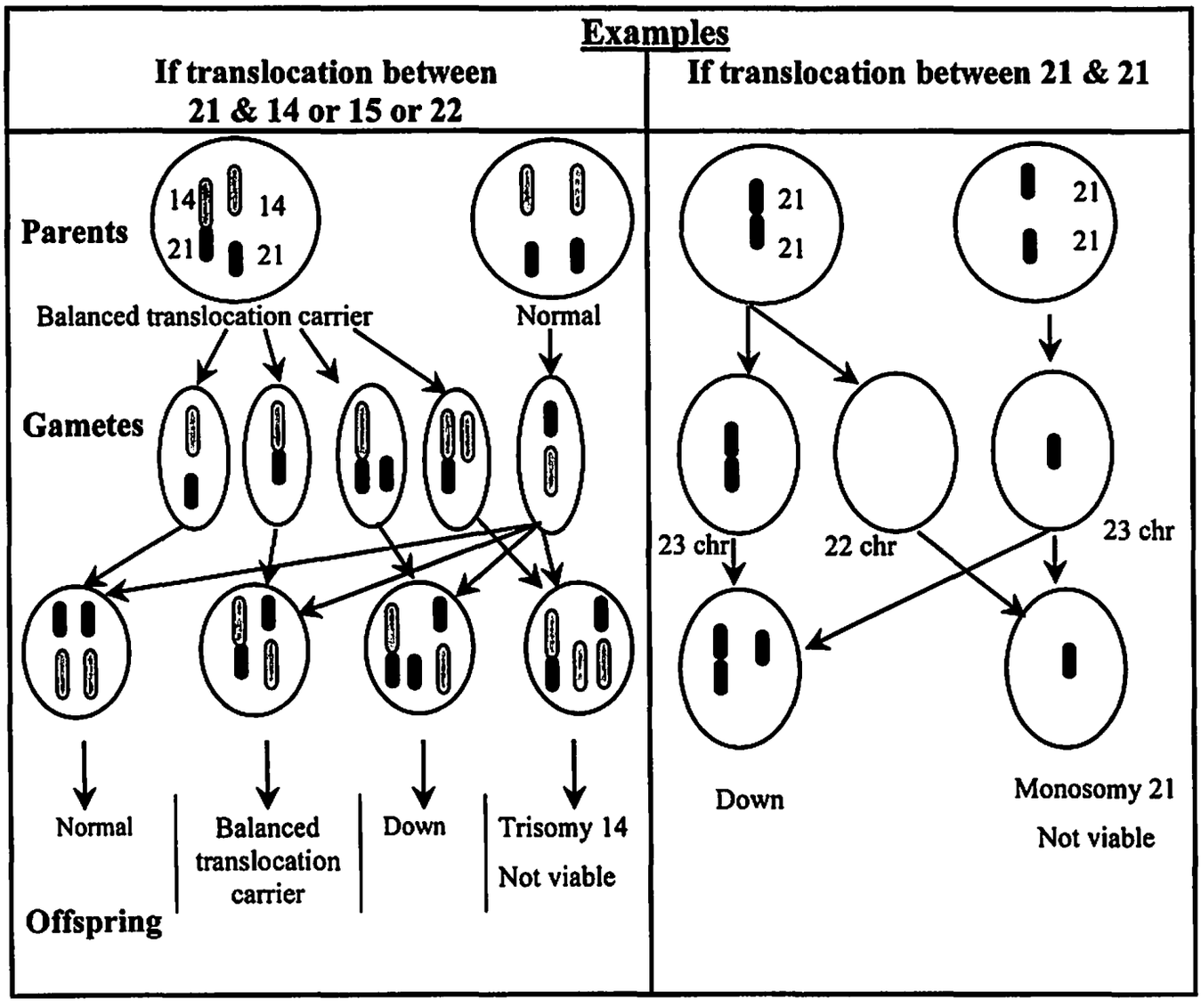
- In translocation between chromosome 21 & either 14, 15, 22
  - ↓ Four possibilities
    - → Abortions
    - → Balanced translocation carrier.
    - → Down syndrome
    - → Normal
- In translocation between chromosomes 21 & 21
  - ↓ Two possibilities
    - → Abortions
      or
    - → Down syndrome

    i.e. 100% of viable will be Down.

Chromosomal study

* For baby → e.g. 46 ,XX ,(t 21q / 14q) **or** 46 ,XY, (t 21q / 14q).
* For parents → may show balanced translocation carrier .
  e.g. Balanced translocation carrier mother : 45 ,XX ,(t 21q / 14q)

Examples

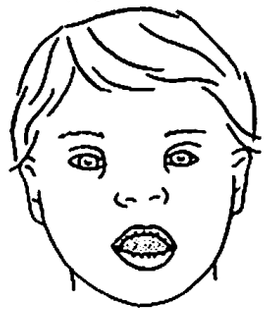


Clinical picture

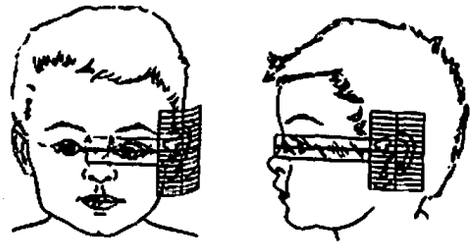
1. Delayed mental milestones → Mental retardation

2. Delayed motor milestones: Due to hypotonia → hyperflexible joints; Acrobat sign.

3. Head:



* Skull : - Mild microcephaly
  - Brachycephaly (short anteroposteriorly)
  - Wide posterior fontanel (at birth)
  - Large anterior fontanels
  - Fine silky hair
* Eyes : - Hypertelorism
  - Epicanthal fold
  - Upward slanting of eyes
  - Bruchfield spots (speckled iris)



* Ears : - Low set ears
* Nose : - Small nose with depressed bridge
* Mouth : - Small mouth
  - Protruding, fissured (scrotal) tongue in a child > 6 yrs
  - Delayed teething

4. Heart - Congenital heart disease in about 50% of cases
- Endocardial cushion defect and VSD are the most frequent.

5. Abdomen - Distended with umbilical hernia
- Visceroptosis

6. Genitalia - Small sized (hypogonadism)
- Undescended testis is frequent

7. Hands - Short & broad
- Simian crease : one transverse crease
- Clinodactyly : incurved little finger due to rudiment middle phalanx
- Wide a.t.d angle

8. Feet - Short & broad
- Wide gap between 1st & 2nd toes
- Leading crease (Ape crease).

Complications

1. Immunodeficiency → recurrent infections → chest, skin, otitis media
2. Neurological:
   - Moderate to severe mental retardation(mean IQ 50%)→ accidental trauma
   - Autism
   - Increased risk of senile dementia of Alzheimer.
   - Atlanto axial instability with risk of spinal cord injury.
3. Cardiac: Congenital heart disease → recurrent heart failure& recurrent chest infection

4. Respiratory: - Recurrent chest infections
   - Obstructive sleep apnea(due to large tonsils, adenoids, tongue)
5. Genitourinary: Renal anomalies and hypogonadism.
6. Hematological: Acute myeloid leukemia (*20 times more common*).
7. Endocrinal : - Acquired hypothyroidism
   - Diabetes mellitus
   - Addison disease
8. Gastrointestinal anomalies: - Doudenal atresia
   - Hirschsprung disease.
   - Imporforate anus
   - Annular pancreas
9. Others: Obesity , hearing loss , psychiatric disorders

Investigations

1- Karyotyping

a. For the baby to:
   - Confirm Down syndrome
   - Decide the type of Down syndrome and then the risk of recurrence

b. For the parents if the baby translocation type

2- For suspected anomalies e.g.

a. Echocardiography.

b. Hormonal assay

3- Prenatal diagnosis

1- A screening method can suspect up to 95% of fetuses with Down using:
   * Maternal age
   * Fetal ultrasound at 15-20 weeks → Nuchal pad thickness ≥ 6mm
   * Maternal α feto protein (Low).
   * Unconjugated estriol (Low)
   * β Human chorionic gonadotropin (Elevated).
   * Pregnancy associated plasma protein A

(Nelson 2008)

2- Karyotyping for maternal amniotic fluid cells **or** chorionic villous sample for early diagnosis in suspected cases

Management of Down syndrome

1- Genetic counseling of the parents and education of them about the case and possible progression.

2- General health support e.g good nutrition, vaccination, vitamin supply, ...

3- Management of complications.

4- Rehabilitation as any case of mental retardation.

Other Trisomies

	Trisomy 18 (Edward's Syndrome)	Trisomy 13 (Patau syndrome)
Incidence	1/6000 live births	1/10.000
Karyotyping	47,XX, +18 or 47,XY, +18	47,XX, +13 or 47,XY, +13
Clinical picture		
Head and face	* Microcephaly * Dysmorphic face * Prominent occiput.	* Microcephaly * Dysmorphic face * Scalp defects(cutis aplasia) * Brain malformations * Cleft lip and palate
Extremities	* Hypertonia * Closed fist with overlapping fingers * Rocker bottom heel	* Polydactyly * Overlapping fingers &toes
Chest	Congenital heart diseases (VSD, PDA , ASD)	
General	* Mental retardation * Renal anomalies * Prenatal and post natal growth retardation * Only 5% live > 1 year	* Mental retardation * Visceral and genital anomalies * Prenatal and post natal growth retardation * Only 5% live > 6 months

Nelson (2008)

Infections

Scarlet Fever

Etiology

* Organism: Group A-β hemolytic streptococci (producing erythrogenic toxin).
* Route: Droplet infection
* Incubation period : 2-4 days.

Clinical picture

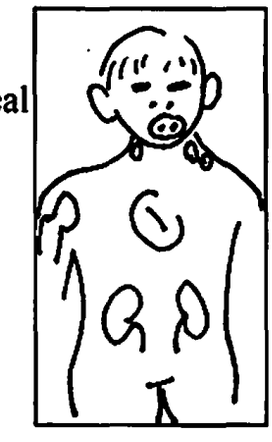
1. Sudden onset of fever& sore throat ⇒ the tonsils are red, enlarged with patches of exudates which may form a membrane
2. The tongue show:
   - In the 1st two days: white strawberry tongue ⇒ white coated tongue with red edematous papillae
   - By the 5th day: Red strawberry tongue ⇒ shedding of the white coat
3. Skin rash :
   - Appears in the 2nd day of the disease.
   - Starts in around neck then spread to the trunk.
   - Red maculopapular, fine punctate
   - In face it spares the peri oral area → flushed face with circumoral pallor
   - In deep creases (elbow, axilla, groin) → rash is more intense producing linear hyperpigmentation which don't blanch on pressure (Pastia's Lines).

Investigations

- Lecucocytosis with ↑ neutrophils.
- Positive throat culture.
- Raised ASO titer & Anti-DNase β titre
- Blanching of area of rash with intradermal antitoxin injection (Schultz-Charlton test)

Differential diagnosis: From other causes of maculopapular rash(see later)

Complications



1- Suppurative (septic) → in the 1st week
   a. Local : acute otitis media , sinusitis , mastoiditis , retropharyngeal abscess , and cervical lymphadenitis
   b. Distant: Bronchopneumonia , meningitis , arthritis

2- Non suppurative (aseptic) → after a latent period.
   a. Acute rheumatic fever
   b. Acute glomerulonephritis
   c. Erythema nodosum → red, raised, tender nodules.

Treatment

1. Symptomatic treatment including bed rest , light diet.
2. Specific treatment :
   - Oral penicillin V 250-500 mg / dose bid or tid for 10 days
   - Alternative : Benthazine penicillin 600.000-1.2 million units single IM injection
   - Erythromycin for penicillin sensitive patients.

Diphteria

Etiology

* Organism: Corynebacterium diphteria → G +ve bacilli producing powerful exotoxin.
* Route: Droplet infection
* Incubation period : 2-4 days.

Clinical picture

Start with malaise, prostration (due to toxemia) & low grade fever.

Clinical types

Pharyngeal diphteria	Laryngeal diphteria	Rare forms
The tonsil show grayish white dots → coalesce to form a membrane which is: - Usually unilateral. - Exceeds the tonsil. - Adherent → if removed leave raw bleeding area.	↓ Either 1ry or 2ry to pharyngeal type. · Squeals: - Stridor - Hoarsness. - Respiratory obstruction	- Nasal diphteria: nasal discharge ↓ unilateral; offensive; serosanguinous - Cutaneous - Conjunctival - Vulvovaginal

• Cervical lymphadenitis. with surrounding oedema (Bull neck).



Differential diagnosis

1- Pharyngeal diphteria → From other causes of pharyngeal membrane:

- ☆ Follicular tonsillitis (high fever- bilateral- ↑WBCs- throat swab).
- ☆ Post tonsillectomy
- ☆ Infectious mononucleosis.
- ☆ Oral moniliasis.
- ☆ Agranulocytosis.
- ☆ Vincent's angina.

2- Laryngeal diphteria → From other causes of acute stridor

Investigations

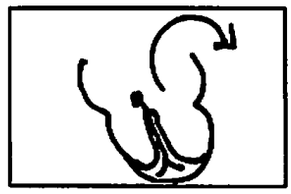
1- Isolate the organism on Loeffler's media in suspected cases.

2- CBC → WBCs is normal or slight ↑

Complications



1. **Respiratory complications:**
   - Airway obstruction by bull neck
   - Lung collapse (due to aspiration of detached membrane)
   - Bronchopneumonia



2. **Cardiac:**
   - Toxic myocarditis
   - Cardiogenic shock (paralysis of vasomotor center).
   - Heart block



3. **Polyneuropathy:**
   - Palatal paralysis : nasal tone and regurgitation of food
   - Ocular paralysis :- ptosis, squint
   - Pharyngeal & laryngeal paralysis: dysphagia , dysphonia
   - Generalized paralysis
   - Phernic nerve paralysis → respiratory failure

Treatment

1- Cases:

* Isolation & bed rest for 2weeks
* Diphteria antitoxin 20.000- 120.000 IU- IM or IV single dose.
  (avoid anaphylaxis by prior skin testing or concomitant steroids).
* Antibiotic : - Erythromycin(40 mg/kg/d) or Penicillin G (150.000 unit/kg/d iv)
  - For **14** days.

* After recovery : - Perform throat culture twice to ensure clearance
  - Vaccinate with diphtheria toxiod

2- Contacts:

* Diphteria antitoxin & penicillin course for **10** days.
* Booster dose of the diphteria toxoid vaccine may be given.

3- Prevention:

* DTaP vaccine.

Prognosis

- Recovery from myocarditis and neuropathy is slow but complete
- Mortality varies from 3-25% mainly related to myocarditis or respiratory failure

Pertussis (whooping cough)

Etiology

* Organism: Borditella pertussis & Borditella parapertussis (G -ve cocco bacilli)
* Route of infection: Droplet infection (mainly in child < 5y.).
* Incubation period: 1-2 weeks.

Clinical picture

1- Catarrhal stage (1-2 weeks)

- Coryza (mucoid rhinorrhea), conjunctivitis, cough, mild fever.
- The most infectious stage

2- Paroxysmal stage (4-6 weeks up to 10 weeks)

i- Paroxysms of cough:

- Series of > 5 cough in single expiration followed by a whoop (forcible inspiration against narrow glottis).
- During the attack; There's face redness, bulging eyes, tongue protrusion distended neck veins.
- Post tussive vomiting is very common especially in infants
- No abnormal signs on chest examination.
- Usual paroxysm is usually absent in infants < 2 months

ii- Triggers: Attacks may be triggered by eating, drinking , exertion.

3- Convalescence stage (1-2 weeks).

- Gradual decline in severity of paroxysms but cough may last for months

Complications: (more frequent in infants and young children)

1- Respiratory

- Otitis media
- Bronchopneumonia & pneumonia caused mainly by staph or strept
- Activate latent T.B focus
- Apnea & cyanotic attacks in infants < 6 months
- Atelectasis
- Bronchiactasis

2- Convulsions; may be due to:

- Brain damage (due to hypoxaemia)
- Intracranial hemorrhage.
- Tetany (severe vomiting → alkalosis → ↓ ionized Ca).

3- Mechanical ⇒ with severe paroxysms.

- Subconjuctival hemorrhage, epistaxis & intracranial heamorrhage in severe cases
- Ulcers of tongue frenulum.
- Pneumothorax
- Hernias ; umbilical & inguinal.
- Rectal prolapse.

4- Malnutrition due to anorexia , vomiting , and faulty food restriction

Diagnosis

* Clinical : Pertussis is suspected in:
  - Absent fever, exanthemes , sore throat , tachypnea , wheezes nor rales
  - Cough ≥ 14 days with at least 1 paroxysm , whoop or post tussive vomiting
  - Apnea or cyanosis in infants less than 3 months
* Nasopharyngeal swab and:
  - Microscopic examination.
  - Culture on Regan – Lowe charcoal agar
  - PCR
* CBC : leucocytosis with absolute lymphocytosis.

Differential diagnosis: from other causes of chronic cough

1. Adenovirus infection ;associated with fever , sore throat and conjunctivitis.
2. Chlamydia trachomatis infection ; associated with staccato cough, purulent conjunctivitis, wheezes and rales.
3. Bronchial asthma:
   - Recurrent wheezy chest
   - Related to allergens or exercise
   - Respond to bronchodilators
   - Relatives with asthma
4. Foreign body inhalation
5. Pulmonary tuberclosis
6. Mycoplasma pneumonia
7. Suppurative lung syndromes e.g. Cystic fibrosis , immunodeficiency

Treatment

1- Cases: (admit young infants).

General:

- Isolation for 5 days after starting antibiotics or 3 weeks after start of paroxysm
- Bed rest
- Symptomatic treatment; avoid triggers of cough.
- Care of feeding: small frequent feeds or tube feeding

Antibiotic:

* Values: Reduction of infectivity period and possible clinical improvement.
* Choice:
  - Azithromycin 10 mg/kg/day for 5 days
  - Clarithromycin 15 mg/kg/day for 7 days
  - Erythromycin 50 mg/kg/day for 14 days

2- Contacts:

- Antibiotic as for cases regardless immunization state.
- ± Booster dose of DTaP.

3- Prevention:

- DTaP vaccine

Prognosis: Directly related to patient age; highest mortality in infants < 6 months.

Enteric Fever (typhoid fever)

Organism : Salmonella typhi & paratyphi (A,B,C) ⇒ G-ve bacilli

Pathogenesis

- Transmitted by faceo-oral route
- From cases or carriers
- Bacteria proliferate in payer's patches in small intestine
- Followed by primary bacteremia
- Distributed to Reticuloendothelial system (RES) organs

Clinical picture

1- **Prodroma (1st week):**

* Insidious onset of headache, prostration , anorexia and fever
* Fever has a stepladder pattern ; rising up to 39-40 C°
* Coated tongue
* Relative bradycardia
* Diffuse abdominal pain
* Pea-soup diarrhea may occur early but constipation predominates later.
* Rose spots :
  - Erythematous maculopapular rash on the lower chest and abdomen
  - Appear in 25% of patients
  - By the end of 1st week
  - Last 2-3 days
  - Leaves slight brownish discoloration on healing

2- **2nd week:**

* Fever becomes high and continuous
* Patient appear acutely ill , disoriented and lethargic (status typhosus)
* Tachycardia (due to myocarditis)
* Diffuse abdominal pain with splenomegaly and may be hepatomegaly

3- **3rd week:**

* Gradual improvement of general condition & decline of fever
* Complications may occur.

Complications

- Neurologic	Encephalopathy , cerebral edema , Guillian Barre syndrome
- Cardiac	Pan carditis and heart failure
- Pulmonary	Pneumonia , empyema
- Gastro intestinal	Intestinal perforation , intestinal hemorrhage Cholycystitis (possible carrier state) , hepatitis , splenic abscess
- Renal	Pyelonephritis , cystitis (possible carrier state)
- Others	Osteomyelitis , septic arthritis

Investigations

1. CBC → anemia & leucopenia (toxic depression of bone marrow).
2. In the 1st week → Blood culture is positive in 40-60% of cases.
3. In the 2nd week onwards:
   * Positive stool culture.
   * Positive Widal test (titer >1/160) → Detect antibodies against O & H antigens
     → Never used alone to prove diagnosis
4. In the 3rd week → urine culture.
5. Recent investigations:
   - Amplification of S. Typhi specific antigens using PCR.
   - Detect S. Typhi specific antigens using monoclonal antibodies
   - Culture of bone marrow cells (not affected by prior use of antibiotics)

Treatment

1- Cases:

- Bed rest & light diet
- Symptomatic treatment
- Treatment of complications.
- Antibiotics:

Microbial state	Antibiotic	Dose (mg/kg)	Duration (days)
Fully sensitive	- Chloramphenicol	50	14
	- Amoxicillin	100	14
Multi drug resistant	- Floroquinolone	15	7
	- Cefixime	15	14
Quinolone resistant	- Ceftriaxone	75	7-14
	- Azithromycin	10	14

Other effective drugs: ampicillin , cefotaxime

(Nelson 2008)

2- Prevention:

- Food & water hygiene
- Vaccine → Ty21a or Vi capsular conjugate vaccine (TAB vaccine is obsolete)

Prognosis

* With early antibiotic therapy; mortality is less than 1%
* Relapse occur 1-3 weeks later in 10-20% despite appropriate antibiotics

Tetanus

(Lock Jaw)

Etiology

Clostridia tetani (gram positive spore forming, anaerobic bacilli)

↓

Spores excreted in animal execreta → contaminate soil, dust & water

↓

Contaminate wounds, umbilical stump, surgical & vaccine sites

↓

Spores germinate → proliferate locally → produce 2 toxins (tetanospasmin & tetanolysin) which travel along nerve trunk & blood stream

↓

Reach the CNS then redistribute to spinal cord, brain & motor end plate.

Clinical picture

Incubation period: 1-14 days but may be longer

1- Mild tetanus

* Pain & stiffness at site of injury for few weeks
* Occur in patients who received the antitoxin before
* Mortality < 1%

2- Generalized tetanus (typical form)



* Spasms occur in descending form with intact consciousness:
  - Trismus :difficult moth opening due to massetter spasm.
  - Risus sardonicus : grimacing face due to facial muscles spasm
  - Langyngeal spasm → stridor & may be suffocation
  - Opisthotonus → arched back
  - Tonic seizures → flexed adducted arms & extended lower limbs with colonic exacerbations.
* Spasms precipitated by visual or auditory stimuli

3- Cephalic tetanus

- Follow head injury or otitis media.
- Short incubation period with high mortality
- Involve cranial nerves palsy.
- May be followed by generalized form

4. Tetanus neonatorum (tetanus in newborn)

* Infantile form of generalized tetanus
* Manifest within 3-12 days of birth by:
  - Progressive feeding difficulty with crying
  - The umbilical stump may appear dirty (portal of entry of microbe)
  - Paralysis
  - Spasms and stiffness precipitated by touch

Complications

a. Respiratory

- Laryngeal spasm → suffocation
- Aspiration pneumonia
- Pneumothorax
- Lung collapse.

b. Mechanical: (with severe seizures)

- Tongue laceration
- Vertebral fractures
- Muscle heamatoma.

Differential diagnosis

1- Rabies:- History of animal bite.
- Fits tend to be intermittent & clonic.

2- Tetany: Carpopedal spasm

3- Strychnine poisoning:
- History of ingestion
- Muscles relax between spasms.
- Normal temperature.

4- Other causes of trismus e.g.:
- Peritonsillar or retropharyngeal abscess.
- Phenothiazine poisoning

5- Other causes of opisthotonus:-
- Meningitis.
- Meningism

Diagnosis

1- History of wound and typical spasms

2- Normal CSF.

3- Wound culture may be helpful.

Treatment

I. Prevention

1- **Active immunization** (DTaP or DT) at 2,4,6, 18 months & 4 years.

2- **Prevention of tetanus after injury:**

a- Surgical management of the wound (better left opened.)

b- Prophylaxis as follows (according to immunization history):-

1- Unknown or received less than 3 doses of toxoid:
* Booster dose of diphtheria toxiod vaccine
* Tetanus immunoglobulin(500units) or tetanus antitoxin(5000 units) for contaminated wounds

2- If received 3 doses or more of toxoid → ask for time of last toxiod dose:
* In clean wounds , if ≥ 10 years → booster dose
* In clean wounds , if < 10 years → nothing
* In contaminated wounds , if ≥ 5 years → booster dose
* In contaminated wounds , if < 5 years → nothing **(Nelson 2008)**

3- Prevention of tetanus neonatorum:

* Maternal vaccination with at least two doses of tetanus toxiods
* Aseptic cutting of the umbilical cord (see tetanus neonatorum).

II. Curative

1- The patient is kept in quiet, dark room.

2- Supportive → I.V fluids

→ Respiratory Care:- Suctioning.
- Keep patent airway
- Oxygen inhalation
- May need assisted ventilation.

3- Diazepam I.V for spasms (0.1 – 0.3 mg/kg).

4- Toxin neutralization

- Tetanus immunoglobulin 3000-6000 IU
- Anti tetanic serum (tetanus antitoxin) 50.000-100.000 IU
(½ the dose IM & ½ I.V)

5- Anti microbial treatment:

- Penicillin G 200.000 IU/kg/d I.V for 10 days.
- Alternative → Metronidazde I.V infusion.

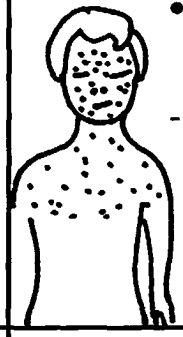
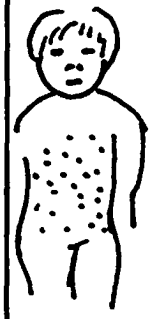
6- Immunization after recovery:

- Patient will need vaccination with tetanus toxiod after recovery

Prognosis

* Fatality is high in: cephalic form, neonatal tetanus and in un immunized.
* If the patient survive 1 week, recovery is likely
* Favorable cases: seizures decline over 3 weeks.
* Unfavorable cases: deterioration & death from cardiac or respiratory failure.

	Measles (Rubeola)	Rubella "German Measles" (3 days measles)	Roseola infantum (6th disease)	Erythema infectiosum (5th disease)
A/E	RNA virus One antigenic type, so, one attack gives life long immunity	RNA virus	Human herpes Type -6	Human parvo B19 DNA virus
Route	⇒ direct droplet infection, air borne infection, and via contaminated articles & fomites ⇒ no other modes	⇒ transplacental	(usually from caretaker)	⇒ transplacental
I.P.	1-2 weeks	2-3 weeks	5-15 days	5-15 days
Infectivity	5 days before & 5 days after rash	7 days before & 7 days after the rash	unknown	unknown
C/P	**Catarrhal stage:**  -fever -conjunctivitis -coryza (rhinits) -cough (dry) <u>Koplick's spots</u>: (pathognomonic) • appear on the 3rd day • opposite the lower molar teeth • greyish white dots with red areolae. • disappear 2 days after the rash.	➢ **Catarrhal stage**: (very mild)  -mild fever -nasophanryngitis -rose spots may appear on the soft palate before the rash (Forchhiemer spots) ➢ Tender enlargement of posterior cervical & postoccipital lymph nodes is charachteristic - appear 24hr. before rash and last for up to 1 week.	➢ Peak age 5-15 months. ➢ No catarrhal stage • Abrupt high fever up to 39-40 °C. • Febrile fits is common • Fever fall by crisis at the 3rd – 4th day	• Catarrhal stage very mild

	Measles (Rubeola)	Rubella "German Measles" (3 days measles)	Roseola infantum (6th disease)	Erythema infectiosum (5th disease)
	Eruptive stage • maculopapular rash. • on the 4th day of fever • fever rises up to 40 °C for 2 days then rapidly fall.  • the rash start behind the ear near the hair line <u>then</u>. involve the face & neck <u>then</u> the trunk & arms. • When reach lower limbs, it fade from the face.	• maculopapular rash • on the 2nd day of fever. • fever drops when the rash appear.  • rash start in face then involve trunk & limbs. - when reach the trunk, it fade from the face.	• maculopapular rash rose-like • appear 12-24 hours after fever drop.  • rash start on the trunk → then rise to involve neck, face & lower limb. • rapidly fade in 2 days	• maculopapular rash - sudden appearance of livid erythema in face →(slapped cheeks)  • rash start on the trunk & extremities • rash is pruritic • fade with central clearing → reticulated appearance.
	Convalescence stage Rash fade in order of appearance with fine branny desquamation (except in palms & soles)	Rash fade on the 3rd day (⇒ 3 days measles) with little or no desquamation	Rash fade rapidly without desquamation	Rash may last from 2-39 days, then, fade without desquamation
	Clinical types: • <u>mild</u> → rash doesn't reach legs. • <u>attenuated</u> → if gamma globulin is given during incubation period • <u>severe</u> → bullous rash <u>or</u> → hemorrhagic; black measles: (confluent rash; cover whole body with bleeding rash & orifices)	• ordinary type • congenital rubella syndrome if the mother catches infection during pregnancy specially in 1st trimester		

	Measles (Rubeola)	Rubella "German Measles" (3 days measles)	Roseola infantum (6th disease)	Erythema infectiosum (5th disease)
Investigations	➢ Virus isolation from blood. & nasopharyngeal secretions ➢ Rising antibody titre	➢ Virus isolation from nasopharynx during rash ➢ Rising antibody titre		➢ PCR → detect viral DNA ➢ Parvo B19 IgM
Complications	**Respiratory:** 1- Secondary bacterial infection with streptococci is very common suggested by: - marked increase of fever. - malaise and prostration - lecocytosis  ➢Otitis media → very common. ➢Sinusitis & tonsillopharyngitis ➢Laryngitis & tracheobronchitis (viral or 2ry bacterial infections) ➢Pneumonias; may be:- - viral → early (severe course) - Bacterial → late (mild course) 2- Hect's pneumonia → viral pneumonia with multinucleated giant cells in the lungs. 3- Activation of T.B focus due to temporary loss of hypersensitivity to tuberculoprotein for 4-6 weeks. **GIT**  • ulcerative stomatitis up to cancrum oris • enterocolitis • gastro enteritis • may be complicated with malnutrition. **Neurologic** ⇒ rare ♦Brain:- encephalitis → direct viral or slow virus infection which manifest years after measles attack. (Subacute Sclerosing Panencephalitis) which leads to intellectual deteriorations, convulsions, motor defects, usually ending in death.	♦Thrombocytopenia may occur 2 weeks past infection ♦Encephalitis ♦Arthritis of small joints ♦Congenital rubella syndrome ♦ Progressive rubella pan encephalitis	Complications are rare : ♦Encephalitis ♦Pneumonia	♦ Arthritis lasting for 2-4 weeks, resolve without residuals. ♦ Erythroblastopenic crisis in chronic hemolytic anemia. ♦ Fetal hydrops

	♦ Meninges → aseptic meningitis. ♦ Blood vessels → thrombophlebitis & hemiplegia Cardiac → myocarditis, Hematologic: → DIC, thrombocytopenia.			
Prevention **Treatment**	♦Measles vaccine ♦vitamin A → single dose with the vaccine (immune enhancer) **1- For cases:** - symptomatic e.g. eye care - care of feeding - antibiotics for 2ry infection. - vitamin A → 100.000-200.000 IU single oral dose reduce measles morbidity in malnourished ,immunodeficiency and in infants aged 6mo-2years **2- For contacts:** passive immunization with measles immunoglobulin 0.5 ml/kg , IM 1- If given within 6 days of exposure → Prevent the disease but vaccine is needed 2 months later "seroprevention" Indicated in: ➢ Immunodificient contacts ➢ Infants less than 6 months of non immune mothers. 2- If given after 6 days of exposure → attenuate the virus → mild disease plus immunity "seroattenuation"	♦Rubella or MMR vaccine given between 15 mo-puberty. **1- For cases** ➢ symptomatic: ➢ for pregnant females → test immunity twice 4 weeks apart by - enzyme immunoassay or - fluorescent immunoassay 1- If immune (high titre of IgG), continue pregnancy 2- If not immune either: - Give I.V immunoglobulin Or - Therapeutic abortion (better) **2- For contacts** for pregnant females test immunity & manage as before	**For cases:** ➢ Symptomatic ➢ Ganciclovir for complicated cases	**For cases:** ➢ Symptomatic ➢ IV immunoglublin for immunodificients and chronic hemolytic anemia patient.

Infectious Mononucleosis

(Glandular Fever)

Etiology: Ebstein Barr virus (DNA, oncogenic virus)

↓

Infection occur via

droplet infection — rarely

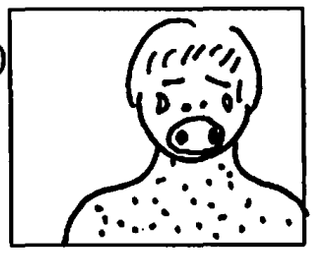
blood borne

Incubation period = 1 – 2 months

The virus infect the epithelium then establish in B-lymphocytes

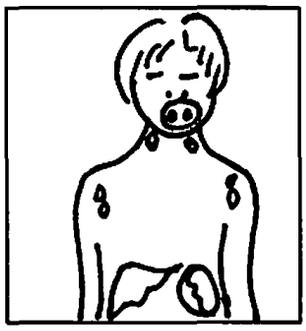
Clinical picture

I. Prodroma



- Fever (gradual ↑ up to 39 °C then decline over 7 days)
- Sore throat
- Fatigue
- Skin rash → maculopapular; in 15% of cases
  (in up to 90% if ampicillin is given)

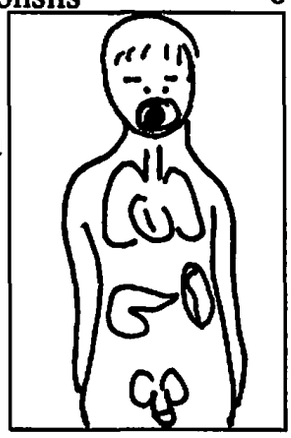
II. Full Blown picture



- Tonsillopharyngitis → with thick white membrane over the tonsils.
- Generalized lymphadenopathy.
- Splenomegaly (rapidly occurring → tender).
- Hepatitis.

Complications

1- Upper airway obstruction by enlarged tonsils



2- Pneumonia

3- Myocarditis

4- Rupture spleen; even with minor trauma

5- Hematologic disorders:
- Aplastic anemia.
- Auto immune hemolytic anemia.
- Thrombocytopenia.

6- Rarely:
- Meningitis & encephalitis.
- Parotitis
- Pancreatitis
- Orchitis

Investigations

1- Absolute lymphocytosis with atypical lymphocytes.

2- Detection of heterophil antibodies by Paul Bunelle test & monospot test

3- Detection of EBV IgM. (specific)

N.B. EBV is ocogenic virus incriminated in:

☆ Nasopharyngeal carcinoma
☆ Burkitt's lymphoma

Treatment

➢ Symptomatic treatment:
- Antipyretics (avoid aspirin)
- Bed rest
- Avoid contact sports in the first 2-3 weeks (to avoid rupture spleen)

➢ Steroids for: - Tonsillar enlargement with upper airways obstruction.
- Auto immune hemolytic anemia.
- Thrombocytopenia.
- Seizures and meningitis.

➢ Treatment of complications

Differential diagnosis of maculopapular rash

1- Viral infections:
* Measles
* Rubella
* Roseola infantum
* Erythema infectiosum
* Infectious mononucleosis.
* Entero viral infections: - Mild constitutional manifestations
- Mild eruption
- Serologic diagnosis

2- Ricketssial infections: - Rash sparing the face
- Serologic diagnosis

3- Bacterial infections:
* Scarlet fever.

4- Vasculitis (No prodrome like previous infections)
* Kawasaki disease: Fever at least for 5 days plus 4 out of five:
- Bilateral non purulent conjunctivitis
- Unilateral cervical lymphadenitis
- Strawberry tongue, cracked lips
- Maculopapular rash
- Erythema and peeling in digits
* Meningococcaemia :
- Marked toxemia
- Absence of cough
- Positive blood culture & CSF examination.
* Serum sickness and drug eruption :
- History of drug intake
- Marked itching
- Absence of cough

5- Insect bites (e.g. fleas) → Itching ; insect may be seen
→ Lesions fade on pressure.

Chicken Pox
(Varicella)

Etiology

* Virus : Varicella Zoster (DNA, human herpes) virus which can cause:
  - Varicella in children
  - Herpes Zoster (if reactivated in adult)
* Transmission : - Droplet infection from cases
  - Contact with skin lesions from cases
* Incubation period : - 2-3 weeks
  - Patients are infective 2 days before the rash and till the rash crusted

Clinical picture

a. Prodroma :- mild ; slight fever, anorexia.

b. Eruptive stage:-

* The rash start on the trunk then involve the face, with little involvement of the limbs.
* The rash start as red papule → vesicles (tear drop on erythematous base) → crusts → pustules may forms.
* Lesions are pleomorphic (all stages can be seen at the same time).
* Rash is itchy.
* In mucus membranes → viscles may ulcerate.

c. Clinical forms of chicken pox

Classic form as before	Hemorrhagic form in immunodeficient ↓ Hemorrhagic rash with thrombocytopenia	Varicella bullosa ↓ Bullae instead of viscles in child less than 2 years

Complications

1. Secondary bacterial infection of the vesicles
   - The commonest complication ; mainly due to streptococci & staph. aureus
   - Result in bullous impetigo, cellulitis, erysipelas.
2. Rye's syndrome ⇒ 10% follow varicella especially if aspirin is given.
3. Thrombocytopenia & purpura fulminans → Fatal course if adrenal hemorrhage occur.
4. Neurologic: - Cerebellar ataxia
   - Guillian barre syndrome.
   - Encephalitis with fits & coma.

5. Respiratory → laryngitis & viral pneumonia.
6. Pancarditis.

♦Death may occur in:

- Children receiving steroids & chemotherapy.
- Children with depressed T-cell immunity.
- Adults

Treatment

I. Prevention ⇒ chicken pox vaccine:

- Live attenuated.
- Given at 12-18 months age.
- Dose: - Single dose between 12 months to 12 years.
  - Above 12 years → 2 doses 4 weeks apart
- Protective value up to 95%.

II. For cases

* Symptomatic treatment e.g. - antipruritic
  - antipyretic (paracetamole).
* Antibiotics for 2ry bacterial infection.
* Antiviral ⇒ acyclovir 20 mg/kg/dose, given 4 doses per day, for 5 days.
  - For children more than 12 months
  - Value: modify clinical picture and prevent complications.

III. For contacts

* Avoid aspirin (to avoid Rye syndrome)
* Zoster immunoglobulin for:
  - Immunodeficient contacts.
  - Newborn to mothers with maternal varicella.
* Oral acyclovir in late incubation period may be protective.

Mumps

(Epidemic Parotitis)

Etiology

* Virus: RNA virus affecting salivary glands.
* Transmission: Droplet infection from human cases
* Incubation period: 2-3 weeks.
* Incidence : - Common age = 5-15 years.
  - One attack gives life long immunity.
  - Trans placental immunity last for 6 months
  - More in winter.

Clinical picture

* about 25-30% are subclinical
* Prodroma → mild fever, malaise & myalgia.
* **Salivary gland swelling** ⇒ parotid and may be submandibular & sublingual

Parotid gland	Submandibular gland	Sublingual gland
- Tender parotid swelling → push the ear forward - Swelling increase by teeth clinching and decrease by mouth opening. - Hyperemic and obstructed stenson duct orifice. - Swelling increases to maximum over 3 days and decline over 5 days. - Usually one side precede the other.	- May be with parotitis. - Alone in 10%. - Less painful but lasts longer.	- Least common. - Produce submental swelling. - May be associated with chest wall edema.

Differential diagnosis

1- Parotid stone (acute obstructive parotitis)
- Pain increase by mastication.
- Stone may be felt under the skin or detected by X-ray.
- Swelling may be intermittent.

2- Parotid abscess
- Mainly due to staph aureus.
- High fever:
- Throbbing pain.
- Pus may oozes from Stenson duct orifice.

3- Mickulic's syndrome: - Enlarged lacrimal & parotid glands

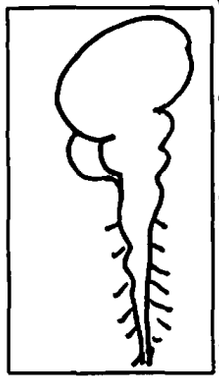
4- Uveal parotid fever
- Parotitis & irridocyclitis
- In T.B & sarcoidosis

5- Endemic parotitis → bilateral painless swelling of parotids due to malnutrition, ankylostoma, chronic anemia.

6- Upper deep cervical lymphadenitis:
- Well defined border.
- Swelling lie below angle of mandible.
- Raising angle of mandible is not tender in contrast to parotitis

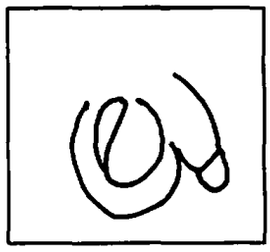
Complications

1- Meningeo encephalo myelitis ⇒ occur in ≈ 10% of cases



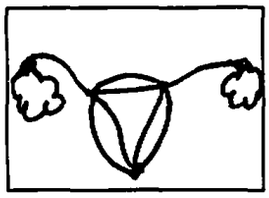
- Incidence: - The most frequent complication in children
  - Occur in 1:400 cases
- Due to either: - Viral infection of neurones (occur with parotitis)
  - Post infectious (10 days after parotitis)
- C/P → fever
  → vomiting
  → severe headache → convulsions → coma.
- Investigation: CSF show viral infection (↑protein -↑ lymphocytes)
- Fate → respond well to supportive treatment.
  → may result in aqueduct stenosis and hydrocephalus

2- Orchitis & epidydimitis



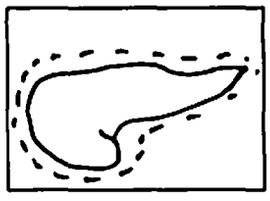
- Incidence: - more in adolescents boys (≈ 20%)
- Usually follow parotitis even may occur with out parotitis.
- C/P: → Fever, chills & lower abdominal pain.
  → Testis are enlarged, red, hot & tender.
  → Usually unilateral (Bilateral in 30%).
- Fate: Impaired fertility may occur due to tough tunica albuginea → testicular atrophy.

3- Oophoritis



- Incidence: - More in post pubertal girls (≈ 7 %).
- C/P: → pelvic pain & tenderness.
- Fate: No impairment of fertility due to loose connective tissue ovarian capsule.

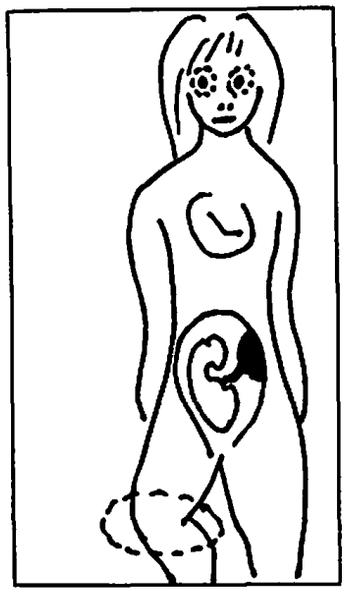
4- Acute hemorrhagic pancreatitis



- Incidence: - Rare (usually occur 10 days after parotitis).
  - May occur even without parotid swelling.
- C/P → epigastric pain with tenderness, vomiting, fever & prostration.
- Investigation → increase serum & urinary amylase is characteristic.

5- Other rare complications

- Ocular
  - Dacryoadenitis
  - Optic neuritis
  - Scleritis
- Thrombocytopenia
- Migratory polyarthralgia & Polyarthritis of big Joints



- Deafness, usually unilateral
- Thyroiditis
- Myocarditis
- Mumps emberyopathy:-
  - Abortion or
  - Enocardial fibroelastosis of fetal heart

Diagnosis

1- Clinical picture.
2- CBC: Leucopenia with relative lymphocytosis.
3- Increased serum amylase.
4- Detection of mumps IgM or rising titre of IgG.
5- Isolation of mumps virus.

Treatment

i- Prevention

Active: - MMR vaccine at 18 month age.
- Another dose is recommended at 4-6 years.

Passive: Hyper immune mumps gamma globulins.

ii- Cases

✧ Isolation.
✧ Rest till swelling disappear.
✧ Diet → soft (avoid sour fluids).
✧ Treatment of complication e.g orchitis → support testis
→ analgesics
→ with or without steroids

Poliomyelitis

Causes: - RNA enterovirus with 3 serotypes (I, II, III)
- No cross immunity between these serotypes (so, reinfection may occur)

Transmission

Droplet infection ⇓
The virus reach the tonsils then to deep cervical lymph nodes

Faeco oral infection ⇓
The virus reach the intestine → multiply in peyer's patches then spread to mesenteric lymph nodes

This is followed by viremia ⇓
In favourable conditions the virus reach CNS

Incubation period → 1-3 weeks.

Outcome of infection ⇒ Not all infected cases develop the disease
→ incidence is 1 for 10.000 depending on.

Virulence of the virus (type I is the most potent)

Host factors ⇓
Incidence increase with :-
- Muscular fatigue, trauma, I.M injection
- Recent tonsillectomy
- Extremes of age
- Inoculations e.g. DPT vaccine.

Outcome of the disease :
Damage to motor nuclei in spinal cord (anterior horn cells) and brain stem → atrophy of muscles supplied by these motor cells.

Clinical Forms

❶ **Abortive poliomyelitis** (minor illness):-
- Occur mainly in children.
- The commonest form (80-90%) may present as:-
  a. Upper respiratory symptoms → fever, rhinitis and sore throat.
  or
  b. Abdominal symptoms → vomiting ± diarrhea

❷ **Non paralytic poliomyelitis ⇒ as abortive plus picture of aseptic meningitis:**

- Pain & stiffness in neck, back & extremities



- If the baby lifted ⇒ head drops backwards due to weak neck muscles.
- Tripod sign ⇒ ask the baby to sit ⇒ there will be 3 points of support = buttocks, hands behind & feet in front.

> *N.B:* Progression to paralytic polio is evidenced by:
> 1- Disappearance of superficial reflexes.
> 2- Change of deep reflexes (↑ or ↓); both occur hours before paralysis.

❸ **Paralytic poliomyelitis:** characters of paralysis ⇒

- ✧ Lower motor neurone ⇒ hypotonia, hyporeflexia with muscle wasting
- ✧ Asymmetric ⇒ one limb is affected more than the other.
- ✧ Patchy distribution ⇒ affect some groups (esp. the large) sparing others in the same limb.

Types of paralysis

Spinal ⇓
- Limbs → 2ry inability to walk.
- Respiratory muscles → Respiratory failure.
- Trunk muscles → scoliosis.

Bulber ⇓

Paralysis of medullary nuclei

Motor nuclei ⇓

Cranial nerves 9,10,11,12 ⇓

Palato-pharyngeo-laryngeal paralysis

Vital centers ⇓
- Respiratory center → irregular breathing
- Vasomotor center → labile blood pressure & arrythmias.

Bulbospinal

Encephalitic form
- Fever, vomiting
- Headache → fits → coma.

Fate
- 50% recover without residual paralysis
- 25% have mild disability.
- < 25 suffer severe permanent disability.

Diagnosis: Polio is suspected clinically in polio epidemics, investigations include.

Suggestive	Diagnostic
• ↑ serum antibodies 1 week after onset of the disease	Viral isolation from
• CSF → as in aseptic meningitis	• Stool
	• Throat
	• Blood & CSF

Differential diagnosis

1- Non paralytic: from causes of
- Meningitis
- Meningism.

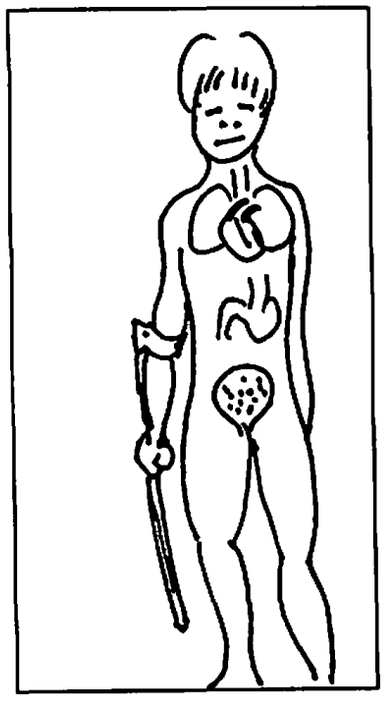
2- Paralytic: From causes of acute flaccid paralysis (See Guillian Barre syndrome)

Complications

1. Respiratory failure due to:
   - Respiratory center paralysis
   - Bulbar palsy → recurrent aspiration
   - Respiratory muscles paralysis
   - Hypostatic pneumonia

3. Gastro intestinal:
   - Paralytic ileus
   - Melena due to superficial gut erosions

5. Urinary :due to urine retention ;
   - Urinary tract infection
   - Chronic renal failure



2. Cardiac:
   - Labile blood pressure.
   - Arrhythmias

4. Permanent flaccid paralysis

Management

❶ Prevention ⇒ Polio vaccines.

❷ Abortive & non paralytic polio:
- Bed rest.
- Analgesics (avoid injections).
- Hot packs for muscle pain.

❸ Paralytic polio:
- As above plus.
- Sedatives.
- Care of bladder (parasympathomimitics ± catheter)
- In chronic stage → physiotherapy & orthopedic consultation
- For Bulbar paralysis: - Care of respiration.
  - Monitor blood pressure.
  - Care of nutrition

Parasitic Diseases

Nematodes

* Ascaris
* Enteroblius vermicularis

} Infection occur by. Ingestion of eggs.

* Ankylostoma (hook worm)
* Strongyloids

} Infection occur by. Skin penetration by larvae.

Clinical features

- Asymptomatic
- Abdominal pain
- GIT bleeding.

} May impair growth

* In Ankylostoma & Strongyloids → skin penetration may lead to → pruritic maculopapular rash at the site of penetration (Ground itch)
* Ascaris & ankylostoma may lead to pulmonary symptoms due to larval migration
* Ascaris may lead to intestinal obstruction.
* Enterobius (oxyuris) may lead to → enuresis & irritability.
  → nocturnal anal pruritus.
* Diagnosis: Detect the worm or the characteristic eggs in stool.
  Test for complications: occult blood in stool, fe deficiency anemia.

Treatment

- Hygienic instructions: hand washing, fingernails kept cut &clean, avoid bare footed
- Mebendazole or flubendazole 100 mg twice daily for 3 days
  (once in oxyuris & may repeat in 2 weeks with treatment of all family contacts).

Schistosomiasis: Exposure to water channels → cercariae penetrate skin which mature into worms which travel to:

- Urinary bladder→ Schistosoma heamatopium
- Intestine →Schistosoma mansoni

Clinical features

* Pruritic papular dermatitis may occur at site of cercarial entry
* Schistosoma heamatopium: → cystitis & terminal heamaturia
  → late ⇒ cancer bladder.
* Schistosoma Mansoni: → bleeding per rectum
  → tenesmus
  → late ⇒ liver fibrosis ⇒ portal hypertension.

Investigation: → Urine & stool analysis for ova.
→ Rectal snip or bladder biopsy & search for ova.

Treatment: Praziquantel 40 mg/kg/d in two doses for 1 day.

Cestodes

* Taenia saginata
* Taenia solium

} due to ingest of undercooked meat.

* Hymenolepis nana → due to ingestion of eggs.

Clinical features: - Abdominal pain - Weight loss.

Treatment: - Niclosamide or - Praziquantel 25 mg/kg/d

Compulsory Vaccines

	BCG	Oral polio vaccine	DTaP	Hepatitis B vaccine	Measles vaccine
Nature	Live attenuated T.B bacilli (bacilli of Calmette & Gaurin)	Trivalent live attenuated polio virus types 1,2,3 **(Sabin vaccine)**	Diphteria & tetanus toxoids with acellular pertussis vaccine (DPT is no longer used)	Recombinant HBs Ag prepared by DNA technology.	Live attenuated measles virus grown in chicken embryo cell culture.
Indications	Compulsory Vaccination Started during the 1st year of life			- Chronic blood product receivers - Hemodialysis patients.	
Administration	0.05 ml in neonates 0.1 ml in elders Intradermal in left upper arm.	3 drops oral	0.5 ml I.M in left thigh	- 0.5 ml before 10th year. - 1 ml afterwards. IM (in left thigh or deltoid)	- 0.5 ml S.C
1ry doses	In the 1st 2 months	Zero dose at 0-15 days. 2,4,6,9 months	2,4,6 months	2,4,6 months (in other conditions 0,1,6 months).	9 months with 1st dose of Vit.A
Booster doses	At beginning of every school period for tuberculin –ve	- At 18 months - At 4 years (frequent doses is recommended)	- at 18 months - at 4 years. - at every school period	- can be given every 4 years	at 18 months (MMR) with a 2nd dose of Vit.A
Reaction	Small papule which crust then disappear in 10 weeks leaving permanent scar.	No reaction, has many values; - Low cost - Give both local & humoral immunity. - Virus excreted in stool → transmitted to others → community immunity.	- Fever - Local tenderness - Irritability and crying for > 3 hours. - Shock like; hypotonic hyporesponsive episode - Convulsions - Encephalopathy.	- Local reaction : pain tenderness, swelling & erythema. - Fever - Headache	- Mild fever - Faint skin rash may occur 1-2 weeks after vaccination → last for 1-2 days.

With measles vaccine: the 1st dose of Vitamin A = 100.000 IU and the 2nd dose = 200.000 IU

(Nelson 2008)

	BCG	Oral polio vaccine	DTaP	Hepatitis vaccine	Measles vaccine
Complications	• Local lymphadenitis • Abscess formation • Spreading infection if given to immunodef. ⇒ need anti- TB. Drugs.	• Failed vaccine due to - defect storage - vomiting or diarrhea • Vaccine associated paralytic polio (incidence: 1/ 750.000)	Severe previous reaction (usually due to pertussis vaccine)	• Failed vaccine due to:- defect storage - injections in buttocks	• Encephalitis.
General contraindications and precautions ✧ **Contraindications to all vaccines** - Serious allergic reaction (e.g., anaphylaxis) after a previous vaccine dose - Serious allergic reaction (e.g., anaphylaxis) to a vaccine component ✧ **Contraindications to live virus vaccines** - Immunosuppressed patient (immunosuppressive therapy or diseases) - Malignancy - Pregnant mother ✧ **Precautions:** Moderate or severe acute illness with or without fever				**Untrue contra indications (vaccine can be given)** - Mild acute illness with or without fever - Mild to moderate local reaction - Current antimicrobial therapy - Convalescent phase of illness - History of nonvaccine allergies	
Additional contraindications	• Tuberculin +ve reactors • Prematures.	• Immunodeficient contacts • In nurseries	See later	See later	See later
Other forms		**Inactivated polio vaccine (Salk)** * Dose ⇒ 0.5 ml S.C. * Given if sabin vaccine is contraindicated * Dose of Salk before OPV reduce OPV associated paralysis by 90%	**TdaP** and **Td** contain reduced dose diphtheria toxoid to be given as boosters to adolescents when pertussis vaccine is unnecessary		**MMR** vaccine is live attenuated vaccine for mumps, measles & rubella given at 18 months 0.5 ml S.C.

(Nelson 2008)

Specific contraindications and precautions to commonly used vaccines

Vaccine	True contraindications and precautions	Untrue
DTaP	**Contraindications** - Encephalopathy (e.g., coma, prolonged seizures) within 7 days of previous dose - Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy (Decision: defer DTaP until neurologic status stabilized) **Precautions** - Fever of > 40.5 °C ≤ 48 hours after receiving a previous dose - Shock like state ≤ 48 hours after receiving a previous dose - Seizure ≤ 3 days of receiving a previous dose - Persistent crying lasting ≥ 3 hours ≤ 48 hours after receiving a previous dose .	- Temperature of < 40.5 °C, or mild drowsiness after a previous dose - Family history of seizures - Family history of an adverse event after DTP or DTaP administration - Stable neurologic conditions (e.g., cerebral palsy, controlled convulsions, developmental delay)
MMR	**Contraindications** - Pregnancy - Known severe immunodeficiency . **Precautions** - Recent (≤ 11 months) receipt of antibody-containing blood product - History of thrombocytopenia or thrombocytopenic purpura	- Positive tuberculin skin test - Immunodeficient family member - Asymptomatic or mild HIV infection - Allergy to eggs
Hepatitis B	**Contraindication** - Pregnancy - Autoimmune disease (e.g., systemic lupus erythematosis or rheumatoid arthritis) **Precautions** - Infant weighing < 2,000 grams	

(Current Pediatrics 2007)

Non Compulsory Vaccines

General indications : - High risk patients - Household contacts - Travelers to endemic areas

Vaccine	Nature	Dosage (0.5 ml)	Special indications
Heamophilus influenza type B (HiB) vaccine	Antigenic part of the capsule	- I.M. - at 2,4,6 months - booster dose at 15 mo.	♦ Hyposplenism ♦ Prior to splenectomy ♦ Resistant nephrotic syndrome
Polyvalent pneumococcal vaccine	Capsular polysaccharide of 23 serotypes	- I.M.	
Meningeoccocal vaccine	Capsular polysaccharide of types A, AC, C, W135	- S.C	- Hyposplenism
Hepatitis A (Havrix)	Inactivated	- I.M.; 2 doses 6 months apart - Given above 2 years	
Typhoid vaccines **- Vi capsular vaccine**	Conjugated vaccine	- I.M single dose - Given above 2 years	
- TY 21a	Live attenuated	- Oral single dose.	
Cholera vaccine (Koll's)	Inactivated	- S.C 2 doses 1 month apart	
Influenza vaccine	Inactivated viruses type A&B	- IM 2 dose 1 month apart - Common type for season	* Chronic lung diseases * Patients on long term aspirin.
Chicken pox vaccine	Live attenuated	- SC → single dose (< 12y) → 2 doses (> 12 y)	* Patients on long term aspirin
Yellow fever (17D) vaccine	Live attenuated	- SC single dose	

Other recent vaccines

1. Rota virus vaccine : - Live attenuated , given orally ; 2 ml/dose at 2,4,6 months
- The first dose must be before 3 months and final dose must be before 8 months

2. Human papilloma virus vaccine : - Recombinant vaccine ,given as three doses in females aged 11-12 years of age.
- The 2nd dose should be administered 2 months after the 1st, and the 3rd dose, 6 months after the 2nd dose
- Intramuscular: 0.5mL/dose

(Nelson 2008)

Diarrheal Disorders

Diarrheal Disorders

Definition of diarrhea

* Passage of three or more watery or loose motions per day. Or single motion containing blood.
* WHO defines it as : increased volume, fluidity, or frequency of motions relative to the usual pattern of individual

Normal pattern of motions per day

* From birth to 4th month → Breast fed : 1-7 motions / day
  → Formula fed : 2-3 Motions / day
* From 4th month to end of 1st year → 1-3 motions / day (Firmer)
* Above 1year → 1-2 motions / day (adult like)

Classification of diarrhea

i. Acute Diarrhea :
- Starts acutely,
- Watery without visible blood ,
- Last less than 14 days.

(**Desentry** is acute diarrhea with visible blood in stool)

ii. Persistent diarrhea : Started as acute diarrhea (watery **or** desentry) but persist more than 14 days.

iii. Chronic diarrhea :
- Diarrhea of gradual onset, lasting ≥ 1month **or** recurrent due to non infectious cause
- Stool output is more than 10 gm /kg/day.

Mechanisms of diarrhea

i- Osmotic diarrhea

Due to presence of non-absorbable solutes in GIT → osmotic load → shift of water to intestinal lumen.

Examples:

1- Lactase deficiency; either primary **or** 2ry to gastroenteritis (Lactose intolerance).
2- Congenital glucose-galactose malabsorption.
3- Ingestion of non-absorbable solutes (e.g. lactulose, sorbitol)

ii- Secretory diarrhea Due to either:

1- Damaged absorptive villi cells **with** intact secretory crypt cells that migrate to cover the raw villi → excessive secretions & diminished absorption

Causes:
- Viral diarrhea e.g Rota virus.
- Bacterial e.g Shigella, Entero invasive E-coli
- Parasitic e.g Giardia lamblia (induce mucosal adhesion)

2- Entero toxins release → stimulate adenyle cyclase in crypt cells → excessive intestinal secretions

Causes :- Vibrio cholerae
- Entero toxigenic E-Coli

	Osmotic diarrhea	Secretory diarrhea
Volume	< 200ml / day	> 200 ml/day.
Effect of fasting	Diarrhea will stop	No effect.
Food type	Usually related.	Unrelated
Stool analysis		
- Stool pH	< 5	> 6
- Reducing substance	May be present	Absent
- Fecal sodium& chloride	Low (< 70 meq/L)	High (> 70 meq/L)

iii- Change in intestinal motility
- Decreased motility →↓ transit time e.g thyrotoxicosis
- Increased motility →↑ bacterial overgrowth e.g stagnant loop syndrome.

iv- ↓ intestinal surface area e.g short bowel syndrome → both osmotic & motility disorders.

Acute Diarrhea

Definition
Mechanisms
1- Osmotic 2- Secretory. } as before

Causes

i- Acute non infective diarrhea

1- Dietitic
1- Over feeding
2- Under feeding: Starvation diarrhea (scanty, greenish, excessive mucus)
3- Bad feeding: - Change in milk type **or** concentration
- New unsuitable food.
4- Lienteric diarrhea: Hyperactive gastro-colic reflex → motion short after every feed

2- Drugs: e.g.
1- Oral antibiotics (e.g ampicillin)
2- Laxatives e.g. magnesium sulphate to the baby or to lactating mother.

3- Parentral diarrhea (better called 2^{ry} gastro enteritis).
- Due to infections outside GIT e.g otitis media, respiratory infections, urinary tract infections
- Possible mechanisms: - toxic absorption
- reflex gastro intestinal irritation
- The term parentral diarrhea is no longer used due to possible associated intestinal infection.

ii- Acute Infective diarrhea (Gastro Enteritis)

Gastro-enteritis involve enteritis & reflex gastritis → vomiting & diarrhea.

Risk Factors

i. Host factors:

1. Failure of breast feeding
2. Bottle feeding.
3. Infants in ages 6-24 months due to:
   - Fading maternal acquired immunity.
   - Little active immunity.
   - Contaminated weaning.
   - Picking up contaminated objects.
4. Malnutrition: delay repair of damaged gut mucosa
5. Impaired immunity: in severe malnutrition and following measles
6. Incomplete vaccination especially against measles.

ii. Maternal factors:

1. Failure of exclusive breast feeding in the first 4-6 months
2. Use of easily contaminated feeding bottles
3. Unsanitary storing of foods
4. Unsanitary food handling
5. Unsanitary disposal of feces.

Severity

* Mild = 4-6 motions /day
* Moderate = 6-10 motions /day
* Severe > 10 motions /day

Causes of Gastroenteritis

1. Viral (60%)

Due to: - Rota virus.
- Adenovirus
- Enteroviruses (e.g. Echo & coxachie)
- Norwalk virus

Criteria:

- Age usually less than 2 years.
- Common in winter
- May be associated upper respiratory tract infections
- Pyrexia if present usually less than 38.5 °C.
- Diarrhea is: - Mild to moderate.
  - Transient = (5-7 days).
  - Watery
  - Odorless

2. Bacterial

Criteria: - Common in summer
- With high fever
- Cramping abdominal pain
- Usually severe diarrhea which may be:-

* Bloody with: - Salmonella
- Shigella desentyrie type 1.
- Entero invasive E-Coli.
- Entero hemorrhagic (Shiga toxin producing) E-Coli

* Watery with: - Shigella (diarrheal type)
- Entero pathogenic E-Coli
- Entero toxigenic E-Coli
- Vibrio cholerae O1.

* Watery offensive for 2-4 days then turn bloody → Campylobacter jejuni.

3. Protozoal

Etiology & criteria

1- Giardia Lambelia
- Watery
- Offensive
- No fever nor vomiting

2. Entameaba histolytica
- Bloody ± tenesmus
- No fever nor vomiting

3- Cryptosprodium parvum:
- Coccidian protozoan that infect mainly the immunodeficients.
- Diarrhea is watery with fever & vomiting

Complications of Gastroenteritis

1- Dehydration - Due to vomiting, diarrhea and anorexia **(see later)**
- The main cause of death in gastroenteritis

2- Shock

Types: - Hypovolemic shock with severe dehydration
- Septic shock.

Clinically: 1- Hypotension & rapid thready pulse
2- Decreased vital organ perfusion:-
- Brain → lethargy
- Kidney → oliguria

3- Decreased peripheral perfusion:-
- Pallor
- Skin mottling
- Cold extremities

3- Acute renal failure (ARF)

Due to:

1- Hypovolemia →↓ renal blood flow (pre renal failure).

2- Untreated pre renal failure → tubular necrosis → intrinsic renal failure

Clinically:

- Oliguria or anuria
- Edema
- Acidotic breath (Rapid, deep breathing).

4- Metabolic Acidosis

Due to:

* Loss of bicarbonate in stool
* Acute renal failure.

Clinically:

- Acidotic breath
- Disturbed consciousness.
- Arterial blood gases (↓pH, ↓$PaCO_2$, ↓HCO_3)

5- Electrolyte disturbance:

i- Hypokalemia: (serum potassium < 3 meq /L)

* Due to loss of potassium in stool in severe gastroenteritis.
* Aggravated by vigorous correction of acidosis.

Clinically:- Apathy (disturbed consciousness)

- Cardiac arrhythmias
- Abdominal distension (paralytic ileus)
- Hypotonia (atony).

ii- Hypocalcemia:

* Occur especially in:
  - Rackitic patients
  - During rapid correction of metabolic acidosis → calcium shift to bones and decreased ionized calcium (post acidotic tetany).

Clinically:- Tetany or convulsions.

iii- Hypo or hyper natremia.

6- Convulsions → possible causes:

- Hypoglycemia ; mainly in mal nourished.
- Febrile convulsions
- Hyper or hyponatremia(best treated with ORS)
- Toxic (e.g. with shigella)
- CNS infections
- Hypocalcemia
- Brain edema due to (over hydration espicially in hypernatremic dehydration).

7- CNS infections : meningitis & encephalitis due to shigella or neurotropic virus

8- Bleeding

Possible causes	Clinically
i- DIC due to shock, sepsis or acidosis	- Bleeding from puncture sites - May be necrotic skin patches
ii- Hypoprothrombinemia due to - prolonged oral antibiotics - loss of bacteria flora with diarrhea	 - Bleeding from puncture sites - May be skin ecchymosis
iii- Intussusception with severe diarrhea → part of the intestine invaginate in the distal part (usually ileum in colon)	- Attacks of abdominal pain (screaming) - Vomiting with constipation - Red currant jelly stool - Sausage shaped abdominal mass - P/R → head of intussuceptum may be felt - Ultrasonography is diagnostic & safe - Air contrast enema → can be therapeutic
iv- Renal vein thrombosis due to severe dehydration → hypovolemia → venous stasis	- Heamaturia - Renal mass - If bilateral → acute renal failure

9- Persistant diarrhea

10- Malnutration (PCM) In recurrent or prolonged diarrhea.

11- Others:

1- Hepatitis → toxic or infectious.

2- Encephalopathy → due to: - Prolonged acid-base disorder.
- Cortical vein thrombosis.
- Hypernatremia.

3- Rectal prolapse.

Workup of Gastroenteritis

1- For the cause :

- Stool analysis
- Stool culture

2- For the complications :

- Serum electrolytes → potassium, sodium and calcium.
- Arterial blood gases (ABG) → for metabolic acidosis.
- Renal functions tests
- Lumbar puncture → for CNS infections.
- Abdominal X-ray → multiple fluid levels in intestinal obstruction.
- Coagulation screen → PT, PTT, FDPs, platelets for bleeding.

Treatment of Gastroenteritis

1- Supportive

1- Gastroenteritis without dehydration (plan A)

Home management consisting of: Plenty of fluid , plenty of food &follow up

1- Fluid therapy

➢ Main aim of treatment is to avoid dehydration by plenty of fluid:

✧ The best fluid is oral rehydration solution (ORS).

✧ Amount of ORS:

Age	ORS amount after each loose motion	ORS amount to be used at home
< 2 years	50-100 ml	500 ml
2-10 years	100-200 ml	1000 ml
> 10 years	As much as wanted	2000 ml

✧ How to give ORS:

- One tea spoonful/1-2 minutes for a child under2 years .
- Frequent sips from a cup for an older child
- If vomiting occur ,wait 10 minutes and give ORS more slowly.

✧ Food based fluids : - For infants >6months or weaned
- Rice water, soup, yogurt drinks , belila water
- Avoid hyperosmolar fluids as it increase diarrhea

✧ Continue fluids till diarrhea stops

2- Plenty of feeds to avoid malnutrition:

✧ Continue breast feeding

✧ If not breast fed → give the usual milk formula.

✧ For infants >6months or weaned, give: mashed potatoes, cereals, rice pudding, mashed banana(supply potassium)

✧ Feeds given 6 times a day.

✧ Continue food after diarrhea stop and give extrameal each day for 2 weeks

3- Follow up for detecting early cases of dehydration:

Inform mother to seek medical consultation if there's:

✧ No improvement for 3 days

✧ Presence of a warning sign: - High fever.
- Refusal of oral fluids or feeding.
- Frequent vomiting.
- Marked thirst
- Bloody motions.
- Frequent watery motions

2- Gastroenteritis with dehydration (plan B & C) ⇒ See later

2- Specific treatment

1-Antibiotics

* Indications : largely depends on clinical judge;
  - If bacterial cause is identified or strongly suspected.
  - Associated bacterial infection (e.g otitis media or pneumonia)

  (Fever perse even high is not an indication for antimicrobial therapy)
* Route: - Oral usually.
  - Parenteral with severe vomiting or life threatening infections.
* Choice: 1. Bloody diarrhea(probably shigella): 5 days course of
  - Trimethoprim/sulphamethoxazole(10/50 mg/kg) or
  - Nalidixic acid 60 mg/kg or
  - Others : Ampicillin , cefotriaxone , ciprofloxacin

  2. Suspected cholera : 5 days course of
  - Trimethoprim/sulphamethoxazole or
  - Erythromycin (or azithromycin) or
  - Tetracycline; 50 mg/kg/day (for children > 9 years).

2-Anti-parasitic

* Entameoba histolytica : Metronidazole **40** mg/kg in 3 doses for **10** days oral.
* Giardia lamblia : Metronidazole **30** mg/kg for **7** days.
  or furazolidone **25** mg/kg for **5** days.

3- Treatment of complications

1- Acute renal failure : usually pre renal → responds to volume expansion.

2- Metabolic acidosis:- Mild → improves with adequate hydration with ORS.
- Severe → Na Hco_3 1-2 meq/ kg- slow i.v.

3- Electrolyte disturbances:
- Hypocalcemia → Calcium gluconate slow i.v.
- Hyponatremia and hypokalemia → Can respond to ORS
- Hypoglycemia→ Give 20% glucose 2.5 ml/kg iv

4- Convulsions: - Anticonvulsants (e.g. i.v. diazepam) and treat the cause.

5- Bleeding is treated according to the cause: e.g.
- DIC → fresh blood or plasma transfusion
- Intussusception → reduction by enema & surgical consultation.

4- Additional therapy:

a. Probiotic non pathogenic bacteria e.g. *lactobacillus ,bifidobacterium*

b. Racecadotril(Acetorphan) ,an enterokinase inhibitor, reduce stool output

c. Nitazoxnide : antimicrobial agent active against many pathogens e.g. Rota virus , Giardia, Entamoeba histolytica,....

d. Ondansetron : anti emetic , a single sublingual dose of 2 mg for older child with severe vomiting

(Nelson 2008)

Prevention of gastroenteritis

1. Promote breast feeding:
   - Exclusive for the first 4-6 months
   - Continued for 2 years
   - Continued during illness including diarrhea
2. Proper weaning practice:
   - Started at 6 months
   - Proper choice of weaning food
   - Sanitary measures in preparing, giving and storing foods.
3. Measles vaccine:
   - Cost effective in reducing diarrhea
   - Prevent up to 25% of diarrhea associated mortality in children < 5 years.
4. Hygienic measures:
   ✧ Water sanitation:
      - Frequent hand washing
      - Protect water sources from contamination
      - Boil water for few seconds if contamination is suspected
   ✧ Safe disposal of stool of young children
   ✧ Use of safe sanitary latrines

Persistent Diarrhea

Definition

- Started as acute diarrhea (watery or dysentery) but persist more than 14 days
- About 5-10% of acute diarrhea progress to persistent diarrhea
- Persistent diarrhea account for 35-50 % of diarrhea associated fatality

Etiology

1. Persistent infection:
   - Giardia lamblia is the commonest cause of persistent watery diarrhea
   - Others : salmonella, shigella , cryptosprodium ; in severely malnourished.
2. Post-enteritis malabsorption:
   - Due to mucosal damage → damaged villi with 2^{ry} digestive enzymes deficiency

Risk Factors

* Repeated gastroenteritis in infants in ages 6-24 months due to:
   - Fading maternal acquired immunity.
   - Little active immunity.
   - Contaminated weaning.
   - Picking up contaminated objects.
* Malnutrition: delay repair of damaged gut mucosa
* Prolonged I.V. fluids
* Impaired immunity: in severe malnutrition and following measles
* Recent introduction of animal milk or formula.

Clinical picture: in post-enteritis malabsorption

1- Refeeding diarrhea that may appear with:
   - Breast & cow milk→ suspect 2^{ry} lactase deficiency (lactose intolerance)
   - Sucrose containing formula (e.g Isomil) → suspect 2^{ry} sucrase deficiency

2. Vomiting
3. Abdominal distension & cramps
4. Perianal soreness (due to watery acidic motions).

Diagnosis

1- For post enteritis malabsorption:-
   - Symptoms resolve with suspected milk elimination
   - Reducing substance in stool. } In carbohydrate malabsorption
   - Stool pH < 5
   - Small intestinal biopsy → villous atrophy in cow milk protein allergy.

2- For persistent infection:-
   - Stool analysis.
   - Stool culture.

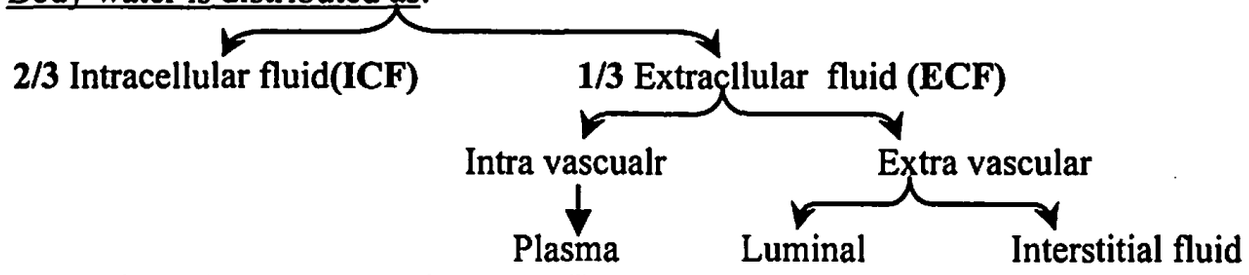
Treatment

1. Adequate hydration according to WHO plans.
2. Treatment of the cause: Indicated if stool is bloody(treat for shigella) or stool culture reveal specific pathogen as giardiasis
3. Nutritional therapy:-
   A. If still breast fed: give more frequent breastfeeds day and night
   B. If taking other milk:
      - Replace with increased breast feedings or
      - Replace with fermented milk products, such as yoghurt or
      - Replace half the milk with nutrient – rich semisolid food as rice, beans and vegetable soup.
      - Limit animal milk to < 50 ml/kg/day
      - Feeds given in frequent small meals at least 6 times daily
   C. If lactose intolerance is suspected → use lactose free milk for **1-2** weeks (till villi regeneration occur).
   D. Supplemental vitamins & minerals once daily for 14 days
      - Vitamin A 8000 iu
      - Folic acid 100 micro gram
      - Iron 20 mg
      - Zinc 20 mg
      - Copper 2 mg
      - Magnesium 150 mg

Dehydration

Introduction

Body water is distributed as:



Serum electrolyte concentrations(meq/l):

* Cations		* Anions	
- Na	135-145	- CL	105
- K	3.5-5	- HCO_3	26
- Ca (total)	9-11 (mg/dl)		
- Mg	1.6 – 2.6		

Q Infants are more susceptible to dehydration than adults, why? due to
- Relative excess of total body water .
- Higher daily requirements of water in infants (150 ml /kg/d)
- Higher frequency of diarrheal diseases in infants & children
- Smaller metabolic reserve of water and electrolytes
- Limited power of the kidneys to concentrate urine

Definition

Dehydration means loss of water & electrolytes from ECF ; The ICF **may be** secondarily affected.

Etiology

1- Diarrheal diseases

2- Others : - Decreased intake e.g. starvation, coma
- Vomiting e.g.: - Congenital pyloric stenosis, intestinal obstruction.
- Hyperventilation.
- Burn
- Excessive sweating
- Polyuria (e.g. diabetes mellitus, diabetes insipidus, chronic renal failure)

Degrees of dehydration

1- According to degree of body weight loss → Mild < 5%
→ Moderate 5-10%
→ Severe > 10%

N.B: Loss of > 15% of body weight due to dehydration is incompatible with life !!!

2- Laboratory: From degree of rise of hematocrit ,hemoglobin, urea, plasma proteins.

Drawbacks: These tests are of limited value unless values prior to the onset of dehydration is known

3- According to WHO plans:

	Plan A	Plan B	Plan C
Definition	**No dehydration**	**Mild to moderate dehydration.**	**Severe dehydration**
General appearance	Normal, alert No shock	*Irritable, restless* No shock	***Shocked***→hypotension,↑ pulse → lethargy, oliguria → cold mottled skin.
Eyes → look → tears	Normal Present	Sunken Absent	Deeply sunken. Absent
Mouth→ tongue → thirst	Moist Absent	Dry *Drinks eagerly*	Very dry (woody) *Unable to drink.*
Skin pinch (turger)	Normal Goes back quickly	*Goes back slowly*	*Goes back very slowly*
Fontanel	Normal	Depressed	Depressed

N.B : - *Key signs of dehydration include: general appearance, thirst, & poor skin pinch.*
- *2 or more signs including at least 1 key sign should exist to assign certain category*

Types of dehydration

Hypotonic(Hyponatremic).	**Isotonic**(Isonatermic)	**Hypertonic**(Hypernatremic)
Serum Na < 130 meq/ L osmolality < 275 m osml/L	130- 150 meq/ L 275-295 m osml/L	> 150 meq/ L. > 295 m osml/L
A/E: Excessive intake of water or hypotonic fluids during diarrhea → net Na loss greater than water loss → Overhydrated cells → Marked collapse of ECF	balanced loss of Na & water leading to:- → No change of cellular hydration → Collapsed ECF	Excessive intake of hypertonic fluids during diarrhea → poor absorption →↑ osmosis → net water loss greater than Na loss → Dehydrated cells → No collapse of ECF
Clinical features **Manifestations of ICF affection**		
• Tongue: - Moist • Brain: - Lethargy - Coma - Convulsions	- Dry; thirsty - Irritable	- Very dry (woody); marked thirst - Irritable - Hyperreflexia - Convulsions
Manifestations of ECF affection		
• Shock - Rapidly occurring	- Slowly occurring	- Usually absent
• Skin turgor - Marked loss	- Moderate loss	- Normal (or doughy)
• Fontanels - Markedly depressed	- Moderately depressed	- Normal or bulging
• Eyes - Markedly sunken	- Moderately	- Mildly sunken

Complications of dehydration: (SEARCH For DIC)

1. Shock
2. Acute Renal failure
3. Metabolic Acidosis due to:
   - Bicarbonate loss in motions
   - Renal impairment
   - Ketosis from starvation
   - Lactic acidosis from hypovolemic shock
4. Metabolic Alkalosis:
   i- If vomiting more severe than diarrhea.
   ii- Manifested by → shallow, slow respiration.
   → tetany (due to decrease ionized Ca).
5. Electrolyte disturbances.
6. Convulsions.
7. **DIC**
8. **Hemoconcentration** → phlebothrombosis especially in cortical & renal veins.
9. Complications of Fluid therapy
   i- Hypervolemia (overhydration) → edema & heart failure.
   ii- Electrolyte disorders:
   * Hypokalemia → aggravated by rapid correction of acidosis → intracellular shift of potassium
   * Hyperkalemia :
     - Aggravated by: Acidosis and excessive potassium infusion in presence of renal impairment.
     - Manifested by: - Restless
       - Cardiac arrhythmias(bradycardia, cardiac arrest)
       - Peripheral collapse.
10. Complication of Hypernatremic dehydration:
    a- Seizures may be due to:
    * Intracranial hemorrhage: Brain cells dehydration →↓ brain volume → tear of intracerebral & bridging blood vessels.
    * Rapid lowering of serum Na → brain cells overhydration → brain edema.
    * Associated Hypocalcemia is common.
    b- Permanent cerebral injury
    c- Renal tubular injury → acute renal failure.
    d- Heart failure

Treatment of dehydration

I-Mild to moderate dehydration (Plan B dehydration)

❶ **Deficit therapy:**

* Definition: Replacement of abnormal water & electrolyte losses due to disease process before medical consultation.
* Type of rehydration fluid: Oral rehydration solution (ORS).
* Amount: 75 ml/kg (but if child wants more, give more) over 4 hours.
* How to give ORS :
  - One tea spoonful/1-2 minutes for a child below 2 years .
  - Frequent sips from a cup for an older child

Problems during deficit therapy:

Problem	Management
- Vomiting	* Wait 10 minutes * ORS is given at slower rate (spoon / 2-3 minutes)
- Refusal of ORS - Frequent vomiting	* ORS can be given more slow by nasogastric tube
- Coma - Persistent vomiting - Abdominal distension - Paralytic ileus. - Rapid loss of stool - Severe metabolic acidosis	* Deficit therapy is given by intravenous route: - Amount of fluid: 70 ml/kg - Type of fluid: Poly electrolyte solution (Polyvalent) or Glucose: Saline mixtures as follow: -1:1 or 2:1 for hypotonic dehydration. - 3:1 for isotonic dehydration. - 4:1 or 5:1 for hypertonic dehydration

❷ **Feeding:**

* If breast fed → continue it
* If non breast fed → give 100-200 ml clean water during first 4 hours then give usual formula.
* If child > 6 months or weaned → give plenty of fluid and food as in plan A.

❸ **Assessment after deficit : After 4 hours**

i- Improvement:

* Criteria:
  - No signs of dehydration
  - Baby fall asleep
  - Pass urine
* Decision: Continue as for plan A at home(see gastroenteritis)

ii- If child's eyes get puffy → stop ORS & give breast milk or clean water.

iii- Still dehydrated

* Decision: Repeat the deficit

iv- Severe dehydration (shocked)

* Decision: Manage as for plan C.

If the mother have to leave before completing the 4 hours therapy then:

- Show her how much ORS to give to finish the 4 hours treatment at home
- Give enough ORS packets for an extra 2 days as in plan A
- Show her how to prepare ORS
- Remind her of the 3 rules in plan A(fluids, feeds, follow-up)

II - Severe dehydration (Plan C dehydration)

1. If IV treatment is available nearby within 30 minutes

❶ **Start iv fluids immediately** (if can drink, give ORS while drip is set up)

- Type of fluid : lactated Ringer (**or** physiological saline if ringer unavailable).
- Route: by intravenous route (intraosseus if no i.v line)
- Amount : **100** ml/ kg.

Age	First give 30 ml/kg(shock therapy) in	Then give 70 ml/kg in
< 1year	1 hour	5 hours
Older	30 minutes	2 1/2 hours

- Check every 1-2 hours:

i- If patient still shocked (lethargic, weak radial pulse)

- Decision : - Repeat shock therapy.
  - Increase infusion rate.

ii- Satisfactory response:

- Criteria: - Improved consciousness
  - Return of strong radial pulse
  - Able to drink
  - Pass urine
- Decision: As soon as the child can drink, give ORS 5ml/kg/hour (usually after 3-4 hours in infant or 1-2 hours in child)

❷ **Assessment**

After 6 hours in infants<1 year and after 3 hours in older child

Finding	Decision
Severe dehydration	- Restart rehydration therapy as for plan C - Think of and treat complications
Mild to moderate dehydration	- Continue as plan B; give deficit therapy as ORS or parenteral
No signs of dehydration	- Continue as plan A - Before removal the iv access ,be sure that patient can tolerate ORS without vomiting for at least 1 hour)

❸ **Feeding** ⇒ as in plan B.

Do not forget:

- After complete rehydration observe for **6** hours to be sure that the mother can maintain hydration by ORS by mouth.
- Specific treatment (e.g. patient > 2 years in cholera area given appropriate therapy)
- Treat complications (as in page 112).
- Persistent signs of dehydration may be due to: very rapid stool loss or underestimation of fluid therapy

2. <u>If IV treatment not available nearby within 30 minutes</u>:

I- If patient can drink:

- Decision: - Start rehydration by ORS by mouth at a rate of 20 ml/kg/hr for 6 hours (total 120 ml/kg)

II- If patient can not drink:

- Decision:- Start rehydration by ORS with nasogastric tube at a rate of 20 ml/kg/hr for 6 hours (total 120 ml/kg)
  - Reassess / 2hours
  - If there's repeated vomiting or abdominal distension → give fluids more slow.
  - If there's no improvement within 3 hours → send for urgent iv fluid therapy.

N.B.: <u>Precautions during hypernatremic dehydration correction</u>:-

1- Type of fluid: Glucose: saline mixture 4:1 <u>or</u> 5:1
2- Under correction → give **60%** of deficit + **70%** of maintenance over **24** hours
3- Monitor serum Na & Ca closely during treatment.
4- Slow correction → never reduce serum Na > 10 meq/L/day.
5- If convulsions occur during treatment → treat the cause:
   - Rapid lowering of Na → NaCl 3% 2-4 ml/kg very slow i.v
   - Hypocalcemia → Ca gluconate 10% 1-2 ml/kg very slow i.v
   - Brain edema (due to rapid or over hydration) → mannitol 20% over 20min.
6- Severe hypernatremia with acute renal failure → Peritoneal dialysis .

<u>Composition of Rehydration Fluids</u>

1- <u>Oral rehydration solution</u> (ORS)

* **Mechanism of ORS** → co absorption of Na & glucose <u>or</u> certain amino acids even via damaged intestinal mucosa → other electrolytes <u>esp</u>. Chloride are absorbed 2^{ry} to Na.

1- <u>Standard ORS</u>:

i- Rehydran sachets: each sachet contain:-

Sodium chloride	0.7	Gram	} dissolved in **200 ml** clean water.
Tri-sodium citrate	0.5	Gram	
Potassium chloride	0.3	Gram	
Glucose	4	Gram	

ii- WHO ORS (2005) → dissolved in 1 liter

Ions	m mol/l
Sodium	75
Potassium	20
Citrate	30
Chloride	65
Glucose	13.5

(Nelson 2008)

2- Other types of ORS:

i- Lohydran → with low Na cl (Na = 65 m.mol/l, cl = 55 m.mol/l)
→ used for: infants < 6 months & hypernatremic dehydration.

ii- ReSoMal:

- ORS containing less sodium more potassium with added magnesium, copper & zinc.
- Mainly for rehydration of severely malnourished infants.

Advantage of ORS	Limitations of ORS.
fit for	**Not fit for**
1- All types of dehydration	1- shocked cases
2- Any age even the newborn	2- if i.v fluids is indicated (page 118)
3- Any type of diarrhea	3- glucose malabsorption (rare)
4- Associated fever, acidosis or vomiting are not contraindications	- ORS will not be absorbed → osmotic diarrhea will occur

2- Parentral fluids

	CHO (gm%)	Na	K	CL	HCO_3	Ca	Comment
Glucose 5%	5	–	–	–	–	–	not retained in ECF. without electrolytes
Saline (0.9%)	–	154	–	154	–	–	not physiologic as * ↑ Na → hypernatremia * ↑ CL → hyperchloremia
Ringer	-	147	4	155	-	4	
Lactated Ringer	–	130	5	111	29 (as lactate)	2	can correct metabolic acidosis
Polyvalent	11	90	15	65			similar to ratios of ORS
Kadalex (Glucose 5% + KCL)	5	–	27	27		–	**never** used in metabolic acidosis **or** suspected renal failure.
Na HCO_3 (8.4%)	-	1000	-	-	1000	-	Correct metatolic acidosis

N.B. - Electrolytes in previous solutions as meq/L

Chronic Diarrhea

Definition and Mechanisms : See pages 113 , 114

Etiology

1. **Malabsorption syndrome**

1- Impaired digestion

* Hepatic
  - Biliary atresia (bile salt insufficiency)
  - Chronic hepatitis
* Pancreatic :
  - Acid hypersecretion (Zollinger Ellison syndrome)
  - Cystic fibrosis
  - Chronic pancreatitis

2- Intestinal stasis

- Protein caloric malnutrition (acini atrophy).
- Stagnant loop syndrome& short bowel syndrome.
- Inflammatory bowel diseases:
  - Crohns' disease
  - Ulcerative colitis

3- Impaired absorption

* Chronic infection
  - Giardia lamblia, tuberculous enteritis
* Food intolerance
  - Lactose intolerance (1^{ry} or 2^{ry})
  - Cow milk protein allergy
  - Celiac disease
* Acrodermatitis enteropathica (autosomal recessive disorder);
  Zinc deficiency leads to
  - Dermatitis → around orifices & acral
  - Alopecia.
  - Chronic diarrhea→ protein losing enteropathy

2- **Endocrinal** e.g thyrotoxicosis

3- **Immunodeficiency**

4- **Neoplasia e.g.** - Neuroblastoma → due to vaso active intestinal peptide (VIP)
- Zollinger Ellison Syndrome → due to increased gastrin.

5- **Chronic non specific diarrhea** (toddler diarrhea)

Clinical picture

1- Pattern of motions may be:

- Watery.
- Steatorrhea → with fat malabsorption = pale, bulky, greasy, offensive stool
- Bloody

2- Manifestations of malabsorption

- General ill health with pallor & weakness
- Abdominal distension & flatulence
- Lost subcutaneous fat & loss of weight.
- Muscle wasting
- May be nutritional edema
- Mouth ulcers & glossitis
- Hypoglycemia, vitamins & mineral deficiency.

3- Manifestation of the cause e.g

- Hepatomegaly & jaundice in chronic liver disease.
- Relation to certain food in food intolerances.

4- Toddler diarrhea (diagnosed by exclusion)

* In toddler (1-3 years) who drinks frequently especially juices and snacks throughout the day.
* Loose stool 3-6 motions / day, stool occur during the day & not overnight.
* Normal growth & physical examination.

Diagnosis of chronic diarrhea

Phase I:

1- History including amount of ingested fluid per day.
2- Physical examination for nutritional assessment and searching for possible cause.
3- Stool examination:
   a. To prove malabsorption
      * For carbohydrate malabsorption :
         - Stool pH (may be acidic)
         - Reducing substances in stool.
         - Breath hydrogen test.
      * For fat malabsorption:
         - ↑ stool fat globules.
         - ↑ stool fat content.
      * For protein malabsorption.
         - ↑ fecal α_1 antitrypsin.
   b. Detect ova, parasites, leucocytes:
4- Stool culture for bacterial overgrowth.
5- Blood studies: - CBC, ESR
   - Electrolytes
   - Urea, creatinine.

Phase II:

1- Sweat chloride test for cystic fibrosis.
2- Stool electrolytes (is it secretory or osmotic)

Phase III

1- Endoscopic studies
2- Small and large bowel biopsy.
3- Barium studies for intestinal narrowing or stricture.

Phase IV:

Hormonal studies e.g vasoactive intestinal peptide (VIP) and gastrin.

Other investigations e.g.: - Celiac workup
- Immunologic assay.

Treatment

1- Treat the cause (medical or surgical)
2- Adequate nutrition → Avoid causative food
→ Reduce fluid intake
→ Medium chain triglycerides
→ Minerals & vitamins.
3- Toddler diarrhea treated by eliminate snacks and fluids in-between meals.

Celiac disease

Definition

* Familial disease due to intolerance to gliadin fraction of gluten (in wheat , rye and barely) → severe intestinal mucosal damage (gluten sensitive entropathy).

Pathology

1- Factors interacting in celiac disease:
- Genetic predisposition.
- Toxicity of some cereals.
- Environmental factors.

2- Gluten sensitize mucosal lymphocytes → damage surface epithelium → villous atrophy. Later on → generalized defects in mucosal transport → malabsorption.

Clinical picture

- Chronic diarrhea(steatorrhea) with large pale, bulky, greasy, offensive stool
- Present around 6th – 12th month with feeding gluten diets
- Failure to thrive due to steatorrhea& marked anorexia
- Abdominal distension & pain → irritability
- Features of malabsorption syndrome(*see before*)
- Finger clubbing
- Associations with celiac disease → IDDM, selective IgA deficiency, intestinal lymphoma and rheumatoid arthritis

Diagnosis

* IgA anti tissue trans glutaminase antibodies and IgA anti endomysial antibodies with total serum IgA are the Gold standard screening test.
* Small intestinal biopsy → Definitive diagnosis (villous atrophy).
* Therapeutic trial → gluten free diet for 1 week → clinical improvement.
* Anti gliadin antibodies (has 10% false positive rate).

Treatment

* Gluten free diet life long (use maise & rice)
* Nutritional support: supplemental calories , vitamins and minerals
* Follow up clinically and serologically to prove compliance & adequate growth.

Neonatology

Neonatal Resuscitation

Definition

Steps to be initiated if newborn breathing or circulation is impaired with the aim of optimizing the airway, breathing and circulation as quickly as possible.

Requirements

1. Anticipate the problem
2. Come early to the delivery room
3. Review the maternal history
4. Check resuscitative equipments and drugs

Resuscitation steps

1- Place the newborn under the radiant warmer.

2- Dry the newborn completely

3- Suction the mouth, oropharynx and nares gently

- If meconium stained amniotic fluid is present and the infant is not vigorous; suction the oropharynx and trachea as quickly as possible .

4- Rapid evaluation of the infant by **Apgar scoring**

* At 1 minute → Decides the need and method for resuscitation.
* At 5 minutes → Reflects adequacy of resuscitative efforts.
  → Determines the need for further efforts.

Sign	0	1	2
1- Color (Appearance)	Blue or pale	Pink with blue extremities.	All pink.
2- Heart rate (Pulse)	Absent	under 100 / min	over 100 / min
3- Response to nasal catheter (Grimace)	No response	Grimace	Cough, sneezing.
4- Muscle tone (Activity)	Limp "flaccid"	Some flexion	Active motion
5- Respiration	Absent	Slow , irregular	Normal and crying

Interpretation of Apgar score

A- Score of > 7

- Indicate good general condition ⇒ No asphyxia
  - Maintain body temperature (adequate wrapping).
  - Aseptic cutting of the cord
  - Antibiotic eye drops.
  - Discharge after detailed examination(*see neonatal examination*)

B- Score of 6- 4

- Indicate mild to moderate asphyxia:
  - Gentle suctioning of airways.
  - Free O_2 inhalation.
  - Tactile stimulation of breathing by slapping the soles, rubbing sternum or spine.
  - If no response → bag & mask ventilation using 100% O_2 at rate of 40-60 breath/min.

C- Score of < 4

- Indicate severe asphyxia:
  1- Endotracheal intubation and bag ventilation with 100% O_2
  2- Proceed to cardiac massage at a rate of 120/min If there is:
     - Heart rate < 80 beat/minute and not rising despite adequate ventilation
     - Heart rate < 50/minutes at 1 minute
     - Absent heart rate at birth unless macerated **or** extreme prematurity(< 500 gm)

➢ If heart rate become greater than 80 beat/minute and rising → stop cardiac massage and continue ventilation till spontaneous respiration is regained.

➢ if no improvement: i.e Heart rate remain < 80 /minute for 1-2 minutes despite 100% O_2 ventilation and cardiac massage → insert umbilical catheter & give resuscitative drugs.

Resuscitative drugs

1-Epinephrine

- Indications: - Bradycardia < 80/minute despite adequate ventilation with 100% O2 and chest compressions for 1-2 minutes
  - Initial heart rate is zero
- Dose: 0.1 – 0.3 ml/kg of 1:10.000 solution.
- Route: intravenous or intra tracheal.
- Dose may be repeated every 5 minutes.

2- Naloxone (Narcan)

- Opiate antagonist
- Indication: if mother received narcotic analgesic within hours of delivery.
- Dose: 0.1 mg/kg I.V. or intratracheal.

3- Na bicarbonate

- Indication: documented metabolic acidosis if 2 doses of epinephrine were ineffective.
- Dose: 2 meq/kg slow I.V.

4- Volume expanders

- Indication: hypovolemic shock due to intrapartum blood loss.
- Use: - Isotonic saline
  - O –ve fresh whole blood
  - Albumin 5% or plasma
- Dose: 10 ml/kg.

5- Dopamine

- Indication: cardiogenic shock due to prolonged asphyxia.
- Dose: 5-20 μg/kg/min continuous I.V. infusion

If no improvement despite previous medications.

Always check:
1- Head is not overflexed (should be in neutral position)
2- The bag deliver 100% O_2.
3- Adequate ventilation pressure.
4- Endotracheal tube is patent & well placed.
5- No air leaks (e.g. pneumothorax)
6- Adequate cardiac massage.

Developmental Reflexes

(Primitive Reflexes)

Idea

* Cerebral cortex in newborn is not fully developed → subcortical centres (spinal cord or brain stem) mediate some primitive reflexes → with time → maturation of the cerebral cortex occur → successive disappearance of these reflexes.
* They appear prenatally at variable gestational ages and disappear posnatally during the first year of life as cerebral cortex matures.

General significance of the primitive reflexes

1- Absence at the time they should present signify damage to the subcortical concerned areas.

2- Persistence beyond the time they should disappear signify failure of development of the cortical area which suppress the reflex.

1. Moro reflex

Time	Present at birth and disappear by 5-6 months
Stimuli	a- Sudden dropping of the head from semisiting position in examiner hand (avoided in preterm & suspected intra cranial hemrrhage) b- Making a loud noise near the ear c- Sudden withdrawal of the blankets from underneath the infant.
Response	- Extension of the trunk. - Extension and abduction then flexion and adduction of upper limbs with little share of lower limbs (embracing movement). - Loud crying follow.
Value	1. Normal reflex in normal time signifies normal CNS. 2. Absence: a- Bilateral: * Premature < 28 weeks * CNS: - Depression by anoxia, narcotic or anaesthesia - Intra cranial hemorrhage * Bilateral injury to: - Brachial plexus - Clavicles or humerus. b- Unilateral (Asymmetrical): * Erb's palsy * Fracture clavicle or humerus * Dislocated shoulder. 3. Sluggish response in: * Sedation * Sepsis. * Early kernicterus 4. Exaggerated reflex in → CNS irritation as in late kernicterus. 5. Persistence: beyond 6 months → cerebral palsy ; mental retardation.

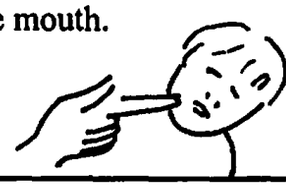
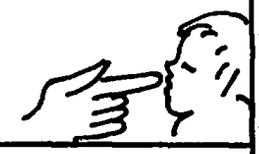
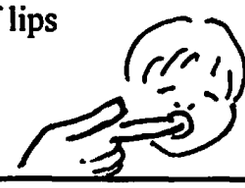
2. Grasp reflex

	Palmar grasp	Solar grasp
Time	From birth to 2 months	From birth to 10 months
Stimulus	Light touch to the palm	Light touch to the sole
Response	Grasp response	
Value	- Help estimation of the gestational age; develops at 28 weeks and become fully mature by 32 weeks. - Absent in klumpke's palsy.	

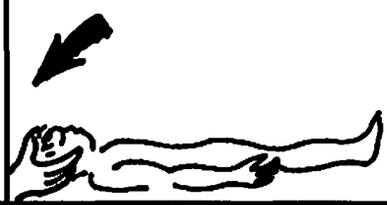
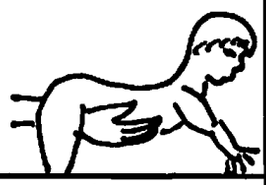




Other neonatal reflexes

Reflex	Stimulus	Response	Time
3- Rooting reflex	Finger stimulation near the angle of the mouth. 	Turning of mouth to the stimulus 	From birth -To 4 months awake -To 7 months asleep
4- Suckling reflex	Stimulation of lips 	Suckling movements	
5- Stepping reflex	The infant is held upright with his soles touching a flat surface. 	Walking movement 	From birth To 6 weeks
6- Placing reflex	The infant is held upright with the sole of one foot touching a surface of table and the dorsum of other foot touching the under edge of the table. 	The baby will flex then extend the leg to place it on upper surface of the table. 	
7- Glabellar reflex	tapping fore head by examiner finger	Blinking	From birth → Persist

Other primitive(non neonatal) reflexes

Reflex	Stimulus	Response	Time
1- Tonic-neck reflex	While infant is supine the head is rapidly turned to one side. 	Extension of upper & lower limbs on the side of turning and flexion of the other side. 	From 1 month To 6 months
2- Neck rightening reflex	While infant is supine the head is slowly turned to one side. 	The trunk will rotate to the new head direction. 	From 6 months To 24 months
3- Landau reflex	The infant is raised in prone position supported from beneath abdomen by the hand. 	Extension of head, trunk and limbs. 	From 3 months To 24 months
4- Parachut reflex	Suspend the baby from the trunk → then sudden withdrawal 	Extension of upper limbs → protective reflex 	From 9 months → Persist

Birth Injuries

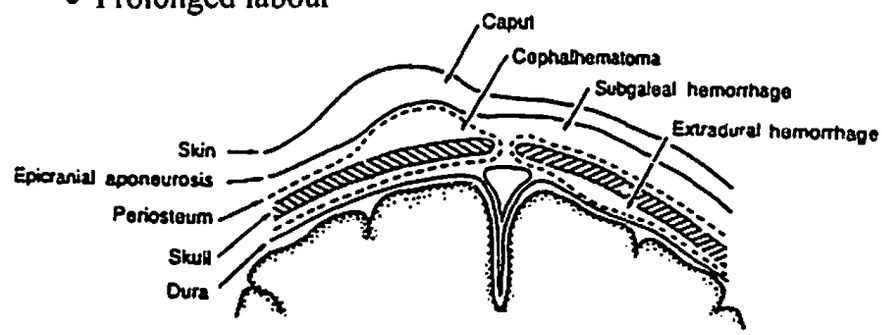
Risk factors of birth injuries

Baby
- Prematurity.
- Anomalies
- Malpresentation.
- Macrosomia.

Mother
- Oligohydramnios.
- Contracted pelvis.
- Prolonged labour

Physician
- Instrumental delivery

Cranial Injuries



I- Scalp lesions

	1- Caput succedaneum	2- Cephalhematoma
- Nature	- Subcutaneous extraperiosteral fluid collection, occasionally hemorrhagic	- Sub-periosteal blood collection.
- Onset	- Immediate after birth	- Few hours after birth.
- Site	- Over the presenting part	- Any bone (commonly parietal or occipital)
- Extent	- Diffuse (cross the suture lines)	- Localized (the sutures prevent its spread).
- Consistency	- Soft	- Firm
- Association	- Ecchymotic skin pathches	- Linear fracture in 15-20% - Anemia and jaundice (if large).
- Fate	- Usually disappear gradually within few days	- Resolve spontaneously over 8 weeks (infection, calcification or ossification may rarely occur).
- Treatment	- Nothing	1- Observation 2- Treat - anemia (blood transfusion). - jaundice (phototherapy). - infection (antibiotics). 3- Incision and drainage are contraindicated. (Except if infected)

3- Subgaleal hematoma

- Bloody collection in the subgaleal space (potential space between periosteum and aponeurosis). It extends from orbital ridges anteriorly to the occiput posteriorly and up to ears laterally.
- Very soft
- May lead to anemia, jaundice, shock (may be more severe than cephalhematoma)

II- Intracranial Hemorrhage (ICH)

Risk factors	- Birth trauma (e.g. forceps). - Bleeding disorder. - Perinatal asphyxia (esp. in premature). - Vascular anomalies
Types of ICH	1- Subdural hemorrhage (SDH) : usually due to trauma 2- Subarachnoid hemorrhage (SAH): may be - Spontaneous (? vascular malformation) - 2ry to perinatal asphyxia. - Extending from parenchymal hemorrhage 3- Germinal matrix hemorrhage / intraventricular hemorrhage (GMH/IVH): - Mainly in preterm ; 90% occurring in 1st 3 days after birth. - Hemorrhage starts in the periventricular subependymal germinal matrix then may extend to the ventricular system. - Highly vascular, fragile, pressure passive blood vessels in germinal matrix rupture easily with fluctuation of cerebral blood flow(e.g. in perinatal asphyxia).
Clinical picture	1- Asymptomatic: - With very small hemorrhages - Common with GMH / IVH. 2- Large hemorrhages: present early after birth: * Features of blood loss : pallor, hypovolemic shock. * Features of neurologic dysfunction: - Seizures - Abnormal respiration ; shallow, irregular, apnea. - Raised intra cranial tension : - full fontanels - irritability - lethargy, coma. 3- Subtle symptoms; common with GMH / IVH: - Lethargy - Poor feeding & suckling. - Apnea. - Weak moro.
Complications	* SDH→ Chronic subdural effusion develop over months. * GMH / IVH → Periventricular hemorrhagic infaction. → Post-hemorrhagic hydrocephalus (PHH)

Diagnosis	1- CT scan or MRI - Detect small hemorrhages. - Detect associated parenchymal lesions. 2- Lumbar puncture: - Exclude CNS infection. - Give hemorrhagic CSF in SAH. - Avoided with marked increase of intracranial tension . 3- Cranial ultrasonography: - Very sensitive & rapid in diagnosing GMH/IVH. - Routine serial cranial ultrasonography should be performed for newborn < 32 weeks for excluding IVH, done at the 1st day after birth then again at 4-7 days. 4- Coagulation profile (PT, PTT, platelets). 5- CBC for anemia
Treatment	i- Preventive: 1- Prevent risk factors e.g. trauma & prematurity. 2- Antenatal steroids reduce incidence of GMH/IVH. ii- Curative: 1- Supportive: - Incubator care - O_2 inhalation. - Minimal handling. - I.V. fluids 2- Symptomatic treatment: * Convulsions → I.V. phenobarbitone. * Anemia → fresh, packed RBCs transfusion * Raised intracranial tension : - Mannitol I.V. - Mechanical hyperventilation. 3- Specific treatment: a- SDH : All require surgical evacuation b- PHH : - Acetazolamide (Diamox) - Serial lumbar punctures / 3 days. - Shunt operation .

Nerve Injuries

1- Facial nerve injury

Clinical picture: Peripheral facial nerve injury result in paralysis of whole face on the same side:
- Absent nasolabial fold.
- Asymmetric cry.
- Deviation of the mouth to healthy side.
- Inability to close the eye firmly.

Treatment:
- Care of the eyes with → eye drops & ointment.
- Care of feeding
- Physiotherapy → if persist more than 3 months → neuroplasty

2- Brachial plexus injury

* Injury to upper nerve roots (C_5, C_6) → Duchenne-Erb's palsy
* Injury to lower nerve roots (C_7, C_8, T_1) → Klumpke's palsy.
* Entire brachial plexus injury → whole limb flaccidity with loss of all reflexes.

	Duchenne-Erb's palsy	Klumpke's palsy
Affected muscles	- Deltoid → loss of abduction - Supra and infraspinatus → loss of external rotation. - Biceps and supinator → loss of supination. * The net result will be adduction, internal rotation and pronation → **(Waiter's tip posture)**	- Paralysis of all intrinsic muscles of the hand.
Reflexes	- Absent Moro and preserved Grasp reflex on the affected side	- Absent Grasp and preserved Moro reflex on the affected side
Association	- Impaired sensation over the external surface of the upper limb. - Phrenic nerve palsy (C_3, C_4, C_5) in up to 75% of cases	- If injury to sympathetic fibres of T_1 → Horner syndrome (ptosis, meiosis, enophthaloms and anhydrosis).
Treatment	1- Partial intermittent immobilization in position opposite to the lesion i.e. abduction, external rotation and supination (statue of liberty splint). 2- Physiotherapy after one week (after resolution of nerve oedema) to prevent muscles contractures .	1- Hand is kept in neutral position with pad of cotton in the fist → hand writing position. 2- Physiotherapy.
Prognosis	* If nerve root are intact, full recovery will occur in more than 90% by 3 months * If no improvement within 3 months, consult neurosurgery for nerve grafting or neuroplasty.	

3- Phrenic nerve injury ($C_{3,4,5}$)

Clinical picture
- Respiratory distress
- Paradoxical breathing (no abdominal bulge during inspiration).
- Diminished breath sounds on the affected side

Investigations
- X-ray chest → elevation of copula of diaphragm on affected side with mediastinal shift to the other side.
- Fluroscopy → paradoxical movement of the affected copula of the diaphragm

Treatment
- Place the infant on the affected side with ventliatory support &O_2
- If no spontaneous recovery within 2 months surgery is recommended (diaphragmatic plication)

4- Spinal cord injury

Clinical picture
- Low Apgar score at birth with apnea
- Complete flaccid paralysis below the level of the lesion
- Urine retention and constipation

Treatment
- Confirm diagnosis by CT and MRI
- Care of bladder and bowels

4- Recurrent laryngeal nerve injury

Clinical picture
- Unilateral injury: unilateral vocal cord paralysis → hoarse cry & stridor
- Bilateral injury: bilateral vocal cord paralysis with severe respiratory distress.

Treatment
- Direct larygoscope to rule out other causes of stridor
- Unilateral injury: resolution usually occur by 4-6 weeks.
- Bilateral injury : endotracheal intubation ± tracheostomy .

Bone Injuries

1- Fracture clavicle

Clinical picture
It is the commonest bone to be fractured in neonates
- Absent Moro reflex on the affected side.
- Pseudo paralysis of the affected limb.
- Crepitus and bone irregularity on the affected side.

(In green stick fracture it may be asymptomatic).

Investigations
- X-ray chest confirm the diagnosis

Treatment
- Immobilization of arm and shoulder (figure 8 bandage).

2- Fracture long bones

Clinical picture
- Loss of spontaneous limb movement and Moro reflex.
- Swelling and painful movement of the limb.

Treatment
- Splint or cast

Soft Tissue Injuries

1- Sternomastoid muscle injury

Clinical picture
- Commonly present in the 1st 2-3 weeks of life
- firm mass (sternomastoid tumor) calcified muscular hematoma
- 2ry shortening of the muscle → torticollis

Treatment
- Physiotherapy to lengthen the short muscle; Most recover over 4 months
- cosmotic Surgery is required in up to 20%

2- Visceral injury

i- Liver or Spleen

Clinical picture
- Severe pallor → up to hypovolemic shock .
- Indirect hyperbilirubinemia
- Abdominal distension with discoloration of abdominal wall.
- Abdominal ultrasound is diagnostic.

Treatment
- Blood transfusion.
- Surgical exploration

ii- Adrenal hemorrhage

Risk factors
- Neonate adrenals are large, friable, highly vascular .
- Unilateral in 90%; mainly on the right side.

Clinical picture
- Pallor
- Flank mass
- Adrenal insufficiency : vomiting , poor feeding , shock .
- Abdominal sonar → diagnostic

Treatment
- Blood transfusion
- Intravenous fluids
- Steroids replacement

Neonatal Septicemia

Definition: Clinical syndrome characterized by systemic illness with decumentation of infection (multiplication of bacteria with their toxins in the blood)

Pathogenesis

	Early sepsis	Late and nosocomial sepsis
Onset	In the 1st week	After the 1st week
Risk factors	1- Prematurity 2- Premature rupture of membranes > 18 hr. 3- Chorioamnionitis 4- Maternal intrapartum fever > 37.5 °C. 5- Maternal bacteruria.	1- Prematurity. 2- Hospitalization 3- Umbilical catheterization 4- Endotracheal intubation 5- Mechanical ventilation. 6- Other disorders: - Meningeomyelocele - Tracheosphageal fistula - Congenital heart diseases - Intracranial heamorrhge.
Organism	1- Group B streptococci (GBS) 2- E.Coli 3- Listeria monocytogenes 4- Others: - Hemophilus influenza - Klebsiella	1- Staphylococcus Aureus. 2- Hemophilus influenza 3- Klebsiella. - Pseudomonas. - Viral or candida

Clinical picture

1- **Presence**: of one or more risk factors espicially in premature or mechanically ventilated baby with persistant metabolic acidosis should suspect sepsis until prove otherwise. (antibiotics must be used till negative cultures are obtained).

2- **Early manifestations** ⇒ Non specific = **not doing well baby**
- Respiratory distress and apneic attacks.
- Lethargy
- Poor feeding and vomiting
- Unstable temperature (mainly hypothermia)
- Poor Moro and suckling reflexes

3- **Late manifestations** = focal infections
* Respiratory⇒ Pneumonia with respiratory distress(tachypnea,retractions,...)
* Neurologic⇒Meningitis: - Seizures
  - Tense bulging fontanelle
  - High pitched cry
  - Irregular respiration
  - Hypotonia & hyporeflexia
* Cardiac: - Shock→ pallor, cold skin, hypotension, oliguria
  - Heart failure→ tachycardia, tachypnea, tender liver, cardiomegaly

* Gastrointestinal: - Vomiting, diarrhea .
  - Direct hyperbilirubinemia due to hepatitis.
  - Hepatosplenomegaly
  - Necrotizing enterocolitis .
* Heamtologic: - Pallor
  - Purpura / DIC
  - Bleeding tendency
* Skin: Sclerema = hardening of the skin → poor prognosis.

Investigations

1- Sepsis screen :Septicemia is suggested when:

i- CBC: show
- Leucopenia < 5000/mm^3 & neutrophil count < 1000/mm^3 (with severe sepsis)
- Toxic granulations in neutrophils.
- Bandemia: Band cells (immature)>20% of total neutrophil count.
- Less commonly leucocytosis (> 25.000 / mm^3)

ii- Markers of inflammation:
- Serial determination of C-reactive protein (CRP)
- ESR
- Haptoglobin

2- Identification of the causative organism
- Blood cultures over aerobic & unaerobic media.
- Cultures of CSF, urine, stool and endotracheal aspirate.
- Detections of GBS or E-Coli antigens in CSF by latex agglutination.

3- Detect foci of infection

1- Chest x ray for pneumonia.

2- Lumbar puncture:

* Biochemical: CSF analysis in neonatal meningitis show:
  - Increased cells, protein , pressure
  - Decreased glucose.
* Culture and gram stain

Management

Prophylaxis: Maternal intrapartum ampicillin if there is risk factors.

Curative:

1- Incubator care in neonatal intensive care unit (NICU): for
- Slow rewarming
- Support respiration: → O_2 inhalation
  → Mechanical ventilation
- Support circulation: → I.V. fluids
  → Packed red blood cell transfusion.
  → Fresh plasma transfusion.
  → Dopamine infusion.
- Support nutrition: → Prolonged cases need total parenteral nutrition

2- Specific treatment:

* Immediate parenteral antibiotics is initiated after taking appropriate cultures.
* Antibiotics are given according to culture and sensitivity.
* While waiting for culture results ; empiric antibiotic combinations is given:
  - Ampicillin: 100 mg /kg /dose every 12 hours.
  - Gentamicin: 5 mg/kg/day divided every 12 hours
  - Third generation cephalosporin(cefotaxime) can be added for critically ill.
* All antibiotics should be given parenterally for **2-3**weeks .

3- Immunotherapy: (Controversial benefits)

1- Exchange transfusion.

Value: - Remove bacteria, toxins, inflammatory mediators.
- Supply antibodies & platelets.

2- Intravenous immunoglobulin.

3- Granulocyte transfusion.

4- Granulocyte colony stimulating factor (G-CSF).

5- Granulocyte-monocyte colony stimulating factor (GM-CSF).

4- Treatment of complications

Congenital Infections (TORCH)

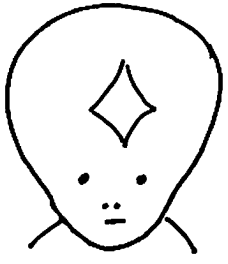
Toxoplasmosis	Rubella	CMV = cytomegalovirus	Herpes simplex
Organism :Protozoan; toxoplasma gondii → inhabit cats' gut → oocytes in their stool → contaminate food, water & in raw meat of infected cattle.	Maternal infection with German measles especially in the 1st trimester.	DNA virus infection can be: - Transplacental. - Perinatal (via secretions) - Breast milk	HSV type II; DNA virus infection occur either. * Transplacental → rare. * Contact with genital lesions during delivery→ common.

Clinical picture

a. History: Previous abortions, skin rash during pregnancy, fever during pregnancy, skin or genital vesicles

b. General features : May be

- Abortion or intra uterine fetal death.
- A viable baby with:
  - * Low birth weight (intra uterine growth retardation or pretmaturity).
  - * Hepatosplenomegaly and generalized lymphadenopathy.
  - * Anemia and thrombocytopenic purpura.
  - * Hepatitis (conjugated hyperbilurbinemia)
  - * Seizures, chorioretinitis, microcephaly.

c. Special features: May be: Hydrocephalus Microphthalmia 	CNS: - Miningeoencephalitis Eye: - Cataract, glaucoma. CVS: - Patent ductus arteriosus - Pulmonary stenosis Mouth:- Cleft palate (rare) Late signs: - Sensorineural deafness - Mental retardation - Diabetes - Thyroid disease Previous features are referred as: **Congenital rubella syndrome**		In perinatal infection: • Skin and mouth vesicles and ulcers. • Keratoconjunctivitis. • Encephalitis • Disseminated form: multi organ affection ⇒ septic shock like.

Toxoplasmosis	Rubella	CMV = cytomegalovirus	Herpes simplex
Diagnosis			
a. Specific: 1- Detection of specific IgM **or** a rising titer of specific IgG			
2- Isolation of the organism from:			
* Blood.	* Urine or oropharyngeal secretions	* Urine	* Vesicles, urine or conjunctival smears.
b. Non Specific:			
i. Skull X-ray, CT, MRI:			
- Diffuse calcifications	- No calcifications	- Periventricular calcifications	- Diffuse calcifications
ii. For clinical features e.g. CBC, Fundus examination, liver function tests.			
Treatment			
i. Prevention	* Rubella or MMR vaccine	* Hyperimmune anti-CMV immunoglobulin.	* Cesarean section for mothers with genital lesions.
* Food hygiene	* Pregnant female with german measles, either:	* Blood products screening for CMV.	* Acyclovir for pregnants with primary HSV.
* Spiramycin for infected pregnant	- Induction of abortion or		
	- I.V. Immunoglobulin.		
ii. Curative			
☆ Symptomatic treatment	☆ Symptomatic treatment	☆ Symptomatic treatment	☆ Symptomatic treatment
☆ Triple chemotherapy for up to 1 year		☆ Ganciclovir	☆ Acyclovir or
- Pyrimethamine		☆ Interferon	☆ Vidarabine
- Folonic acid			
- Sulphadiazine			

Neonatal Jaundice

Jaundice: is yellowish discoloration of skin and mucus membranes due to increased serum bilirubin above normal levels

* Normal cord bilirubin is less than 3 mg/dl.
* Jaundice is obvious clinically in neonate when serum bilirubin exceeds 5 mg/dl ; versus 3 mg /dl in adults.

Bilirubin Metabolism

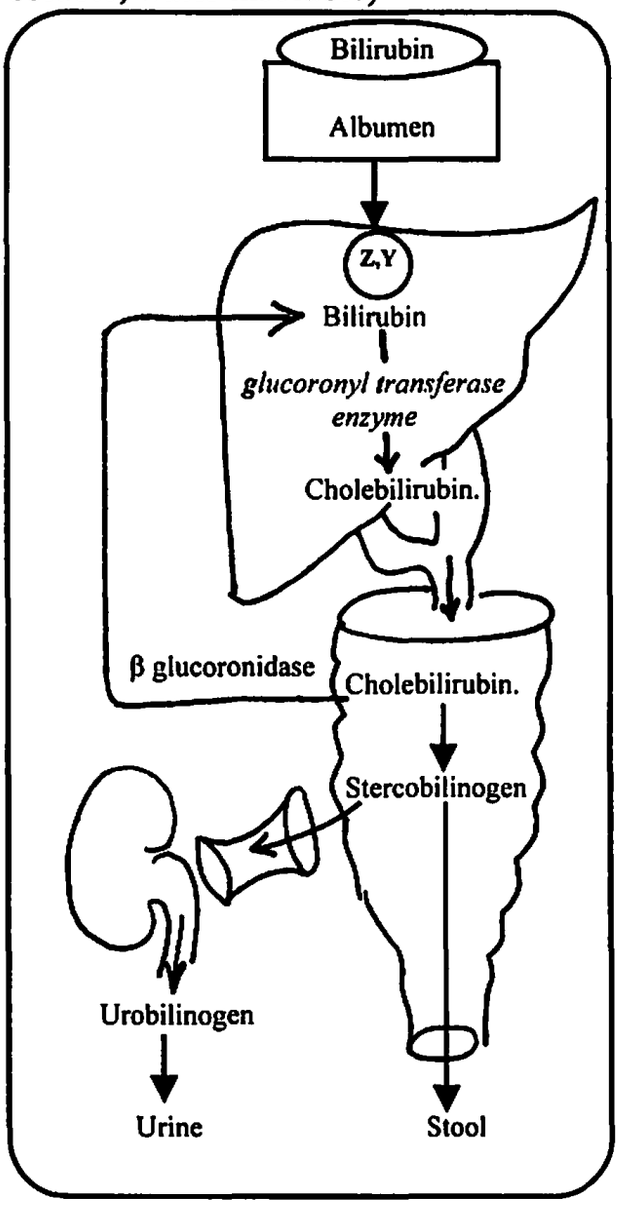
1- Production: Bilirubin is produced mainly from old RBCs

Old RBC's

Iron ← Heme ← | → Globin → Amino acid pool

Heme oxygenase ↓

Bilivirdin → Bilirubin (lipid soluble, water insoluble)



2- Transport:
Bilirubin is carried on albumin (so called unconjugated or hemebilirubin)

3- Uptake by hepatocytes:
Bilirubin bind to cytoplasmic ligandins ; Z & Y proteins to deliver it to endoplasmic reticulum where conjugation occur.

4- Conjugation:
Conjugation of bilirubin stimulated by glucoronyl transferase **enzyme** give rise to conjugated or cholebilirubin which is water soluble and lipid insoluble

5- Secretion:
Active secretion of conjugated bilirubin by liver cells into bile canaliculi.

vi- Excretion:
Excretion of conjugated bilirubin & bile salts into the intestine.

6- Bilirubin in intestine:

* Some amount is deconjugated by mucosal enzyme; β glucoronidase → unconjugated bilirubin → reabsorbed to the liver (entero- hepatic circulation)
* Some amount changed to stercobilinogen → stool
* Small amount of stercobilinogen reach the systemic blood (urobilinogen) → urine.

Unconjugated Hyperbilirubinemia

Considered if total bilirubin above normal & conjugated fraction < 15 % of total bilirubin

Causes

1- Over production of bilirubin

1- Increased rate of hemolysis (reticulocyte count elevated).

a- Patients with positive Coomb's test.

- Rh. incompatibility.
- ABO blood group incompatibility
- Minor blood groups incompatibility

b- Patients with negative Coomb's test eg:.

- Spherocytosis.
- α Thalassemia.
- Glucose-6-phosphate dehydrogenase deficiency.

2- Non hemolytic causes (normal reticulocyte count.)

a- Extra vascular hemorrhage

- Cephalhematoma.
- Extensive bruising.
- Internal hemorrhage (e.g intracranial hemorrhage).

b- Polycythemia: increased RBCs load → increased RBCs turnover.

c- Exaggerated enterohepatic circulation of bilirubin.

- Gastro intestinal tract obstructions e.g. congenital pyloric stenosis.
- Intestinal obstruction

2- Decreased Rate of Conjugations

Glucoronyle transferase enzyme may be:

a- Absent → Criggler – Najjar syndrome type I.

b- Deficient → Criggler – Najjar syndrome type II.

→ Gilbert syndrome

c- Immature → Physiologic jaundice.

d- Under stimulated → Hypothyroidism, hypoglycemia, hypoxia.

e- Inhibited → Breast milk jaundice, Lucy- Driscoll syndrome.

Clinical features

1- Color of sclera and skin → bright yellow or orange.

2- Color of urine → usually normal.

3- Color of stool → may be dark.

4- Possible Concurrent problems:

* Risk of kernicterus: if indirect bilirubin exceed binding sites on albumin or increased blood brain barrier permeability.
* Risk of anemia: if hemolysis is present.

5- Timing of Clinical jaundice:

* In 1st day of life	- Rh. incompatibility (*until prove otherwise*). - ABO incompatibility
* In 2nd - 3rd day	- Physiologic jaundice - Criggler Najjar syndrome
* After the 1st week	- Breast milk jaundice - Hemolytic anemia
* Persistent during 1st month	- Criggler-najjar syndrome - Prolonged physiologic jaundice in infants with hypothyroidism or GIT obstruction - Breast milk jaundice

N.B: - Jaundice is evident on face with serum bilirubin is around **5** mg/dl
- On mid abdomen with level around **10** mg/dl
- On soles of feet with levels around **20** mg/dl.

Physiologic Jaundice

Incidence	- The commonest cause of neonatal jaundice
Etiology	1- Decreased glucuronyl transferase enzyme activity (main cause). 2- Short life span of neonatal RBC's (40 - 60 days) . 3- Reduced Z & Y proteins (Ligandins) during the 1st week. 4- Contributing factors : - Inadequate calories & dehydration due to delayed milk production - Polycythemia, bruises and enhanced enterohepatic circulation
Characters	1. Unconjugated hyperbilirubinemia. 2. Rate of rise → 1-3 mg/dl/day.

	Full term	Premature
3. Incidence	40%	60%
4. Onset	2nd – 3rd day	3rd – 4th day
5. Peak at	4th day	6th – 8th day
6. Disappear	by end of 1st week	by end of 2nd week
7. Peak level	12 mg/dl	15 mg/dl

8. No associated problems ; No pallor, organomegaly nor risk of kernicterus .

Diagnosis	- By exclusion (No hemolysis- No anemia- Normal liver functions)
Treatment	- Usually need no treatment; especially in full term - Phototherapy may be needed for very low birth weight
Differential diagnosis: From pathological jaundice	

Criteria of pathological jaundice

1- Onset : At any time even the 1st day(first day jaundice is always payhologic).
2- Associated problems (e.g. anemia, organomegaly, signs of sepsis, kernicterus).
3- Persistent (> 1 week in full term & 2 weeks in premature).
4- Non response to phototherapy
5- Peak level > 13 mg/dl in full term and > 15 mg/dl in preterm
6- Rate of rise → > 5 mg/dl/day or > 0.5 mg /dl. /hour.
7- Direct hyperbilirubinemia is always pathologic.

Breast Milk Jaundice

Incidence	- Affects 2-4 % of breast fed, healthy full term. - Recurrence rate 70% in subsequent pregnancies
Clinical picture	- Instead of the usual fall of serum bilirubin by the end of first week it continues to rise - With a maximal level of 10-30 mg/dl. - Peaking at 10-15 days of age - Slowly decline by 3-12 weeks of age. - If nursing is interrupted, bilirubin level fall quickly
Etiology	Unknown but may be due to: - Breast milk may contain pregnandiole and non estrified free fatty acids which inhibit glucoronyle transferase enzyme. - β glucoronidase in breast milk (enhance entero hepatic circulation)
Diagnosis	- By exclusion (No hemolysis- Normal liver functions)

Gilbert Disease

Etiology	- Autosomal dominant disorder. - Decreased hepatic glucoronyle transferase level.(was thought to be due to deficiency of Z& Y proteins)
Clinical picture	- Mild hyperbilirubinemia ,usually need no treatment

Criggler-Najjar Syndrome Type I

Etiology	- Autosomal recessive disorder. - Absent glucoronyle-transferase enzyme
Clinical picture	- Severe disease; very high level of indirect bilirubin, in absence of hemolysis , unresponsive to phenobarbitone
Diagnosis	- No glucoronyl conjugated bilirubin in duodenal aspirate - Enzyme assay in liver biopsy

Criggler-Najjar Syndrome Type II

Etiology	- Autosomal dominant disorder. - Partial deficiency of glucoronyl-transferase enzyme
Clinical picture	- Responsive to phenobarbitone (i.e. less severe than type I).

Investigations of indirect hyperbilirubinemia

1- Total bilirubin & direct fraction (direct fraction is below 15 % of total)
2- Coomb's test: - If positive → check blood group of infant & mother.
3- Hemoglobin value: - If high → polycythemia.
- If normal or low (<13gm/dl) → check reticulocyte count.
4- Reticulocyte count: - Normal → extravascular hemorrhage.
- High (> 6%) → Check RBCs shape & osmotic fragility
→ G6PD enzyme assay.
5- Others - Serum T_4 & TSH for hypothyroid.
- Phenobarbitone trial for Criggler-Najjar type II.

Treatment of indirect hyperbilirubinemia

1. Phototherapy

Indications	1- Rise of bilirubin Below the critical levels. - In healthy full term → at 15-20 mg/dl. - In preterm and sick neonates → at lower levels. 2- During waiting for exchange transfusion. 3- Prophylactic in: - Very low birth weight. - Severely bruised neonates. - Immediate after birth if Rh incompatibility is suspected
Avoided	- In direct hyperbilirubinemia → Bronzed baby syndrome
Idea	Exposure to blue or white light with wave length 425- 475nm convert insoluble unconguated bilirubin to non toxic, soluble forms by photoisomerization & photooxidation → execreted in bile & urine
Procedure	1. Baby is completely naked except eyes and genitalia 2. Change position every now and then. 3. Continuous exposure with short intervals for feeding . 4. Intensive phototherapy include over head fluorescent tubes & fiberoptic blankets beneath the baby. 5. Monitor temperature every 6 hours. 6. Discharge from phototherapy when bilirubin is low enough to avoid its toxic effect regarding age & condition (13 ± 0.7 mg/dl in full term & 10 ± 1.2 mg/dl in preterm).
Side effects	1. Loose stool due to excretion of bile salts & unconjugated bile 2. Skin rash and tanning of skin 3. Hyperthermia or hypothermia 4. Dehydration due to insensible water loss 5. Damage to exposed eye or genitalia. 6. Upset maternal - infant interaction

2. Exchange transfusion

Indications	1- In Rh-incompatibility: - Cord bilirubin > 5 mg/dl(normally <3 mg/dl) - Cord hemoglobin < 10 gm/dl. - Rapid rise of bilirubin (> 1 mg/dl/hour) despite phototherapy. - Bilirubin level exceeding: - 10 mg/dl at first day. - 15 mg/dl at second day. - 20 mg/dl at any time. - History of kernicterus in a sibling. 2- In other causes: if serum bilirubin exceeds critical values: - Healthy full term > 20 mg/dl(some consider it above25 mg/dl.) - Preterm and sick neonates → at lower levels.
Idea	- Remove excess unconjugated lipid soluble bilirubin. - Correct anemia - Remove antibodies from the circulation - Provide albumin
Procedure	- Blood used is: * O negative compatible with both maternal and neonatal blood * Fresh, warm. * Amount = double the neonate blood volume (2×80 ml/kg). - Small amounts (10-20 ml) are removed and replaced by equal amounts of the new blood. - I.V Glucose and calcium gluconate are given at 100 ml blood intervals
Drawbacks	- Of umbilical catheterization e.g. embolism, thrombosis, sepsis & portal hypertension in later life. - Heart failure (volume overload on the heart). - Hazards of blood transfusion. - Hypocalcaemia, hypoglycaemia, hyperkalemia

N.B. Indications for exchange transfusion other than hyperbilirubinemia:

1- Neonatal sepsis.
2- Necrotizing enterocolitis.
3- Anemic heart failure → use packed RBCs.
4- Respiratory distress syndrome.
5- Congenital cyanotic heart diseases with marked polycythemia → use plasma
6- Sickle all anemia Crises.

3. Special Cases

*** Intra venous immunoglobulin**

- Can reduce rate of hemolysis and need for exchange transfusion in ABO and Rh incompatibility
- Dose : 0.5-1 gm/kg /dose repeat in 12 hours

*** Criggler Najjar Syndrome type II**

- Phenobarbitone 5 mg/kg/d oral.
- Role: Stimulates glucoronyl transferase enzyme(enzyme inducer).
- Side effect: sedation → poor feeding

*** Criggler Najjar Syndrome type I**

1- Repeated exchange transfusion & phototherapy to keep bilirubin < 20 mg/dl in 1st 2-4 weeks.

2- Oral agar → block enterohepatic circulation of bilirubin.

3- Metalloporphyrin → block heme oxygenase.

4-Hepatic transplantation, gene therapy & enzyme replacement are future therapies.

*** Breast milk jaundice**

- Stop breast feeding for 48 hours (jaundice will disappear and not recur).

*** Treatment of the cause**

- Treat hypothyroidism.
- Avoid drugs which displace bilirubin from plasma protein binding sites.
- Avoid steroids(competitive inhibition of glucoronyl transferase enzyme)

Kernicterus

(Bilirubin Encephalopathy)

Definition

Yellowish staining of the cerebellar & cerebral nuclei (especially basal ganglia) due to deposition of unconjugated bilirubin resulting in neuronal necrosis.

Etiology

1- Level of serum unconjugated bilirubin exceeding critical values

- > 10 mg/dl in 1st day
- > 15 mg/dl in 2nd day
- > 25 mg/dl afterwards.

However kernicterus may occur at a lower levels in presence of risk factors which:

Increase blood brain barrier permeability:	Displace bilirubin from albumin:
- Prematurity & low birth weight	- Drugs (ampicillin, sulpha, aspirin)
- Acidosis	- Hypothermia
- Sepsis	- Hypoalbuminemia
- Hypoxia	
- Anemia	

2- Duration of exposure to the high bilirubin level:

The longer the duration the more risk of kernicterus.

Clinical picture

1. Acute bilirubin encephalopathy : Pass in 3 phases

Phase 1	In the 1st - 2nd days - Poor suckling, lethargy, loss of Moro reflex - Hypotonia and seizures - Apnea
Phase 2	In the middle of the 1st week - Hypertonia, opisthotonos - Fever - High pitched cry
Phase 3	After the 1st week - Hypertonia and stiffness

* Death may occur during these phases

2. Lucid interval : Survivors from previous phase go onto lucid interval for few months → there's apparent recovery or few symptoms.

3. Chronic bilirubin encephalopathy: Picture of Cerebral Palsy:

* Type : chorio asthetoid or spastic.
* Associations:
  - Mental retardation.
  - Sensorineural deafness.
  - Squint & upward gase plasy.
  - Defective speech.
  - Recurrent convulsions.

Differential Diagnosis from other causes of lethargic (not doing well) neonate:

- Neonatal Sepsis.
- Hypoxic ischemic encephalopathy
- Intrarventricular Hemorrhge.
- Hypoglycemia.
- Hypocalcemia
- Hypothermia
- Inborn errors of metabolism

Management

a- Prophylaxis:

* Treatment of indirect hyperbilirubinemia (see before)
* Prevention of other risk factors: e.g. sepsis, acidosis, hypoxia, ...

b- Treatment of established cases: not curable, need only supportive treatment for cerebral palsy.

Conjugated Hyperbilirubinemia

Definition: Rise of total serum bilirubin with the conjugated fraction > 15% of total or > 2 mg/dl.

Cholestasis: Means retention of conjugated bilirubin as well as other constituents of bile (e.g. bile salts)

Causes

1.Defective secretion of conjugated bilirubin by hepatocytes

a .Genetic
- Rotor and Dubin Johnson syndrome
- Bile acid synthesis defects
- Progressive familial intrahepatic cholestasis (PFIC)

b. Acquired: (Neonatal hepatitis) due to:

* Infections :
  - TORCH.
  - Sepsis.
  - Viral hepatitis : Echo, Herpes, Ebstein Barr, Rarely HBV, HCV.
  - Idiopathic hepatitis
* Metabolic :
  - α_1 antitrypsin deficiency
  - Galactosemia
  - Tyrosinemia

2.Defective excretion due to bile flow obstruction

- Intrahepatic:
  - Congenital intrahepatic biliary atresia.
  - Intrahepatic biliary paucity (hypoplasia) e.g. Allagile syndrome
- Extrahepatic:
  - Congenital extrahepatic biliary atresia.
  - Inspissated bile syndrome (Bile plug); may follow severe hemolytic attack.
  - Biliary stones or tumours

Clinical features

1- Color of sclera → olive green.
2- Color of urine → dark (bilirubinuria).
3- Color of stool → pale (or clay).
4- Possible concurrent associations:
   - Hepatosplenomegaly.
   - Liver cells dysfunction.
   - Malabsorption and failure to thrive
   - Underlying systemic disease e.g. sepsis, TORCH, inborn error of metabolism
   - No risk of kernicterus.

5- Timing:

* In 1st day of life (or in the 1st week)	- TORCH infection
* Late in the 1st week of life	- Neonatal sepsis
* Persistent during 1st month	- Neonatal hepatitis (metabolic or infections) - Congenital biliary atresia. - Inspissated bile syndrome

Investigations

- Liver function tests.
- Liver scan (HIDA scan).
- Liver biopsy.
- Metabolic screen for inborn errors of metabolism.
- TORCH screen.
- Sepsis screen.

Treatment

i. Curable causes

- Sepsis → antibiotics.
- Galactosaemia → lactose free milk.
- Extra hepatic biliary atresia → Kasai operation (hepato-porto- enterostomy)

ii. Supportive

- Formula with medium chain triglycerides.
- Fat soluble vitamins.
- Water soluble vitamines
- Chloretics e.g. urso deoxy cholic acid
- Bile acid binders (Cholestyramine) oral →↓serum chlosterol & bile acids.
- Minerals (calcium, phosphate, zinc).
- Liver transplantation for end stage liver failure.

☞ **N.B.:** Steroids & phenobarbitone may be tried in inspissated bile syndrome.

Hemolytic Disease Of The Newborn

(Erythroblastosis Foetalis)

Definition

- Hemolysis of neonatal RBC's due to transplacental passage of maternal antibodies active against fetal RBC's.
- It includes Rh & ABO isoimmunization.

Rh iso-immunization

Pathogenesis

* About 85% of the population are Rh +ve (DD or Dd) .
* Escape of small amount of Rh +ve foetal blood (inherited from Rh +ve father) to the circulation of Rh –ve mother may occur during pregnancy, abortion or at delivery → sensitization of the Rh –ve mother → formation of maternal anti-Rh antibodies (usually of IgG type) which cross the placenta → Destruction of foetal RBC's.
* The first baby usually escape hemolysis as sensitization usually occur near time of delivery (late time to transmit antibodies to the baby), **but the 1st baby** may be affected **if** the mother is already sensitized (e.g. previous abortion of Rh +ve foetus or previous transfusion of Rh +ve blood).
* Rh isoimmunization is much less frequent may be due to:
  - Some Rh +ve fathers are heterozygous (Dd).
  - Not all deliveries are associated with feto-maternal transfusion.
  - Variable maternal immunologic response against D antigen
  - Small family number
  - Associated ABO incompatibility may protect against Rh-incompatibility as entrance of foetal blood group A or B will be rapidly destructed in blood group O mother before stimulation of anti-Rh antibodies.

Clinical picture

According to severity, different presentations may occur:

1- Hydrops foetalis

The most severe form due to severe intrauterine hemolysis

↓

Severe anemia

↓

* Compansatory extramedullary hematopiosis→ huge hepatosplenomegaly.
* If compansation failed → anemic heart failure with:
  - Severe pallor.
  - Severe respiratory distress.
  - Generalized oedema (with ascites & pleural effusion).
  - Death short after birth or the baby borne dead.
  - The placenta is large & oedematous.

2- **Icterus gravis neonatorum** (less severe form); present by:-
- Anemia at birth worsening rapidly during the 1st day.
- Marked unconjugated hyperbilirubinaemia develops within few hours and progresses rapidly.
- Hepatosplenomegaly.
- Untreated cases usually die due to either kernicterus or anemic heart failure.

3- **Hemolytic anemia**
- Mild hemolysis → mild anemia peaking at end of 3rd week.
- Unconjugated hyperbilinibinaemia at range of 16-20 mg/dl.
- May be splenomegaly.

Investigations
- The same investigations for unconjugated hyperbilirubinemia
- Monitor serum calcium and glucose.

Differential diagnosis
1- ABO incompatibility

Differentiated from Rh incompatibility by:
- The mother is usually blood group O and the baby is blood group A or B.
- The 1st baby can be affected as anti-A and anti-B antibodies are naturally present.
- Anti-A and anti-B are of IgM type which can not cross the placenta, however in 10-15% of cases these antibodies are of IgG type which can cross the placenta.
- Milder course.
- Direct Coomb's test is weak positive.
- Mild spherocytosis.

2- Non immune hydropes foetalis. e.g.
- Severe hemolytic anemia (e.g. α thalassemia).
- Severe liver disease
- Choromosomal → trisomies.
- Congenital infections → TORCH and parvo B_{19}.

3- Causes of neonatal jaundice.

Treatment
1- For hydropes foetalis:
- Exchange transfusion with packed RBCs.
- Inotropics (digoxin)
- Mechanical ventiliation
- Monitor Ca & glucose.

2- For indirect hyperbilirubinemia **(see before).**

3- Recently; Intravenous gamma globulin (inhibit hemolysis).

Prevention of Rh-incompatibility

1- Screening of all pregnant females for Rh group

A. If Rh positive → nothing.

B. If Rh negative check father's Rh group → If negative → nothing.

2- If the mother is Rh negative and the father is Rh positive:

A. First pregnancy without previous abortion or blood transfusion Or previously sensitized (e.g. subsequent pregnancies) with low non rising anti Rh antibodies.

Decision:

1. No interference except giving the mother anti-D globulin injection. (at 28 - 32 weeks gestation and again within 72 hrs after delivery) to neutralize escaped fetal RBCs.
2. Dose of anti-D should be given after each ectopic pregnancy, abortion or amniocentesis.

B. Subsequent pregnancies OR previous abortion OR previous blood transfusion

Decision:

1. Determine titre of anti-Rh.(anti D) in maternal blood by ***indirect Coomb's test*** at 12-16 weeks gestation.
2. If High titre (above 1/16) OR rising titre → perform ***amniocentesis*** to check bilirubin level in amniotic fluid → if high (optical density zone 3)

Gestational age ≥ 34 weeks

↓

Induction of labor

- Fetal hydrops
- Fetal hematocrit < 30 %
- Fetal hemoglobin < 8 gm/dl
- Fetal distress too early in gestation for delivery

↓

Intrauterine intraperitoneal or intravascular ***transfusion*** of packed RBCs with the following criteria:

- O blood group
- Rh negative
- Irradiated
- Leukodepleted

(Nelson 2008)

Hemorrhagic disease of the newborn

Definition

Hemorrhagic disorder in early neonatal period due to deficiency of vitamin K dependant clotting factors (II, VII, IX, X).

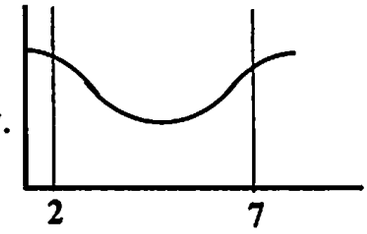
Incidence

- About 2% of neonates not given vitamin K at birth
- Premature is more liable than full term.
- Breast feeder more liable than formula feeder(Breast milk is deficient in vitamin K)

Causes and timing

1- Classic form due to:

- Depletion of transplacental vitamin K by the 2nd day.
- Delay of endogenous vitamin K synthesis to the 7th day. (due to lack of intestinal bacteria flora).
- Liver immaturity in preterm.



2- Early onset hemorrhagic disease

- Present in the1st day of life
- Due to maternal medications during pregnancy inhibiting neonatal vitamin K production e.g. phenytoin, phenobarbitone.

3- Late onset hemorrhagic disease

- Present between 2nd week- 6months
- May occur due to vitamin K malabsorption e.g. cholestasis.

Clinical picture

1- Bleeding tendency:

* When? Usually presents between the 2nd - 7th day of life (may be early or late).
* Sites ? Gastrointestinal, umbilical, circumcision site rarely internal hemorrhage
* Look ? The baby looks healthy except with severe hemorrhage or intra cranial hemorrhage.

2- Hemorrhagic anemia (pallor, tachycardia up to shock).

Investigations

1- Prolonged prothrombin time (P.T.) and partial thromboplastine time (P.T.T)

2- Deficiency of vitamin K dependant factors

3- Normal bleeding time and platelet count

Prevention

- Vitamin K_1 1 mg , intra muscular at birth.
- Vitamin K_1 1-2 mg intravenous with history of maternal anticonvulsant

Treatment

- Vitamin K_1 1-5 mg intravenous
- Fresh plasma transfusion (for preterm and liver diseases) ; if PT greatly prolonged.
- Fresh blood transfusion in severe bleeding.

Neonatal Polycythemia

Definition

Increased RBCs count with venous hematocrit value over 65%

Etiology

- Placental red cell transfusion e.g. delayed cord clamping.
- Placental insufficiency (chronic intrauterine hypoxia →↑ erythropiotine)
- Others e.g. infant of diabetic mother, Wilms tumor

Clinical picture

* Asymptomatic (only plethoric face).
* Symptomatic e.g.: - Respiratory distress
  - Indirect hyperbilirubinemia.
  - Lethargy.
  - Hypoglycaemia
  - Necrotizing enterocolitis (NEC)

Treatment

- Indication: Symptomatic cases and those with hematocrit value > 75%
- Action: Partial exchange transfusion with 5% albumin, saline or plasma.

Neonatal Bleeding

Bleeding in healthy baby

1- Swallowed maternal blood:

Source : During delivery or from fissured nipples

Clinical picture: Bloody vomitus or stool ; usually on the 2nd – 3rd day of life

Diagnosis : Apt test (Alkali denaturation test)

- Foetal blood contains HbF which resists denaturation by alkali (sodium hydroxide) while maternal blood (HbA) is easily denatured.
- Hb A change from pink to yellow brown (alkaline hematin) while Hb F stays pink.

2- Hemorrhagic disease of newborn.

3- Inherited coagulation defects, e.g. hemophilias and Von Willebrand disease.

4- Inherited thrombocytopenia, e.g. TAR syndrome (thrombocytopenia absent radii)

5- Immune thrombocytopenia: Due to transplacental anti platelets antibodies

6- Trauma to the involved site, e.g. thermometer → rectal bleeding.

Bleeding in sick baby

1- Gastric stress ulcer

2- Necrotizing enterocolitis

3- Surgical causes: e.g. volvolus, intussusception.

4- DIC.

5- Severe liver diseases.

Neonatal Anemia

Etiology

A- Physiologic anemia of infancy:

- ✧ Normal hemoglobin concentration at birth = **14-20** gm/dl
- ✧ After birth → blood O_2 saturation increases → decreased erythropiotine production → hemoglobin decline to reach a nadir of **10-11** gm/dl at about **8-12** weeks of age (**7-9** gm/dl in preterm)→ restimulation of erythropiotine release .
- ✧ Hemoglobin Nadir is reached earlier in preterm due to:
  - Decreased RBCs survival.
  - Rapid rate of growth.
  - Vitamin E deficiency.

B- Pathologic anemia:

1- Blood loss	2- Hemolysis	3- ↓ RBC's production
Etiology Perinatal causes: - Twin to twin transfusion - Feto-maternal transfusion - Placental malformations. After delivery: - Gastrointestinal bleeding. - Frequent sampling. - Cephalhematoma, subgaleal hematoma and internal hemorrhages. - Hemorrhagic disease of newborn.	1- Immune hemolysis: - Rh incompatibility - ABO incompatibility - Minor blood groups incompatibility 2- Hereditary hemolysis: - Spherocytosis. - G6PD deficiency - α-thalassemia 3- Acquired hemolysis: - DIC. - Infections	- Congenital infections - Congenital leukemia - Congenital pure red cell anemia
Diagnosis * ↓ RBC's & Hb%. * Normal or ↑reticulocytes * Normal bilirubin. (↑with internal blood loss.) * For the cause.	* ↓ RBC's & Hb%. * ↑ reticulocytes. * ↑ bilirubin. * For the cause.	* ↓ RBC's & Hb%. * ↓ reticulocytes. * Normal bilirubin. * For the cause.

Clinical picture

* Acute blood loss → acute pallor, severe respiratory distress, shock.
* Chronic blood loss → gradual pallor, mild respiratory distress.
* Chronic hemolysis → gradual pallor, jaundice, hepatosplenomegaly.

Treatment

1- Blood or packed RBC's transfusion (20 & 10 ml/kg respectively) in severe anemia or blood loss.
2- Treatment of the cause.
3- Recombinant human erythropiotein in chronic anemia in premature.

Necrotizing Enterocolitis (NEC)

Definition

Syndrome of acute intestinal necrosis of unknown cause usually affects sick prematures with high mortality rate.

Risk factors

1- Weak intestinal wall in prematures is the most important risk factor for NEC.

2- Intestinal wall ischaemia due to:

- Perinatal asphyxia.
- Polycythaemia.
- Patent ductus arteriosus & indomethacin.
- Exchange transfusion & umbilical catheterization.

3- Feeding:

- Non breast feeding with hyperosmotor formula
- Aggressive enteral feeding.

4- Gastrointestinal:

- Congenital gastrointestinal anomalies.
- Colonization with necrogenic organisms.

Pathogenesis

✧ Aggressive enteral feeding of hyperosmotor formula will devitalize the ischaemic already weak intestinal wall especially in the terminal ileum and proximal colon with subsequent sloughing and injury of the intestinal wall.

✧ Superadded infection (Klebsiella, E-coli, Clostridia, Staph, Enterobacter & Viruses: Corona, Rota & Enteroviruses)⇒ Gas formation within the bowel wall → extensive bowel necrosis and Septicemia → perforation & peritonitis.

✧ Platelet activating factor, tumor necrosis factor and cytokines may play role in bowel necrosis.

Clinical picture

Presentation is usually within 1st 2 weeks of life

A. Septicaemic manifestations:

- Respiratory distress and apneic attacks.
- Lethargy
- Poor feeding and vomiting
- Unstable temperature (mainly hypothermia)
- Poor Moro and suckling reflexes
- Septic shock → hypotension, decreased peripheral perfusion, acidosis, oliguria.

B. Abdominal manifestations:

- Feeding residuals and vomiting (of bile, blood or both)
- Abdominal distention , abdominal wall tenderness, cellulitis of abdominal wall.
- Ileus (absent intestinal sounds).
- Bloody stool either obvious or occult blood.

Investigations

A. X-ray abdomen:

- ✧ View: Anteroposterior and cross table (lateral)
- ✧ Should be done and repeated every 8 hours in the first 2 days.
- ✧ Findings:- Pneumatosis-intestinalis → gas in the intestinal wall(pathognomonic).
  - Intrahepatic portal venous gas
  - Pneumo-peritoneum (gas under diaphragm) → if perforation occurs.

B. Laboratory findings:

- The usual triad is: thrombocytopenia, hyponatremia and metabolic acidosis.
- Stool examination for occult blood (Gauiac test).
- Sepsis workup : Culture of blood, stool, and CSF.

Prevention

1- Prevention of risk factors e.g. - Treatment of sepsis
- Prevention of prematurity

2- Breast milk reduce the incidence of NEC.

3- Avoid aggressive feeding in preterm

4- Formula containing egg phospholipids

5- Oral immunoglobulins (IgA & IgG).

6- Prenatal or early postnatal corticosteriods.

Treatment

I- Medical treatment

1- Incubator care in neonatal intensive care unit (NICU): for

* Warming.
* Support nutrition
  - Stop enteral feeding (bowel rest) & start I.V. fluids
  - Nasogastric suction
  - total parentral nutrition for prolonged cases
* Support respiration
  - O_2 inhalation
  - Mechanical ventilation support.
* Support circulation
  - I.V. fluids
  - Packed red blood cell transfusion.
  - Fresh plasma transfusion.
  - Dopamine infusion.
* Symptomatic ttt
  - Na bicarbonate for metabolic acidosis.
  - Platelet transfusion for thrombocytopenia.
  - Correct hytponatremia
  - Exchange transfusion

2- Specific treatment: Antibiotics (Ampicillin/Aminoglycoside/metronidazole) **I.V for 14 days.**

II- Surgical treatment: Resection and anastomosis for: - Perforation
- Failed medical treatment.

Some neonatal gastrointestinal symptoms

Causes of neonatal Vomiting

1- Bilious vomitus

A. Once or twice without abdominal distension may occur in some infants after birth.

B. Persistent is usually due to intestinal obstruction due to:

- Malrotation
- Doudenal, jejunal, ileal or colonic atresia
- Annular pancrease.
- Hirschsprung disease.
- Peritoneal bands.

2- Non bile stained vomitus:

- Forthy: tracheo esophageal fistula.
- Bloody: - Swallowed maternal blood.
  - Hemorrhagic disease of newborn.
  - Gastric erosions / stress ulcers.
- Milk: - Aspirated amniotic fluid.
  - Overfeeding.
  - Milk or formula intolerance
  - Decreased motility e.g. in preterm.
  - Central nervous system lesions.
  - Lesions above ampula of vater e.g. gastro esophageal reflux , pyloric stenosis, rarely annular pancreas.
  - Sepsis with ileus (may be bloody or bilious).

Causes of failure to pass meconium

- Prematurity(reduced intestinal tone)
- Imperforate anus
- Functional intestinal obstruction

Causes of failure to pass stool after passing meconium

- Volvulous
- Malrotation

Causes of scaphiod abdomen

- Diaphragmatic hernia
- Esophageal atresia without tracheosophageal fistula.

Causes of abdominal distension

- Normally gas is seen on x ray film of abdomen as follow:
  - Past the stomach into the upper jejuneum→1 hour after birth
  - At the cecum → 3 hours after birth
  - In the rectosigmiod colon→ 8-12 hours after birth.
- Left upper quadrant distension is seen in complete duodenal atresia
- Generalized distension is seen in lower intestinal obstruction and esophageal atresia with tracheosophageal fistula

Perinatal Asphyxia

Normally: The first breath is stimulated by:

- Drop of PaO_2 on cutting the umbilical cord.
- Rise of $PaCO_2$
- Drop of body temperature
- Tactile stimulation in the delivery room

Definition of perinatal asphyxia

* Failure of the newborn to establish spontaneous regular respiration immediate after birth leading to either death or survival with permanent neurological damage.
* American academy of pediatrics define it as an infant with:
  1. Profound acidemia (pH<7) on an umbilical cord sample.
  2. Apgar score 0-3 longer than 5 minutes
  3. Neonatal neurological manifestations(e.g. hypotonia, seizures , coma)
  4. Multisystem organ dysfunction

Causes

1- Intra uterine causes: (Fetal anoxia)

- Maternal : - Hypoventilation e.g with heart failure& anaesthesia.
  - Hypotension → decreased placental blood flow
- Placental : - Insufficiency e.g. with post maturity & eclampsia.
  - Premature separation
  - Reduced filling due to uterine tetany.
- Umbilical cord compression or knots

2- Intrapartum causes:

- Obstructed or Prolonged labor.

3- Post-natal causes (uncommon):

- Severe congenital cyanotic heart diseases.
- Severe anemia due to severe hemorrhage or severe hemolysis.
- Shock.

Physiology of perinatal asphyxia

* The initial response to hypoxia is an increase in frequency of respiration and a rise in heart rate and blood pressure(increased sympathetic derive)
* Respirations then cease (Primary apnea) as heart rate and blood pressure begin to fall. This initial period of apnea lasts 30-60 seconds.
* Gasping respirations (3-6/min) then begin, while heart rate and blood pressure gradually decline with mixed acidosis.
* Secondary or terminal apnea then occur, with further decline in heart rate and blood pressure.
* Diving reflex : redistribution of blood flow from skin, muscle, kidneys, and GI tract to allows the perfusion of vital organs ; heart, brain, and adrenals.

Clinical picture :Depends on duration & severity of asphyxia

a. In the fetus : Fetal monitoring shows:

- Slow, weak , irregular heart beats(type II deceleration)
- Scalp pH less than 7.2

Action: give mother high O_2 concentration and prepare for immediate delivery.

b. After delivery :

- Meconium staining of the newborn, amniotic fluid and vernix caseosa
- Decreased consciousness with failure of spontaneous breathing.
- Low Apgar score with cyanosis and flaccidity .

c. Later manifestations of perinatal asphyxia :

1. Hypoxic-ischemic encephalopathy (HIE)

Pathology:

* In severe , prolonged asphyxia ; consequences may include:
  - Brain edema : both cytotoxic and vasogenic
  - Intracranial hemorrhage

Pathogenesis:

1. Hypoxia → anaerobic glycolysis → energy depletion → primary neuronal death
2. With reperfusion(resuscitation) → secondary neuronal death may occur due to:
   - Release of excitatory amino acids e.g. aspartate and glutamate
   - Increased calcium & sodium entry into cells→ brain edema
   - Release of neurotoxic mediators e.g. nitric oxide , free radicals and lactate

Sarnat clinical grading

Sign	Stage I	Stage II	Stage III
1- Consciousness	- Hyper alert	- Lethargy	- Coma
2- Muscle tone	- Normal	- Hypotonic	- Flaccid
3- Tendon reflexes	- Hyperactive	- Same	- Absent
4- Moro reflex	- Exaggerated	- Weak	- Absent
5- Pupils	- Dilated	- Miotic	- Variable
6- Respiration	- Regular	- Periodic	- Ataxic, apneic
7- Seizures	- No	- Frequent	- Frequent
Out come	Good	Variable	Death or severe deficits

Diagnosis: Cranial ultrasound, CT or MRI for brain edema and brain injury

2. Cardiac :- Heart failure, hypotension

3. Respiratory :- Meconium aspiration , persistent pulmonary hypertension of newborn, respiratory distress.

4. Renal :- Acute tubular necrosis and hematuria

5. GIT :- Necrotizing enterocolitis and intestinal perforation

6. Metabolic :- Hypoglycemia , hypocalcemia ,hypomagnesemia, hyponatremia lactic acidosis and syndrome of inappropriate secretion of ADH

Management

A. Prevention :

- Prevention of risk factors.
- Neonatal resuscitation **(See pages 133, 134)**

B. Curative :

* Incubator care
  - Slow rewarming.
  - Support respiration: → O_2 inhalation for hypoxia
    → Mechanical ventilation for hypercapnia / apnea
  - Support circulation: → I.V. fluids
    → Keep mean arterial pressure above 40 mmHg.
    → Dopamine infusion.
  - Support nutrition: → May need total parenteral nutrition

* Symptomatic treatment for:
  - Brain edema: restrict fluids by 20% and mannitol 1gm/kg
  - Convulsions: phenobarbitone , clonazepam , midazolam
  - Renal failure: supportive and peritoneal dialysis if necessary
  - Ensure normal blood glucose , calcium and magnesium and pH

N.B: Selective cerebral hypothermia is tried to treat acute HIE to suppress production of neurotoxic mediators

Prognosis

1. Normal MRI and EEG are associated with good outcome
2. Death may occur in severe cases.
3. Hypoxic ischaemic encephalopathy may be severe enough to cause permanent brain damage e.g. cerebral palsy, mental retardation or epilepsy.

Neonatal Seizures

(Neonatal Convulsions)

Definition

Paroxysmal alterations of neurologic functions including motor, behavioral and / or autonomic changes.

Causes

A. Central nervous system

* Incidence: the commonest causes, includes:
- Hypoxic-ischemic encephalopathy (40%).
- Intra cranial hemorrhage and CNS trauma (15%).
- CNS infections including meningitis, encephalitis, TORCH, tetanus (5%)
- CNS malformations e.g. cerebral dysgenesis (5%).
- Bilirubin encephalopathy (Kernicterus).
- Neuro cutaneous syndromes. (e.g. Neurofibromatosis, Tuberous-Sclerosis).

B. Metabolic

1- Hypoglycemia

* Blood glucose less than 40- 45 mg/dl
- Causes: infant of diabetic mother (IDM), preterm, asphyxia , hypopituitarism, Erythroblastosis fetalis, galactosemia

2- Hypocalcaemia

* Serum calcium less than 7mg/dl which either:
- Early onset (in 1st 3 days) → due to IDM, preterm, & asphyxia.
- Late onset (after end of 1st week) → due to decrease calcium intake, hyper phosphatemia, and hypoparathyroidism.

3- Hypomagnesemia (< 1.2 meq/L) → often associated with hypocalcaemia

4- Hyponatraemia (< 130 meq/L) or hypernatraemia (> 150 meq/L)

5- Inborn errors of metabolism: e.g
- Pyridoxine (vitamin B6) dependency.
- Phenylketonuria.
- Hyperammonemia e.g. Urea cycle defects
- Organic acidemias e.g. Maple syrup urine disease

C. Other causes

- Drug withdrawal e.g. maternal narcotics or heroin addiction
- Theophylline at toxic dose
- Administration of local anesthesia during labor
- Neonatal epileptic syndromes: e.g - Benign familial neonatal seizures.
  - Benign idiopathic neonatal seizures.

Clinical picture

1- Onset of convulsions

* 1st 3 days of life: e.g. hypoxic, ischemic encephalopathy, drug withdrawal, intraventricualr hemorrhage or metabolic causes.
* After 3 days: e.g. intra cranial hemorrhage and metabolic causes.
* After the 1st week: e.g. meningitis.

2- Types of seizures

* Subtle seizures:

  The commonest type occur alone or with other types, it may be:
  - Eye movements: blinking, nystagmus or sustained eye opening.
  - Repetitive oral movements: suckling, chewing or lip smacking.
  - Limb movements: pedaling, bicycling or boxing.
  - Epileptic apnea (with initial tachycardia and episodic oxygen desaturation).
* Tonic seizures:
  - Sustained rigid posturing of the body
  - May be focal or generalized.
* Clonic seizures:
  - Rapid alternating contraction and relaxation of muscles
  - May be unifocal , multifocal or rarely generalized.
* Myoclonic seizures:
  - Non rhythmic sudden, fast, shock like movements of limbs
  - May be multifocal or generalized.

Investigations

1- Check initially for blood glucose, serum calcium, magnesium, and sodium.
2- Sepsis screen : complete blood picture, blood culture and CSF examination.
3- Cranial ultrasound, CT& MRI for : brain malformations , ischemic injury and intra canial hemorrhage
4- Electroencephalogram (EEG)
5- Metabolic screen: - Plasma ammonia , pH ,amino acids and lactate
   - Urine for organic acids and amino acids
6- TORCH screen for suspected cases
7- Urine drug toxicology screen for suspected cases

Differential diagnosis

a. Jitteriness: characterized by
- Tremor like movements of limbs (never affect the face)
- Precipitated by sensory stimuli.
- Stopped by holding the limb.
- Not associated with heart rate or EEG changes.
- May occur in normal infant, drug withdrawal, hypocalcemia & hypoglycemia.

b. Non epileptic apnea : usually associated with bradycardia

Treatment

I- **Step 1**:

Aim: Stabilize vital functions:

- Admit neonate to neonatal intensive care unit (NICU).
- Support respiration: suction of secretions and 100% O_2 inhalation.
- Support circulation: I.V. fluids.

II- **Step 2**:

Aim: Correct transient metabolic disturbances

- Hypoglycemia → Glucose 10% I.V 2 ml/kg
  → May require continuous glucose infusion 8 mg/kg/min
- Hypocalcemia → Calcium gluconate 10% slow I.V 2 ml/kg(under monitor)
- Hypomagnesemia → Magnesium sulphate 50% I.M 0.2 ml/kg

III- **Step 3**:

Aim: Specific anticonvulsant agents if seizure prolonged > 5minutes or recur :

1- Phenobarbitone: - Loading dose = 20 mg/Kg slow I.V.
- Maintenance dose = 3-8 mg/Kg I.V.

2- If no response add: Phenytoin (loading & maintenance doses as phenobarbitone).

3- If no response use benzodiazpines: Clonazepam or Midazolam

4- If seizures resistant to preceding drugs → Pyridoxine 50 mg iv therapeutic trial.

IV- **After controlling the attack**:

- Treat the cause e.g. antibiotics for meningitis
- Gradual withdrawal of anticonvulsants in transient causes with low risk of recurrences
- If maintenance therapy required ; usually use phenobarbitone ,clonazepam or sodium valproate and reevaluate at 6-12 weeks intervals.

Neonatal Respiratory Distress

Causes of neonatal respiratory distress

Peripheral

i- **Pulmonary causes**:

1- **Lung**:
- Respiratory distress syndrome.
- Transient tachypnea of newborn.
- Congenital pneumonia
- Congenital lobar emphysema
- Lung collapse, cysts, hypoplasia.

2- **Airway**:
- Meconium aspiration syndrome.
- Obstruction: bilateral choanal atresia, vascular ring, macroglossia,

3- **Pleura**:
- Pneumothorax
- Pleural effusion.
- Diaphragmatic hernia

ii- **Extrapulmonary causes**:

1- **Cardiac**: Heart failure.

2- **Hematologic**:
- Severe Anemia
- Polycythaemia.

3- **Metabolic**:
- Hypoglycemia
- Hypothermia
- Metabolic acidosis

Central

CNS failure: Due to
- Over sedation
- Perinatal asphyxia
- intra cranial hemorrhage.

Manifested by:
- Slow, irregular, gasping respiration.
- Apneic attacks.
- Disturbed consciousness.
- Poor reflexes.

Clinical signs of peripheral respiratory distress:

1- Mild : Tachypnea (> 60 / min) & working alae nasi
2- Moderate : As mild plus → Intercostal & subcostal retractions.
3- Severe : As moderate plus→ Grunting.
4- Advanced : As severe plus → Central cyanosis, disturbed consciousness.

Respiratory Distress Syndrome (RDS)

(Hyaline membrane disease)

Definition

A syndrome of respiratory distress occurs in the newborn due to surfactant deficiency, RDS is the commonest cause of neonatal death.

Surfactant

- Composed mainly of: - Dipalmitoyl phosphatidylcholine (Lecithin).
  - Phosphatidyl glycerol.
  - Surfactant proteins A, B ,C& D.
- Produced by: alveolar cells type II starting at 21–24 weeks of gestation and mature after 35th weeks (near term).
- Functions: reduce surface tension within the alveoli so, prevent their collapse at the end of expiration and reduce the lung stiffness and work of breathing.

Causes of RDS

1- Prematurity:
- The smaller the gestational age the higher the incidence of RDS
- About 60% of prematures < 28 weeks develop RDS

2- Infant of diabetic mother:
- Maternal hyperglycemia → fetal hyperinsulinemia→ reduced fetal cortisone
- Fetal cortisone is essential for surfactant production

3- Cesarean section(CS) and precipitate labor:
- Due to lack of stressful delivery → reduced fetal cortisone.

4- Perinatal asphyxia:
- Due to hypoxemia of alveolar cells type II.

5- Others : Second twin, male sex, RDS in siblings

Pathophysiology

* ↓ Surfactant →↑ alveolar surface tension → diffuse alveolar collapse (atelectasis) during expiration→higher pressure is required to initiate lung inflation→increased work of breathing with impaired gas exchange→ hypoxemia , hypercapnia and respiratory acidosis.
* Hypoxemia→ pulmonary vessels vasoconstriction → alveolar hypoperfusion → ↓ metabolism of alveolar cells type II → more surfactant deficiency → progressive atelectasis.

Pathology

- Diffuse atelectasis
- Esinophilic (hyaline) membrane lining alveoli & small bronchioles.

Clinical picture

* Signs of respiratory distress:
  - Tachypnea, retractions, grunting even cyanosis in severe cases.
  - Develops within hours after birth (4-12 hours).
  - Progressively increases to reach the peak at the 3rd day of life.
* Auscultation:- In severe cases → diminished air entry
  → bilateral fine basal crepitations
* Course: - In mild cases → gradual improvement occurs after the 3rd day.
  - In severe cases → end in death or complications.

Complications

Of the disease	Of treatment
- Hypoxia & acidosis → ↓ myocardial contractility → cardiogenic shock	- Pneumothorax - Pulmonary hemorrhage
- Patent ductus arteriosus → due to hypoxia	- Chronic lung disease
- Intra ventricular hemorrhage.	- Retinopathy of prematurity

Investigations

1- Prenatal diagnosis:

Done on samples from amniocentesis or maternal vagina after ruptured membranes

1- Lecithin/sphingomyelin ratio :

* If > 2.5 → Mature lung → No risk of RDS
* If 1.5-2 → Transitional lung → Risk of RDS
* If < 1.5 → Immature lung → Severe RDS

2- Saturated phosphatidyle choline:

* If >500 μg/dl → immature lung
* If < 500 μg/dl → mature lung

2- Post natal diagnosis:

1- Suspected clinically in cases with respiratory distress in presence of risk factors

2- Chest X-ray:

* Mild RDS:
  - Diffuse reticulo-nodular infiltrates (ground glass appearance)
  - Air bronchogram: out line of air filled large airways against opaque lungs
  - Small lungs volumes
* Severe RDS: - White lungs (opacification of both lungs).

3- Shake test:

* Done on gastric aspirate before baby is one hour age →
* Add 0.5 ml gastric aspirate to 4ml saline and 0.5 ml absolute alcohol→ shaking:
  - Absence of bubbles → indicate absent surfactant
  - Incomplete circle of bubbles → intermediate risk of RDS
  - Double rows of bubbles or more → no risk of RDS (mature lung)

4- Arterial blood gases:

* In severe RDS: hypoxemia + hypercapnia + respiratory acidosis

3- Sepsis workup: Blood picture & blood culture to rule out early onset sepsis.

Prevention of RDS

1- Avoid risk factors:

- Control maternal diabetes
- Avoid unnecessary CS
- Avoid prematurity

2- Antenatal steroid therapy:

- Value: steroid enhance surfactant production and accelerate lung maturity.
- Indications: pregnant women < 34 weeks who are at risk for preterm delivery.
- Contraindications: Chorioamnionitis.
- Dose: Betamethazone 12 mg/IM; two doses 24 hours apart.

3- Immediate postnatal surfactant and/ or nasal CPAP for very low birth weight.

Treatment of RDS

A. Supportive measures

1- Incubator care: with frequent monitoring of vital signs & arterial blood gases.

2- Respiratory support

Aim: Keep PaO_2 between 50 – 80 mmHg (oxygen saturation above 90%).

Methods of oxygen delivery:

Method	Indication
* Incubator oxygen	Infant >1500 gm & >32 weeks and doesn't require more than 30% oxygen
* Head box	- Infants requiring more than 30% oxygen - Infants less than1500 gm or 32 weeks.
* Continuous positive airways pressure (CPAP)	- Pa O_2 < 50 mm Hg in 60% O_2 or greater. - Value: Prevent collapse of surfactant deficient alveoli.
* Mechanical ventilation	- Intractable apnea. - Respiratory failure: (Pa O_2 < 50 mmHg, Pa Co_2 > 60 mm Hg , pH < 7.2) Despite 100 % oxygen and CPAP of 6 - 8 cmH_2O

3- Support circulation

- IV fluids.
- Correct hypotension (plasma, albumin, dopamine).

4- Support nutrition

If oral feeding can't be tolerated within 4-5 days , advise total parenteral nutrition .
(Oral feeding in preterm with RDS may ↑O2 consumption & predispose to NEC)

5- Symptomatic treatment: - correct metabolic acidosis and anemia.

B. Specific treatment

i- Antibiotics

Why indicated ? As it is difficult to differentiate RDS from congenital pneumonia
Choice? Give ampicillin and Gentamycin

ii- Surfactant

Indications:

- Immediate after birth for very low birth weight (prophylactic treatment).
- Cases of established RDS (rescue treatment).

Types:

- Synthetic: Exosurf and recently Surfaxin which mimic human surfactant.
- Natural: Lung extract of bovine (Survanta) , calf (Infasurf) or porcine(curosurf).

Doses:

- 3 –5 ml/Kg per dose in endotracheal tube.
- For 2-4 doses at 6-12 hours intervals.

Prognosis: Inversely proportionate to gestational age.

N.B: Risk of RDS is reduced by :

* Premature rupture of membranes
* Prenatal steroids
* Pre eclampsia.
* Intra uterine growth retardation

Transient Tachypnea of Newborn	Meconium Aspiration Syndrome
Definition Transient respiratory distress in full term.	Severe respiratory distress in post mature or full term exposed to intrauterine asphyxia.
Mechanism * Delayed resorption of fetal lung fluids by pulmonary lymphatics. * Risk factors: - Maternal diabetes - Perinatal asphyxia - Excess maternal analgesia - Cesarian section	Intrauterine asphyxia → paralysis of anal sphincter→ meconium stained liquor→ if meconium aspirated in lung at birth → areas of: - Complete obstruction→ patchy collapse - Incomplete obstruction → Air trapping. - 2ry infection & chemical pneumonitis.
Clinical picture - Mild respiratory distress within few hours after birth. - Spontaneous resolution occur within 2-3 days.	1- Severe respiratory distress (with grunting and cyanosis). 2- Meconium staining of nails, umbilicus and skin.
Chest X-ray - ↑ Pulmonary vascular markings - Mild cardiomegaly - Hyperinflation of the lungs - Fluid in costophernic angle and in horizontal fissures	- Coarse infiltrates - Over inflation - May be pneumothorax.
Treatment 1- O_2 (usually low concentration) 2- Antibiotics 3- IV fluids may be needed for cases with respiratory rates>80/min.	Preventive: 1. Antenatal care & fetal monitoring. 2. Suctioning before the 1st breath Curative: 1- O_2 therapy. 2- Antibiotics. 3- May be mechenical ventilation

Pneumothorax

Causes

- RDS
- Meconium Aspiration Syndrome
- Over resuscitation
- Staph. pneumonia (rare cause)

Diagnosis

- Asymptomatic pneumothorax present in about 1% of all neonates.
- Sudden deterioration in respiration in severe cases.
- Chest X-ray → jet black opacity

Treatment: for tension pneumothorax

- Air aspiration then
- Insert intercostal tube with under water seal.

Neonatal Cyanosis

Definition

- Bluish discolouration of skin and mucus membranes due to presence of more than 5 gm/dl reduced hemoglobin in capillary blood.
- It may be peripheral (not affect the tongue) or central (affect the tongue as well)

Causes

i- With increased work of breathing:

A. Pulmonary e.g.
- Severe RDS
- Congenital pneumonia
- Meconium aspiration syndrome
- Pneumothorax
- Diaphragmatic hernia
- Persistent pulmonary hypertension of newborn

B. Cardiac
- Congenital cyanotic heart diseases with increased pulmonary blood flow e.g TGA with VSD
- Congenital heart diseases with critical obstructions

ii- With normal work of breathing:

A. Cardiac: Congenital cyanotic heart diseases with ↓ pulmonary blood flow.

B. Hematologic: Polycythaemia and Methemoglobinemia.

iii- With decreased work of breathing (hypoventilation)

- Central respiratory failure

Differential diagnosis

Consider evaluation of general condition and gestational age

1- Pulmonary causes → wheezes, crepitation, chest X-ray.

2- Cardiac causes → murmurs, emergency echocardiography.

3- **Hyperoxia test:** differentiate between pulmonary & cardiac causes of cyanosis.
- Perform arterial blood gases in room oxygen then give 100% O_2 and perform arterial blood gases again.
- If PaO_2 become > 150 mmHg after 100% O_2 → pulmonary cause of cyanosis.
- If PaO2 remain below 100 mmHg despite 100% O2 → cardiac cause of cyanosis. These patients should receive PGE1 infusion to maintain ductus arteriousus patent.

4- Blood sample → for polycythemia & methemoglobinemia

Abnormal Gestational Age And Birth Weight

Definitions

1- Premature (Preterm):
- Infant born before 37 weeks gestation regardless to his weight.

2- Full term:
- Infant born between 37-42 weeks. gestations regardless to his weight.

3- Post mature (post term):
- Infant born after 42 weeks. gestation regardless to his weight.

4- Small for date (small for gestational age or intra uterine growth retardation):
- Infant with birth weight < 10th percentile of expected from his gestational age.

5- Appropriate for date:
- Infant with birth weight between 10th and 90th percentile of expected from his gestational age.

6- Large for date (Large for gestational age; macrosomia):
- Infant with birth weight > 90th percentile of expected from his gestational age.

Low Birth Weight

Definition

- Any newborn with birth weight less than 2.5 Kg
- If birth weight less than 1.5 kg. It is called very low birth weight (VLBW).
- It includes:- Premature & Small for Gestational Age.

Small for gestational age

(intra uterine growth retardation "IUGR")

1- Types:

Symmetric IUGR	Asymmetric IUGR
Weight, length & Head circumference < 10th centile	Weight is much more affected than length & head circumference.
Mainly due to: - Insults in early pregnancy. - Congenital infections. - Chromosomal disorders.	Mainly due to: - Insults in late pregnancy. - Maternal malnutrition. - Placental insufficiency.

2- Assessment:

* Detect impaired fetal growth by prenatal ultrasonography:
- ↓ Biparietal diameter.
- ↓ Abdominal circumference.
- ↓ Femur length.

* Neonatal: - Low birth weight.
- Ballard score.

3- Complications:

- Hypoglycemia → due to ↓ hepatic glycogen.
- Polycythemia → due to chronic intrauterine hypoxia.
- Coagulation disorders.
- Pulmonary hemorrhage.

Prematurity

Causes

- Idiopathic: The cause of prematurity is unknown in most cases.
- Maternal factors: e.g. extreme of ages & chronic diseases.
- Fetal factors: e.g. twins, congenital infections.
- Obestetric factors: e.g. abnormal uterus, placenta & Polyhydramnios.

Features of preterm baby

1- Clinical picture of preterm:

- Birth weight: < 2.5kg (except infant of diabetic mother).
- Birth length: < 47 cm (except infant of diabetic mother).
- Head circumference: < 33cm.
- Chest circumference: < 30 cm.
- Scalp hair: fine and wolly.
- Skin: pink, shiny, covered with lanugo hair with little subcutaneous fat.
- Nails: Don't reach the finger tips.

2- Physical appearance; help in assessing gestational age:

- Ear → shapeless and soft (immature ear cartilage).
- Breast nodule → < 3mm diameter (or even absent).
- External genitalia → Female: prominent labia minora.
  → Male: undescended testis.
- Sole creases → Don't reach beyond the anterior 2/3rd of sole (or even absent).

3- Physiological features:

- Respiration: Weak shallow with attacks of apnea due to immature respiratory center.
- GIT: Weak suckling, swallowing, digestion and absorption.
- Activity: Weak crying & activity.
- Physiological jaundice: Delayed (after the 3rd day), prolonged (for 2weeks) and deeper (up to 15 mg/dl).

Complications (Problems) of prematurity

1- Respiratory	- RDS - Apnea of prematurity (cessation of respiration for > 15 sec): - Occur in premature < 34 weeks. - Appear in 1st week of life (2nd – 5th day). - Due to respiratory center immaturity. - More prone to congenital pneumonia. - More prone to bronchopulmonary dysplasia
2- CVS	- PDA → Heart failure. - Hypotension (due to hypovolaemia & cardiac dysfunction). - Bradycardia (due to apnea).
3- CNS	- Kernicterus (bilirubin encephalopathy). - Hypoxic-ischaemic encephalopathy. - Intraventricular hemorrhage
4- Hematological	- More prone to Iron & Folic acid deficiency anemia. - More prone to bleeding (vitamin K deficiency & DIC).
5- GIT	- Prematurity is major risk factor for Necrotizing enterocolitis

6- Renal	- Immaturity of the kidney →↓ capacity to concentrate urine → more prone to acidosis or dehydration
7- Immunologic	- More prone to infection and sepsis due to deficiency of humoral and cellular response & ↓ transplacental antibodies
8- Nutritional	- More prone to rickets, PCM, hypoglycemia and hypocalcaemia Due to: - Weak suckling, swallowing, digestion and absorption. - High growth rate. - Low reserve (e.g. less subcutaneous fat) - Low calcium and phosphate stores
9- Hypothermia	Due to: - Large surface area relative to weight → excess heat loss. - Poor subcutaneous fat. - Immature heat regulating center

10- Retinopathy of prematurity (Retro-lental fibroplasia)

* Definition - Vasoproliferative retinal disorder that occurs mainly in premature exposed to high O_2 tensions for long duration
* Risk factors - High O_2 tension and vitamin E deficiency
* Stages - Stage I : Vasoconstriction of retinal blood vessels.
  - Stage II : Vasodilatation of retinal blood vessels, vitreous hemorrhage.
  - Stage III : neovascularization of the retina.
  - Stage IV : traction on retina by fibrous tissue & organized blood vessels → retinal detachment.
* Clinically - No warning manifestations (so screening is needed)
  - Gradually occurring astigmatism, retinal detachement , amblyopia
* Treatment: Mainly prophylactic:
  - Lowest O_2 for the least duration is essential if O_2 therapy for prematures is indicated.
  - Any premature exposed to prolonged O_2 therapy should be examined by ophthalmoscope at the age of one & three months.

11- Late sequelae of prematurity

Early insult	Late insult
- Hypoxia, ischemia	- Mental retardation, seizures.
- Intraventricular hemorrhage	- Hydrocephalus, spasticity
- Sensorineural injury	- Visual & hearing impairment
- Respiratory failure	- Chronic lung disease and cor pulmonale
- Necrotizing enterocolitis	- Short bowel syndrome, malabsorption , malnutrition
- Nutrient deficiency	- Anemia, rickets
- Social stress	- Child abuse, neglect.

Management of Prematurity (= of LBW)

A. Proper ante-natal care

- Avoid maternal smoking, irradiation & drugs.
- Assessment of the foetus by ultrasound
- In special situation amniocentesis or foetal blood sampling may be indicated.

B. Immediate post-natal care

1- Place the baby under radiant warmer.
2- Drying of the baby & suction of secretions.
3- Apgar scoring & **Resuscitation** if needed.
4- Complete examination (see examination of newborn).
5- Care of the skin and aseptic cutting of the umbilical cord.
6- Vit K1 (1 mg IM) is given for all neonates.
7- If the baby is large premature (> 2 kg) with no critical illness → discharge.
8- If the baby is < 2 kg weight or has a critical illness → incubator care.

C. Incubator care

1. Temperature:

- Is adjusted to keep body temperature around normal (36.5-37.2 °C)
- Value: reduce heat loss & O_2 consumption.

2. Humidity:

- Kept around 40-60%
- Values:
  * Reduce heat loss & water loss from bronchial tree
  * Stabilize body temperature by:
    - Reduce heat losses at lower environmental temperatures
    - Prevent drying and irritation of respiratory airways
    - Thinning viscid secretions and reduce insensible water loss

3. Oxygen therapy:

- Given in lowest concentration
- For the shortest period
- With gradual withdrawal.

4. Prevention of infection:

- All medical personnel must wash their hands before and after examining the baby
- No person with infection should be admitted into the nursery.
- Antibiotic administration if indicated.

5. **Feeding**:

A- Oral feeding:

* Type : - Expressed breast milk or premature artificial milk formula.
* Routes : - Suckling (In large prematures without respiratory distress).
  - Tube (Gavage) feeding through nasogastric tube for neonates less than 1.5 kg and those with mild respiratory distress.
  - Combined Gavage feeding & I.V. fluids.
* Frequency and amount:
  - Begin with small amount → if no vomiting feeding every 2-3hrs.
  - With stable condition increase the amount per feed gradually to reach the daily needs (150 – 180 Cal/kg/day).
  - If there's regurgitation, vomiting, gastric residual prier next feed (intolerance) → stop oral feeding and continue I.V. route.
* Vitamins and mineral supply:
  - Vit K → 1 mg IM ⇒ At birth.
  - Vit D → 800-1000 IU/day
  - Vit A → 1500 IU/day
  - Vit E → 6-12 IU/day ⇒ From 2nd week
  - Folic acid → 1 mg/day.
  - Vit C. → 20-40 mg/day.
  - Iron → 2 mg/kg/day ⇒ When birth weight is doubled.

B- Intravenous fluids:

* Indications: Severe respiratory distress or intolerance to oral feeding.
* Amount: - 60-80 ml/kg/day in 1st day of life
  - Gradually increased to reach 150 ml/kg/d in the 5th day.
* Type: - Glucose 10% in the 1st day.
  - After that Glucose 10%: Saline (4:1);Calcium 1-2ml/kg/day is added to fluids.
* Duration:- Maximum for 3-5 days
  - If oral feeding can't be resumed, initiate total parenteral nutrition

6. **Treatment of associations** e.g.:

- Phototherapy for hyperbilirubinaemia.
- Treatment of PDA (fluid restriction and indomethacin).
- Parenteral antibiotics for sepsis

7. **Discharge from incubator**:

* Indications:
  - Infant > 1750 grams with good suckling.
  - Maintain his temperature outside the incubator.
  - No critical illness.
  - Normal respiration.

* Instructions to the parents:
  1- Maintain body temperature
  2- Keep infant away from infection ; minimize handling and over crowding
  3- Schedule for feeding
  4- Schedule for vaccination ; according to date of birth (not expected date)
  5- Encourage follow up visits
  6- Ophthalmic examination for those exposed to prolonged O_2 therapy

Postmaturity

Definition: Infant born after 42 weeks gestation irrespective to his birth weight.

Causes

- Unknown in most cases.
- High incidence with trisomies or anencephaly.

Features

- Face : opened eye and alert baby.
- Skin : wrinkled, dry ± meconium staining.
- Nails : long nails.

Complications

- Perinatal asphyxia ± Meconium aspiration
- Hypoglycaemia.
- Polycythaemia
- Hypocalcaemia.

Infant of diabetic mother

Definition: - Neonate born to diabetic mother (true or gestational diabetes mellitus).

Features

1- Commonly delivered preterm with increased birth weight (Large for gestational age).

Why? Maternal hyperglycemia → fetal hyperglycemia → increase fetal hepatic glucose uptake, glycogen synthesis & enhance lipogenesis & protein synthesis → macrosomia (increased growth of all organs except for the brain).

2- Plump with puffy plethoric facies.

Common problems

1- High fetal mortality specially in poorly controlled diabetes with ketoacidosis.

2- Hypoglycaemia due to: Maternal hyperglycemia → fetal hyperglycemia → increased fetal insulin production. After birth → interruption of high maternal glucose to the neonate while hyperinsulinemia is going on → hypoglycemia.

3- Respiratory distress may be due to:

- Respiratory distress syndrome.
- Transient tachypnea of newborn.
- Cerebral oedema due to trauma or asphyxia.
- Hypoglycemia.
- Polycythemia.
- Heart failure.

4- Hypocalcaemia due to: transient hypoparathyroidism.

5- Hyperbilirunbinaemia due to: polycythaemia and reduced RBCs life span.

6- Convulsions may be due to: Hypoglycaemia, Hypocalcaemia, birth trauma.

7- Congenital anomalies are 3 fold common, especially congenital heart diseases and neural tube defects.

8- Cardiomyopathy.

9- Macrosomia may predispose to difficult labor & birth injury

10- Renal vein thrombosis

Management

* Proper control of maternal diabetes:
* For the baby

1- Immediate post-natal care and incubator care (see before).

2- Treatment of hypoglycemia:

- Initial treatment: glucose 10% 2-4 ml/kg I.V.
- Maintenance: glucose 10% continuous I.V. infusion at rate of 8 mg/kg/min.
- Monitor blood glucose every 2 hours.
- If blood glucose is controlled, gradually withdraw I.V. fluids and advance oral feeding.
- Hydrocortisone and glucagon can be added in poorly controlled cases.
- Discharge if no hypoglycemia for 24–48 hours and no other complication.

3- Treat complications e.g.: - Jaundice: phototherapy.
- Polycythemia: Partial exchange transfusion.

N.B. Value of neonatal screening? Pick early cases of:

- ➢ Hypothyroidism
- ➢ Phenyleketonuria
- ➢ Hemoglobinopathy.
- ➢ G6PD deficiency.

Examination Of The Newborn

Quick examination

Value: To detect life threatening insults.

1- Apgar scoring ⇒ (done at 1, 5 minutes).

2- Level of consciousness:

- Normal newborn is conscious, active, alert.
- Disturbed consciousness as lethargy, coma or weak suckling may indicate cerebral lesion or severe infection.

3- Color:

- Normal newborn is pinkish in color.
- Abnormal appearance of the newborn may be:
  - Pallor (anemia or shock)
  - Plethora (Polycythemia)
  - Cyanosis
  - Jaundice.

4- Vital signs:

- Heart rate (120 – 150 beat/minute) → - < 100 → Bradycardia.
  - > 160 → tachycardia.
- Respiratory rate (30 – 50 /minute) → - > 60 → tachypnea (RD)
- Temperature (36 – 37.2°C) → - < 35.5 → hypothermia
  - > 37.5 → fever.
- Blood pressure (60/40 mmHg)

After the end of quick examination the newborn will be considered as:

- Normal → proceed to other lines of examination.
- Abnormal → resuscitative measures.

Detailed Examination

Measurements

* Weight: 3 - 3.5 Kg.
* Length: 47- 50 cm.
* Head circumference: 33 - 35 cm.

Regional examination

a- Head

* Fontanels, Eye, Mouth, Nose, Ear, ...

b- Neck

* Short neck or webbing (Turner).
* Goitre (enlarged thyroid).

c- Limbs

* Birth trauma
* Erb's palsy
* Malformations.
* Hip dislocation detected by:
  - Gluteal fold asymmetry
  - Unequal leg length.
  - Limited hip abduction.
  - Hip X-ray

d- Genitalia

* Ambiguous genitalia
* Undescended testis.

e- Skin

* Meconium staining
* Oedema (Hydrops fetalis).

f- Urine and stool

* Normal neonate should pass urine and meconium within 24 hrs after delivery.

Systemic examination

a- Cardiovascular system

☆ Apex beat: Normally in Left 4th space just outside mid clavicular line.
☆ Murmers: Most of murmurs in early neonatal period are transient
☆ The 2nd heart sound may not be splitted in the 1st day of life
☆ Femoral pulsations: If absent Aortic coarctation is suspected.

b- Chest examination

☆ Signs of respiratory distress.
☆ Auscultation for wheezes, crepitations, ...

c- Abdominal examination

☆Liver may be palpable 2 cm in neonates
☆ Both kidneys should be palpable in the 1st day of life
☆ Check for organomegaly, ascitis, umbilicus, ...
☆Causes of neonatal abdominal masses e.g.:

- Hydronephrosis.
- Multicystic – dysplastic kidney.
- Ovarian cyst.
- Intestinal duplication.
- Neuroblastoma.
- Wilm's tumor.

d- Neurological examination

- Level consciousness.
- Muscle tone (normally flexed all limbs).
- Neonatal reflexes.

Special Examination

Check for congenital anomalies

- Cleft lip
- Limb anomalies
- Tracheo-esophageal fistula
- Imperforate anus.

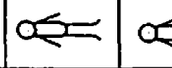
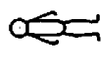
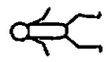
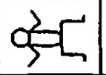
Search of birth injuries

Assessment of gestational age

1- From the history (last menstrual period).
2- From the ultrasound exam. during pregnancy.
3- From the physical and neurological assessment of the newborn:
- For each criteria a definite score is given and the net score indicate certain

gestational age. A lot of scoring systems are available but **New Ballard** score is the most commonly used.

Neuromuscular Maturity

	-1	0	1	2	3	4	5
Posture							
Square Window (wrist)	 >90°	 90°	 60°	45°	30°	0°	
Arm Recoil		 180°	 140°-180°	 110°-140°	 90-110°	 <90°	
Popliteal Angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf Sign							
Heel to Ear							

Physical Maturity

Skin	sticky friable transparent	gelatinous red, translucent	smooth pink, visible veins	superficial peeling &/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald	
Plantar Surface	heel-toe 40-50mm: -1 <40mm: -2	>50mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole	
Breast	imperceptible	barely perceptible	flat areola no bud	stippled areola 1-2mm bud	raised areola 3-4mm bud	full areola 5-10mm bud	
Eye/Ear	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff	
Genitals male	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae	
Genitals female	clitoris prominent labia flat	prominent clitoris small labia minora	prominent clitoris enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora	

Maturity Rating

score	weeks
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Expanded New Ballard Score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard Score, expanded to include extremely premature infants. J Pediatr 119:417-423, 1991.)*

Cardiology

List Of Abbreviations

Lt. V.	: Left ventricle
Rt. V.	: Right ventricle
Lt. A	: Left atrium
Rt. A	: Right atrium
LVH	: Left ventricle hypertrophy.
RVH	: Right ventricle hypertrophy
LAD	: Left atrium dilatation
RAD	: Right atrium dilatation
C.P. angle.	: Cardiophernic angle
$P.H^{+}$	: Pulmonary hypertension
S_1	: First heart sound
S_2	: Second heart sound
P_2	: Pulmonary component of the second heart sound
A_2	: Aortic component of the second heart sound.
RVF	: Right ventricle failure.
LVF	: Left ventricle failure
BVF	: Biventricular failure
COP	: Cardiac output
LPSB	: Left parasternal border
CXR	: Chest X-ray
SBE	: Subacute bacterial endocarditis
RBBB	: Right bundle branch block
VMA	: Vallinyle mandilic acid
BVH	: Biventricular hypertrophy.
PGE_1	: Prostaglandin E1
PFO	: Patent formen ovale.
TOF	: Tetralogy of Fallot
DORV	: Double outlet right ventricle

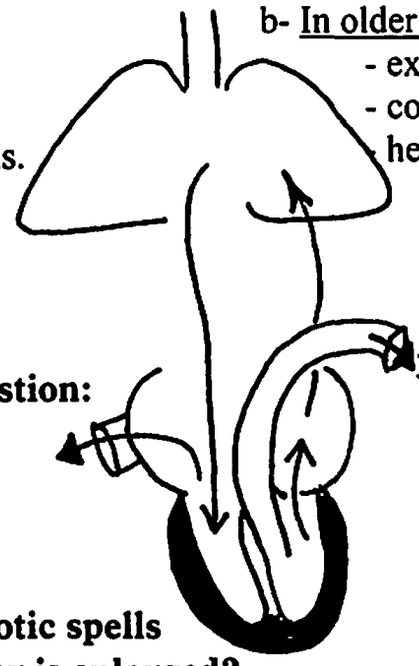
Diagnosis of a cardiac case

I- Suspect cardiac disease from symptoms of

1- Pulmonary venous congestion:

a- In infants:
- dyspnea on suckling
  → poor feeding
- recurrent chest infections.
- recurrent heart failure.
- growth retardation

b- In older children:
- exertional dyspnea.
- cough (exertional& positional) heamoptysis.

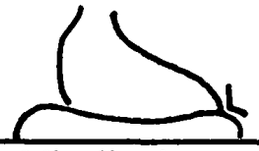
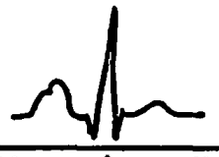
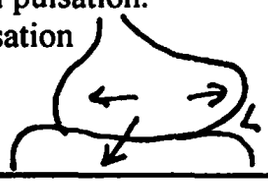
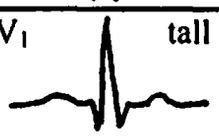
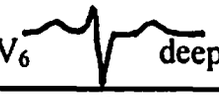
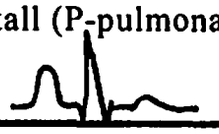


2- Systemic venous congestion:
- enlarged tender liver
- dyspepsia
- generalized edema

3- low cardiac output:
- easy fatigability (exercise intolerance)
- dizziness.
- transient syncopal attacks
- anginal chest pain

4- Cyanosis & hypercyanotic spells

II- Which cardiac chamber is enlarged?

	Precordial examination (inspection/palpation./percussion)	Chest X-ray	ECG
LVH	Apex is localized and shifted down & out 	- Obtuse cardiophernic angle. - Apex shifted down and out 	V_1 deep S  V_6 tall R 
LAD	--	Mitralization  Double contour	P wave is wide & bifid (P-mitrale). 
RVH	- Precordial bulge - Apex is diffuse & shifted out. - left parasternal pulsation. - Epigastric pulsation 	- Acute cardiophernic angle. - Apex shifted direct out. 	V_1 tall R  V_6 deep S 
RAD	--	↑ Right cardiac shadow 	P wave is peaked & tall (P-pulmonale) 

III- What is the organic lesion?

1- Auscultation

i. Heart sound:

1- First heart sounds (S_1):
- Due to closure of atrio ventricular valves.
- Heard over apex & tricusped areas.
- Accentuated in atrio ventricular valves stenosis.
- Muffled in atrio ventricular valves regurge.

2- Second heart sound (S_2):
- Due to closure of semilunar valves; aortic and pulmonary valves.
- Composed of aortic component (A_2) & pulmonary component (P_2).
- Heard over aortic area & pulmonary area.
- Usually both components split during inspiration & unite during expiration.
- Accentuated in hypertension.
- Muffled in semilunar valve stenosis.

3- Third heart sound:
- Due to rapid filling of the left ventricle in early diastole
- May be heard normally in healthy children.
- Heard mostly in congestive heart failure.

4- Fourth heart sound:
- Due to forcible atrial contraction.
- Always abnormal (due to decreased ventricular compliance).

ii. Study of murmers:

1- Timing: systolic or diastolic or continuous.

2- Site of maximum intensity & propagation.

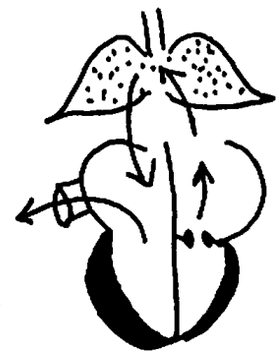
3- Intensity classified as:
- Grade I : Soft, heard with difficulty.
- Grade II : Soft, easily heard.
- Grade III : Loud without thrill
- Grade IV : Loud with thrill..
- Grade V : Louder with thrill.
- Grade VI : Loud + thrill + heard with stethoscope off the chest.

4- Quality: Harsh, soft, musical:

2- Echocardiography & catheterization

Value:
- Describe the cardiac lesions (site – size).
- Measure intracardiac pressures.
- Measure flow across the lesion.
- Assess ventricular function(end diastolic volume , shortening fraction)
- Chamber size.
- Detect complications e.g. Infective endocarditis vegetations.

Common Valvular Lesions



Mitral Stenosis (MS)

Causes: 1- Rheumatic (mainly)
2- Congenital (rare)

Hemodynamics

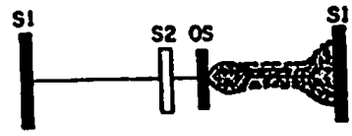
1- MS → Blood accumulate in left atrium → left atrial dilatation → pulmonary congestion.
2- Prolonged pulmonary congestion → pulmonary hypertension ($P.H^+$) → Right ventricular hypertrophy (RVH) & right ventricle failure.

Symptoms

- Pulmonary venous congestive manifestations with or without systemic venous congestive manifestations.

Precordial examination

1- Slapping apex (palpable first heart sound)
2- Pulmonary pulsation and dull pulmonary area in cases with pulmonary hypertension.
3- RVH in advanced cases



Auscultation

1- Apex: - Opening snap.
- Accentuated S_1.
- Murmer: → mid diastolic rumbling with pre systolic accentuation
→ localized to the apex (no propagation)

2- Pulmonary area (in cases with pulmonary hypertension):
- Accentuated S_2.
- Ejection systolic murmer.

Aortic Regurge (AR)

Causes: 1- Rheumatic (mainly)
2- Syphilytic (rare).

Hemodynamics

1- Incomptent aortic valve → In diastole blood returns to the heart leading to:
- Decreased diastolic pressure.
- Large end diastolic volume of left ventricle → increased systolic pressure.

2- High systolic pressure and low diastolic pressure result in hyperdynamic circulation.

Symptoms

1- Manifestations of low cardiac output.
2- Palpitation with exertion.

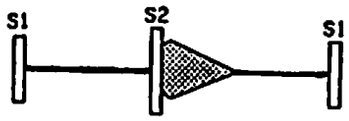
General examination: (peripheral signs suggesting A.R.)

- Corrigan sign = visible arterial pulsations in carotid arteries.
- De Musset sign = head nodding with each heart beat.
- Wide pulse pressure.
- Water hammer pulse.
- Cappilary pulsations (in nail beds and lips).

- Systolic pressure in lower limb is higher than upper limb by more than 20 mmHg.
- Pistol shot due to push of blood in the empty artery.
- Duroisier sign diastolic murmer on pressing femoral artery by stethoscope edge.

Precordial examination

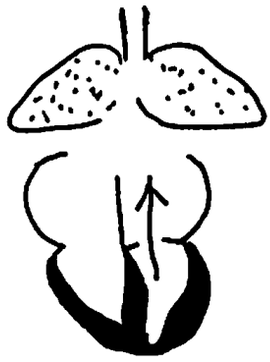
- Hyperdynamic apex. (forcible, non sustained).
- Left ventricular enlargement (LVH).



Auscultation

Aortic area: - Murmer → early diastolic (increase by leaning forward)
on 1st aortic area propagate to 2nd aortic area

Mitral regurge (MR)



Causes: 1- Rheumatic (mainly)
2- Congenital (rare).

Hemodynamics

1- Incomptent mitral valve → in systole blood returns to the left atrium → left atrial dilatation and pulmonary congestion → pulmonary hypertension.
2- Large end diastolic volume of left ventricle → left ventricle enlargement.

Symptoms

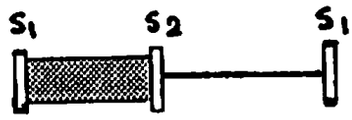
- Palpitation with exertion.
- Pulmonary venous congestive manifestations.

Precordial examination

- Hyperdynamic apex. (forcible, non sustained).
- Left ventricular enlargement (LVH); BVH in advanced cases
- May be apical systolic thrill.

Auscultation

1- Apex: - Muffled S_1.
- Murmer → pansystolic.
→ Propagate to the axilla



2- Pulmonary area (in cases with pulmonary hypertension).
- Accentuated S_2.
- Ejection systolic murmer.

Aortic stenosis (AS)

Causes: 1- Valvular (Rheumatic mainly).
2- Subvalvular (Congenital mainly).
3- Supravalvular (With Williams syndrome).

Hemodynamics

- Left ventricle outflow obstruction:
→ low cardiac out put.
→ left ventricle hypertrophy and left ventricle failure.

Symptoms: - Manifestations of low cardiac output.

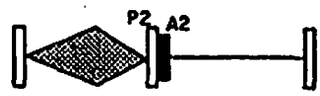
Precordial examination

- Heaving apex. (forcible, sustained).
- Left ventricular enlargement (LVH).
- Systolic thrill over aortic area and the neck.

Auscultation

Aortic area: - Muffled S_2.

- Murmer → Ejection systolic on 1st aortic area propagate to the neck & the apex.



Pulmonary stenosis (PS)

Causes

- Congenital mainly.

Precordial examination

- Right ventricular enlargement (RVH).
- Systolic thrill over pulmonary area.

Auscultation

Pulmonary area: - Muffled S_2.

- Murmer → Ejection systolic on pulmonary area propagate to the left parasternal area.

Treatment of valvular lesions

Medical

1- Afterload reducers e.g captopril for regurgitant lesions.
2- Exercise restriction for severe stenotic lesions.
3- Treat complications:
   - Heart failure
   - Infective endocarditis.
   - Arrythmias
4- Prophylaxis against
   - Infective endocarditis.
   - Rheumatic fever (in rheumatic cases).

Interventional

Balloon valvoplasty for Symptomatic, non calcific, stenotic lesions e.g
- AS
- PS
- MS

Surgical

1- Valvotomy for stenosis
2- Repair for regurge
3- Replacement.

Congenital Heart Diseases

Incidence

- Affect 0.5-0.8% of children.
- The commonest is VSD then PDA & ASD
- The commonest cyanotic congenital heart disease is Fallot tetralogy.
- The commonest cyanotic congenital heart disease at birth is TGA.

Risk Factors

Maternal: → Drugs e.g. warfarin, anticonvulsants, alcohol
→ Diseases e.g.: - Congenital rubella → PDA
- Maternal diabetes .

Chromosomal: → Down syndrome → ECD, VSD
→ Turner syndrome → Co.A.

Previous baby with congenital heart disease.

Congenital Acyanotic Heart Diseases (80%)

With left to right shunt
(potentially cyanotic)

1- Ventricular septal defect (VSD)
2-Patent ductus arteriosus (PDA)
3- Atrial septal defect (ASD)
4- Endocardial cushion defect (ECD).

Common features:

1- Degree of left to right shunt, and consequently clinical manifestations is dependent on:
   a- Size of the defect.
   b- Pressure gradient across the defect.
   c- Pulmonary vascular resistance.
2- Manifestation of increase pulmonary blood flow:
   a- Poor feeding & tachypnea.
   b- recurrent chest infections & chest wheezes.
   c- recurrent heart failure.
   d- Growth failure.
3- Heart failure doesn't occur in neonates but can occur in infancy as pulmonary vascular pressure declines.
4- Prolonged pulmonary blood overflow→ pulmonary hypertension develops→ with time right heart pressures exceed that of the left → reversal of the shunt (Eisenmenger syndrome) → central cyanosis,
   This occur: - Early in large VSD & ECD.
   - Late in ASD & small defects.

Without shunt

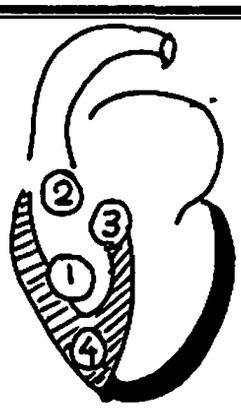
1- Obstructive lesions e.g.
- Aortic coarctation
- Aortic stenosis.
- Pulmonary stenosis

Common features:

1- Severe obstructive lesions can present early in life with heart failure.
2- Low cardiac output manifestations.

2- Non obstructive lesions e.g.
- Dextrocardia.

Ventricular septal defect (VSD)



Definition: Defect in interventricular septum.

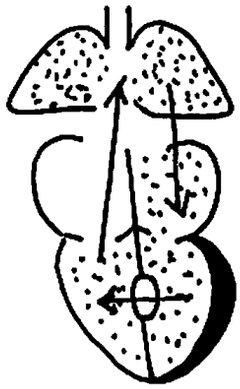
Types of VSDs:

1- Perimembraneous defect: The commonst type (70%)

2- Outlet defect; (also called infundibular **or** subarterial **or** supracristal or subpulmonary).

3- Inlet defect.

4- Muscular defects: Either single or multiple (Swiss cheese).



Hemodynamics

Blood is shunted from left ventricle to right ventricle →↑ pulmonary blood flow →↑ input to left atrium and left ventricle.

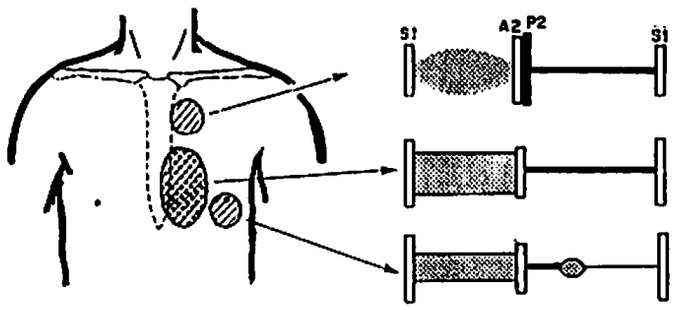
General manifestations

1- Small VSD: Usually asymptomatic, discovered accidentally.

2- Large VSD: - Features of increased pulmonary blood flow
- Congestive heart failure with tachypnea, tachycardia & enlarged tender liver.

Precordial Examination

- Evidence of biventricular enlargement (LVH & RVH)
- Systolic thrill on lower left sternal border.



Auscultation

1- Murmer of VSD:
- pansystolic.
- on lower left sternal border.
- propagate all over the heart.
- Harsh (louder if small).

2- Pulmonary area: Accentuated P_2 & soft systolic murmer indicate pulmonary hypertension.

3- Apical: Soft mid diastolic murmer may be heard due to relative mitral stenosis.

Investigations

1- Chest X-ray:
- Large VSD → Cardiomegaly with biventricular enlargement (LVH & RVH). & increased pulmonary vascular markings (Plethora).

2- ECG:
- Large VSD → Biventricular enlargement (LVH & RVH) & LAD.

3- Echo: diagnostic

4- Cardiac catheter: pre operative.

Complications

- Recurrent heart failure common with large defects.
- Recurrent pulmonary infections
- Infective endocarditis common with small defects.
- Reversal of the shunt.

Treatment

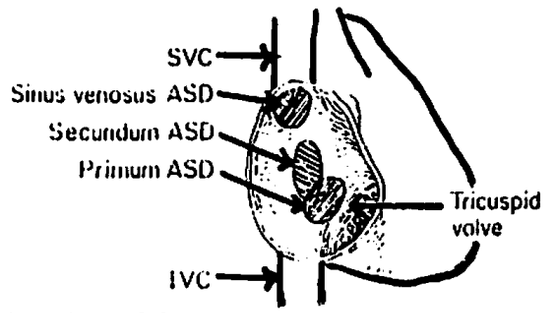
1- Medical:
- Control heart failure (diuretrics, digoxin, vasodilaters).
- Prophylaxis against infective endocarditis.
- Antibiotics for chest infections.
- Follow up with ECG & Echo to confirm spontaneous closure.

2- Surgical:
- Types:
  - a- Palliative: Pulmonary artery banding (less favoured).
  - b- Direct closure of the defect.
- Indications:
  - a- Symptomatic large defects.
  - b- Growth failure uncontrolled medically.
  - c- Pulmonary hypertension.
  - d- Supracristal VSD (aortic cusp may herniate inside resulting in aortic regurge).

Prognosis

30-50% of small defects (especially muscular) close spontaneously within 1st 2-years.

Atrial septal defect (ASD)



Definition: Defect in interatrial septum.

Types of ASDs:

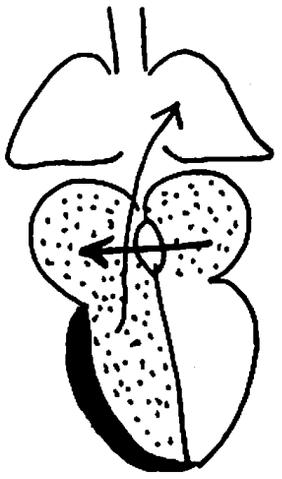
1- Ostium secundum defect :
- The commonest type.
- Lies in the middle part of the septum at the site of fossa ovalis.
- Association: may be with Holt Oram syndrome (Absent radii , 1st degree heart block , ASD).

2- Ostium primum defect: (Partial ECD)
- Lies in the lower part of the septum
- Association: usually with cleft of mitral valve leaflet. → mitral regurge.

3- Sinus venosus defect:
- Lies in the upper part of the septum near orifice of superior vena cava.
- Association: usually with partial anomalous pulmonary venous return.

Hemodynamics

Blood is shunted from left atrium to right atrium → right ventricle →↑ pulmonary blood flow (more with primum defects).



General manifestations

1- Asymptomatic in most cases.

2- Large ASD (especially primum defect) may present with features of increased pulmonary blood flow .

Precordial Examination

- May be evidence of RVH.

Auscultation

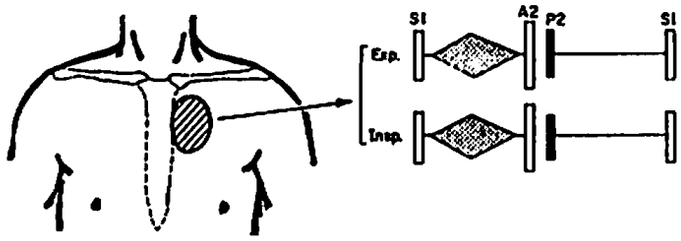
1- Pulmonary area:

a- wide fixed splitting of S_2:

- wide splitting due to large filling of right ventricle & fixed (not vary with respiration) due to constant filling of right ventricle in all phases of respiration..

b- murmur of a relative pulmonary stenosis:

- ejection systolic.
- soft.
- no thrill.
- no propagation
- with accentuated P_2.



2- Apex: pansystolic murmer of mitral regurge in ostium primum defect.

Investigations

1- Chest X-ray:

- Cardiomegaly with RVH & RAD.
- Plethoric lungs.

2- ECG:

- RVH & RAD.
- Right bundle branch block is common.

3- Echo: diagnostic

4- Cardiac catheter: pre operative.

Complications: very rare; more with primum defects.

- Recurrent heart failure may occur with large defects.
- Recurrent pulmonary infections
- Infective endocarditis is extremely rare.
- Reversal of the shunt may occur very late; in adulthood.

Treatment

1- Medical:

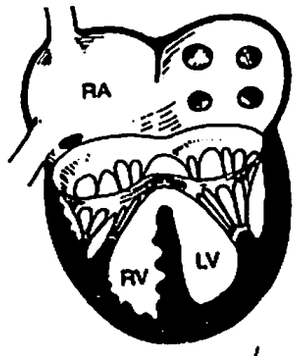
- Control heart failure (diuretrics, digoxin, vasodilaters).
- Prophylaxis against infective endocarditis usually not needed.
- Antibiotics for chest infections.
- Follow up with ECG & Echo to confirm to spontaneous closure.

2- Surgical: Transcatheter or open heart surgical closure at 3-5 years.

Prognosis

40% of ostium secundum defects close in 1st four years spontaneously

Endocardial cushion defect (ECD)



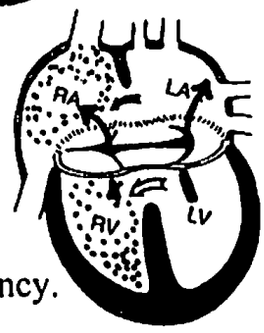
Definition: Defect in atrioventricular septum.

Complete defect is composed of:

1- Ostium primum defect
2- Common & incompetent atrio ventricular valve.
3- Inlet VSD.

Association: common with Down syndrome.

Hemodynamics



1- Blood regurge from both ventricles to both atria → marked increase pulmonary blood flow
2- Early pulmonary hypertension & reversal of the shunt.

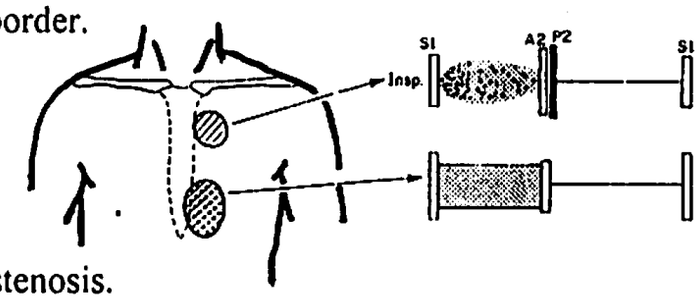
General manifestations

1- Features of increased pulmonary blood flow develop early in infancy.
2- Congestive heart failure occur 1-2 months after birth.

Precordial Examination

- Evidence of RVH (mainly)
- Systolic thrill on lower left sternal border.

Auscultation



1- Lower left sternal border:
   - Pansystolic murmer.
   - Propagate all over the heart.
2- Pulmonary area:
   - murmer of a relative pulmonary stenosis.

Investigations

1- Chest X-ray:
   - Huge cardiomegaly (all chambers are enlarged).
   - Plethora.
2- ECG:
   - RVH mainly.
3- Echo: diagnostic
4- Cardiac catheter: pre operative.

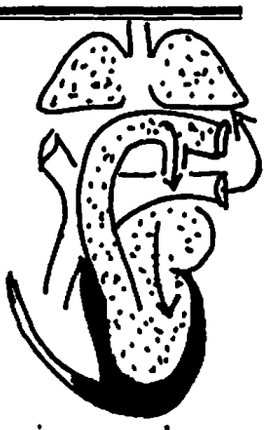
Complications: very common, occur early.

- Recurrent heart failure
- Recurrent pulmonary infections
- Infective endocarditis.
- Reversal of the shunt.

Treatment

1- Medical: - Control heart failure & prophylaxis against infective endocarditis.
2- Surgical: Early surgical repair is mandatory to avoid early pulmonary hypertension and intractable heart failure.
   - Types:
      a- Palliative: Pulmonary artery banding.
      b- Total correction.

Patent ductus arteriosus (PDA)



Definition: Persistent duct connecting the aorta & the pulmonary artery.

Connections:

1- The aortic end is just distal to left subclavian artery.

2- Pulmonary end is at the bifurcation.

Association: Congenital rubella syndrome & prematures.

Incidence: Female : male = 2 : 1.

Hemodynamics

1- Blood is shunted from higher pressure of aorta to pulmonary artery → increased pulmonary blood flow.

2- Hyperdynamic circulation is due to run off of blood from aorta to pulmonary artery during diastole.

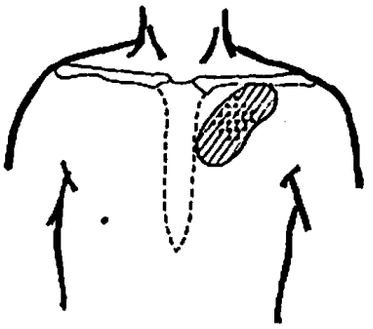
General manifestations

1- Small duct → asymptomatic

2- Big duct → increased pulmonary blood flow manifestations
→ hyperdynamic circulation (wide pulse pressure).

Precordial Examination

- Evidence of LVH.
- Systolic thrill on upper left sternal border.



Auscultation

Left infra clavicular area:

- Machinery murmer.
- May be systolic only in pulmonary hypertension.

Differential Diagnosis of machinery murmurs: e.g.:

1- Aortico pulmonary window.

2- Arterior venous fistula (systemic or pulmonary).

3- Ruptured sinus of valsalva..

Investigations:

1- Chest X-ray:
- Cardiomegaly (LVH & LAD).
- Plethora.

2- ECG: - LVH & LAD.

3- Echo: diagnostic.

4- Cardiac catheter: pre operative.

Complications

- Recurrent heart failure
- Recurrent pulmonary infections
- Infective endoarteritis.
- Reversal of the shunt.

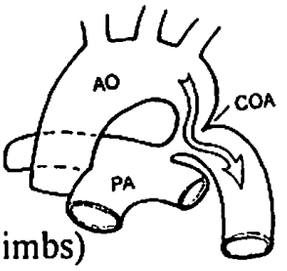
Treatment

1- Medical:
- Control heart failure & prophylaxis against infective endocarditis
- medical closure in preterm by I.V. indomethacin in the 1st week of life (not useful in full terms).

2- Surgical: surgical ligation or transcatheter closure.

Coarctation Of Aorta (Co.A)

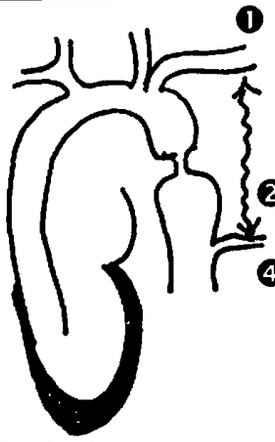
Definition: Constriction of the aorta to varying degrees at any point from arch to the bifurcation.



Types: - 98% of cases occur at the ductus arteriosus (juxta ductal).
- Post & preductal are less common.

Association: Turner syndrome.

Hemodynamics



❶ Hypertension proximal to the CoA (head, upper limbs)

❸ Collaterals develop between proximal & distal aortae.

❷ Hypotension distal to the CoA (lower body & lower limbs).

❹ In severe coarctation blood shunt from pulmonary artery to descending aorta via patent ductus so;
→ Perfusion of lower body is dependent on the ductus.
→ Differential cyanosis (lower limbs blue, upper limbs pink).

Clinical picture

1- Severe coarctation: Present in neonates by:
- Heart failure.
- Lower extremity hypoperfusion& Differential cyanosis.

2- Milder cases may present in older child
- Pulse → prominent in upper limb but weak or absent in lower limb.
→ Femoral pulse is delayed than radial pulse (unlike normal).
- Blood pressure is higher in upper limbs than lower limb.
- Systolic murmer over left lower sternal border and interscapular area.

Investigations

1- Chest X-ray:
- LVH
- Rib notching (Rosler sign) between 4th – 8th ribs due to collaterals, seen in older child

3- ECG: LVH

4- Echo: diagnostic.

5- Cardiac catheter: preoperative.

Complications

1- Systemic hypertension due to renal hypoperfusion.

2- Intracranial hemorrhage due to hypertension or associated aneurysms of circle of Willis.

3- Infective endocarditis.

4- Left ventricular failure.

Treatment

1- Medical treatment: for hypertension and heart failure & prophylaxis against infective endocarditis.

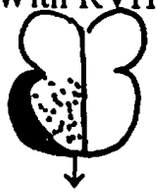
2- Surgical: - Resection & anastomosis with or without conduit insertion.
- Balloon angioplasty.

Cyanotic Congenital Heart Disease (CCHD)

Classification

CCHD with decreased pulmonary blood flow

With RVH



- Fallot tetralogy
- Pulmonary atresia with VSD
- Double outlet right ventricle with pulmonary stenosis

With LVH



- Pulmonary atresia without VSD
- Tricusped atresia
- Ebstein anomaly.

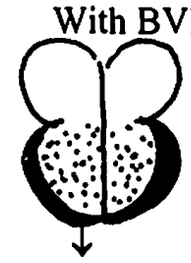
CCHD with increased pulmonary blood flow

With RVH



- TGA
- TAPVR
- Double outlet right ventricle without pulmonary stenosis

With BVH



- Truncus arteriosus
- Single ventricle

Criteria

- Cyanotic spells (common)	- Poor feeding "dyspnea on suckling".
	- Recurrent chest infections.
- Heart failure → rare	- Recurrent heart failure.
- P_2 (pulmonary component of S_2) → ↓	- P_2 → ↑
- Chest X-ray → lung oligaemia	- Chest X-ray → plethora.

- Growth retardation occur in long standing, symptomatic, uncorrected lesions.

Fallot Tetralogy

Definition: Cyanotic congenital heart disease with decreased pulmonary blood flow.

Composed of:

1- Pulmonary stenosis (infundibular in **50%**, valvular in 10%, both in **30%**)

2- RVH → usually mild, due to right ventricle out flow obstruction.

3- VSD → usually large; lies just below aortic valve.

4- Overriding of the aorta → receive mixed blood (right aortic arch in **25%**).

Hemodynamics

i- Degree of pulmonary stenosis (P.S.) determine the degree of right to left shunt:

1- Severe P.S. → early right to left shunt → cyanosis appear in the 1st week of life.

2- Moderate P.S. → balanced shunt → delayed cyanosis. (appear within months).

3- Very mild P.S. → picture of **left** to **right** shunt → increased pulmonary blood flow → liable to heart failure; with time, pulmonary stenosis increases → **left** to **right** shunt decline with appearance of cyanosis & spells.

ii- Pulmonary blood flow is maintained by PDA in neonate **or** aorto pulmonary collateral arteries later on.

Clinical picture

1- Central cyanosis:

- Usually appear later in the 1st year (may be at birth).
- Cases with mild to moderate pulmonary stenosis may not be initially visibly cyanotic (acyanotic or pink Fallot).

2- Squatting position:

After physical effort → dyspnea may occur → the child assume squatting position → ↑ systemic vascular resistance → ↑ aortic pressure →↑ pulmonary blood flow → a trial to increase blood oxygenation in lungs.

3- Clubbing : related to the degree & duration of cyanosis.

4- Paroxysmal hypercyanotic (hypoxic) spells:

* Due to infundibular spasm → decrease of already reduced pulmonary blood flow.
* Usually occur in the morning after crying, feeding or defecation.
* Attacks of → increasing cyanosis.
  → hyperpnea; rapid & deep breathing (respiratory acidosis)
  → irritability (due to hypoxemia).
  → decreasing murmer intensty.
* Severe spell may lead to limpness, convulsions, cerebrovascular accident or even death.

5- Growth retardation (Stunted) → in untreated cases.

6- Cardiac examinations:

- Precordial: - Heart size usually normal (but there may be mild RVH).
  - Systolic thrill over left sternal border.
- Auscultation: - S_2: single (A_2 only is heard)
  - Murmur: systolic (organic PS) on upper and mid left sternal border

Investigations

1- **Chest X-ray:**

- Oligaemic lung fields



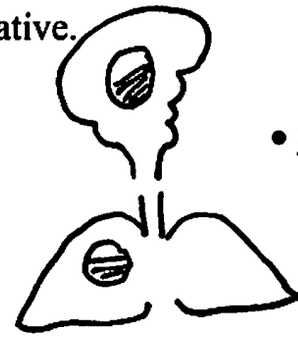
- Coeur en sabot or boot shaped heart:
  - Narrow base.
  - Exaggerated waist
  - Rounded uplifted apex.
  - Heart size is normal or mild RVH

2- **ECG** → RVH

3- **Echo** → diagnostic

4- **Catheter** → pre-operative.

Complications



- Brain abscess:
  Due to septic emboli& lack of pulmonary filtration

- Cerebral thrombosis why?
  1- Long standing hypoxaemia → ↑ erythropiotine → polycythaemia→ sluggish blood flow.
  2- Relative iron deficiency increase polycythaemia
  3- Dehydration → hemoconcentration

- Pulmonary T.B:
  (due to pulmonary oligaemia)
- Infective endocarditis



- Heart failure → rare; may occur in:
  - Pink Fallot
  - Iatrogenic → with big shunt.

Treatment

1- Medical:

1- treatment of hypoxic spells by

- Hold the baby in knee – chest position.
- Morphine 0.1 mg/kg SC to suppress respiratory center
- Sodium bicarbonate slow I.V. to correct acidosis.
- Propranolol 0.1mg/kg slow I.V. to reduce infundibular spasm
- O_2 inhalation? (of limited value)
- After the attack → oral propranolol prophylaxis 0.5-1 mg/kg/6hours.
  → avoid digitalis as it may induce infundibular spasm.

2- Avoid cerebral thrombosis by :

- Treatment of relative iron deficiency anemia.
- Avoid dehydration.
- Partial exchange transfusion **with** plasma or saline for severe symptomatic polycythemia (hematocrit value > 65%) .

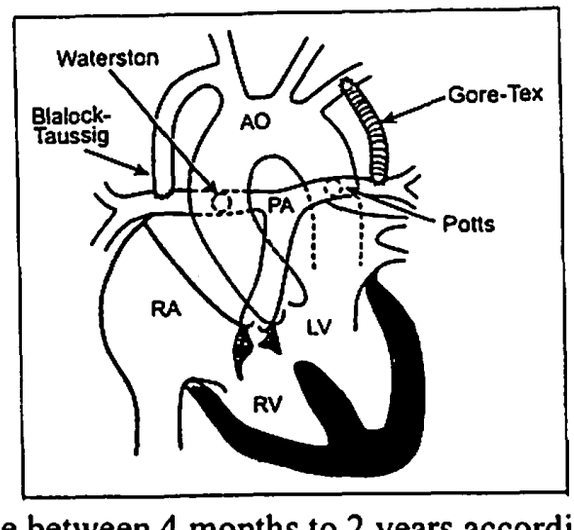
3- In Fallot with severe cyanosis at birth → keep PDA by PGE_1 infusion.

5- Prophylaxis & treatment of infective endocarditis.

2- Surgical

Palliative shunts:

- Idea: anastomosis between aorta & pulmonary artery to allow ↑ pulmonary blood flow.
- Indication: cyanotic infants less than 3 months especially those with poorly controlled hypoxic spells.
- Types:
  1. Modified Blalock – Taussig operation : → anastomosis between subclavian artery & ipsilateral pulmonary artery using Gore – Tex conduit
  2. Waterston operation: anastomosis between ascending aorta & right pulmonary artery (obsolete).
  3. Potts operation: anastomosis between descending aorta & left pulmonary artery (obsolete).



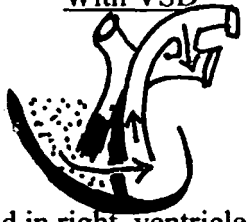
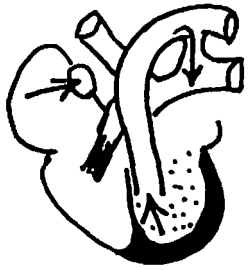
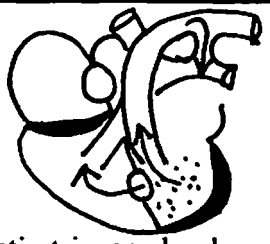
Total correction: can be done between 4 months to 2 years according to severity.

N.B.: Types of Fallot tetralogy:
1- Classic type as before
2- Fallot with pulmonary atresia. (cyanosis at birth & no murmer)
3- Fallot with absent pulmonary valve (mild pulmonary stenosis & pulmonary regurge).

Differential diagnosis of Fallot tetrology:

Other Causes of Cyanotic Congenital Heart Diseases with decreased pulmonary blood flow:

1- Double outlet right ventricle (DORV) with pulmonary stenosis:
- Both pulmonary artery & aorta arise from right ventricle
- Mixing of blood should occur via VSD & PDA.
- Baby is born cyanotic & cyanosis increase with ductus arteriosus closure.

<table>
<tr><th colspan="2">2- Pulmonary atresia</th><th>3- Tricusped atresia</th><th>4- Ebstein anomaly</th></tr>
<tr>
<td>With VSD

• Blood in right. ventricle pass to left ventricle via VSD so, Left ventricle contain mixed Blood → cyanosis.
• Pulmonary blood flow depends on PDA or collaterals between Aorta & pulmonary artery.</td>
<td>Without VSD

• Blood in right atrium pass via patent foramen ovale (PFO) → left atrium → left ventricle → cyanosis.
• PFO & PDA are essential for life.</td>
<td>
• Atretic tricusped valve → Blood in right atrium pass via PFO → left atrium → left ventricle → cyanosis.
• Pulmonary blood flow is dependent on VSD or PDA.
• Right ventricle is hypoplastic.</td>
<td>Composed of:
• huge right atrium
• downward displacement of tricusped valve leaflets.
• tricusped regurge is common.
• small right ventricle

→ Blood may pass via PFO from right atrium to left atrium→ left ventricle → cyanosis.</td>
</tr>
<tr>
<td colspan="2"><u>C/P</u>: - Cyanosis at birth →↑ in intensity with PDA closure.
- S_2→ single (A_2 only is heard).
- No murmers. (may be machinery of PDA or collaterals).</td>
<td>- Cyanosis at birth.
- S_2 → single (A_2 only is heard).
- Murmer of VSD (± PDA).</td>
<td>- May be asymptomatic.
- Splitting of S_1 & S_2.
- may be → mild cyanosis
→ atrial arrythmias
→ pansystolic murmer (tricusped regurge)
- may be heart failure.</td>
</tr>
<tr>
<td colspan="3"><u>Investigations:</u>
- Echocardiography can differentiate it from Fallot tetralogy.</td>
<td>- May be huge cardiomegaly in Chest X-ray.
- Same + ECG → RBBB & RAD</td>
</tr>
<tr>
<td colspan="3"><u>Treatment:</u>
- PGE_1 infusion
- Palliative shunts.
- Total correction.</td>
<td>- Asymptomatic → follow up.
- Cyanosis at birth → PGE_1
- ttt of heart failure & arrhythmias.
- valve replacement</td>
</tr>
</table>

CCHD with increased pulmonary Blood Flow

Transposition of Great arteries (TGA)

Description:

1- Aorta arise from right ventricle.

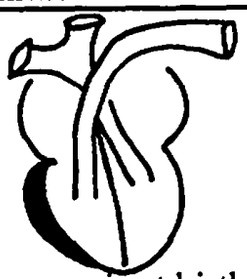
2- Pulmonary artery arise from left ventricle.

3- Mixing of blood. occur via PFO, VSD or PDA

In neonate if ductus arteriosus close → severe cyanosis.

Incidence: Common in infant of diabetic mother, male to female ratio = 3: 1.

Types

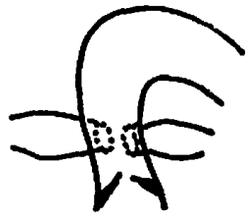
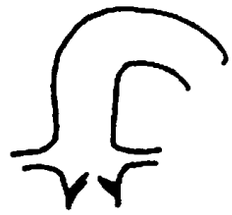
Isolated (intact ventricular septum)	TGA With VSD	TGA With VSD & PS
		
* Severe cyanosis at birth → marked with PDA closure → acidosis & hypoglycemia (medical emergency) * No murmur * Single S_2.	- Mild cyanosis - Manifestations of increased pulmonary blood flow. - VSD murmer.	- minimal cyanosis - mimic Fallot - murmur of pulmonary stenosis
Investigations: ♂ CXR • lung fields ⇒ Normal • Heart → RVH *(egg on side)*	Plethoric	Oligaemic
♂ ECG: RVH.	RVH	BVH
♂ Echo.: Diagnostic ♂ Cardiac catheter: Preoperative	Diagnostic Preoperative	Diagnostic Preoperative
Treatment: 1- Keep PDA → PGE_1 infusion & avoid O_2. 2- Palliative operation: Rashkind balloon atrial septostomy → create large ASD → free intracardiac mixing. 3- Total correction: - Arterial switch operation or - Atrial switch operation.	- Treatment of heart failure. - Arterial switch operation	- Medical treatment as in Fallot. - Palliative shunt. - Total correction

N.B: Avoid cerebral thrombosis & precaution against infective endocarditis (see page 205)

Truncus arteriosus (TA)

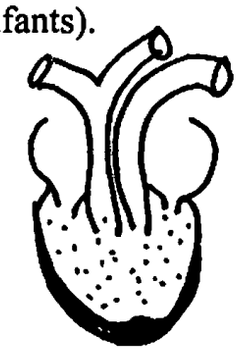
Description: - One arterial trunk leave the heart → give rise to both Aorta & pulmonary artery
- One semilunar valve (Truncal valve).
- Large VSD below the trunk.

Types

Type I	Type II	Type III	Type IV "pseudo truncus"
			
Single pulmonary artery from left. Side	Two pulmonary arteries from the posterior wall	Two pulmonary arteries from the lateral wall	Arteries arising from the descending aorta → supply the lungs.

Clinical picture:

- Cyanosis → variable onset (usually minimal esp. in neonate & infants).
- Features of increased pulmonary blood flow
- S_2 → single.
- VSD murmer.
- Chest X-ray → Right sided aortic arch in 50% of cases.



Treatment:

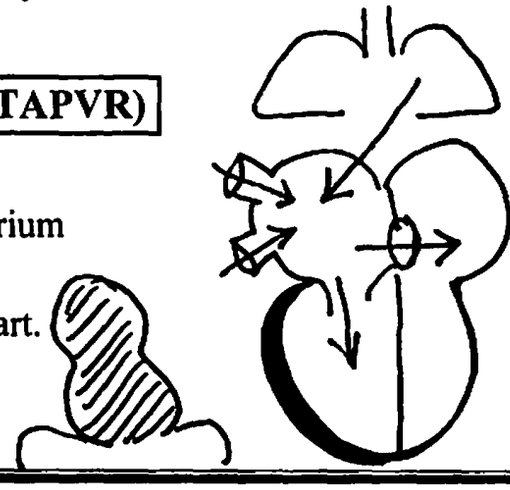
1- Treatment of heart failure.
2- Surgical correction.

Single ventricle

- *Absent interventricular septum* → both Aorta & pulmonary artery arise from common ventricle → free mixing of blood → cyanosis.
- Degree of cyanosis depends on whether pulmonary valve is stenotic or not which determine pulmonary blood flow.

Total anomalous pulmonary venous return (TAPVR)

- Pulmonary veins drain into right atrium
- ASD allow blood in right atium to pass to left atrium → blood mixing → cyanosis.
- Chest X-ray → Snowman **or** figure 8 shaped heart.



Rheumatic Fever

Definition

Immunologic disease affecting connective tissue of the heart, joints & skin.

Risk factors

1- Onset between 5-15 year (rare before 5 years).

2- Low socioeconomic status..

3- Genetic predisposition (Associated with certain HLA).

4- Group A β-hemolytic strept pharyngitis (with M serotypes 1, 3, 5, 6,18, 24)

Pathogenesis

✧ Latent period of 1-3 weeks usually lapse between pharyngitis & acute rheumatic fever

✧ Theories of etiology:

1- Cross reactivity theory :Following strept infection antibodies formed against strept cross react against host connective tissue antigens.

2- Antigenic similarity theory: group A strept antigens is similar to cardiac valve antigens.

✧ Inflammation is either:

- Exudative (as in joints) → resolve without residual damage
- Proliferative → with Aschoff nodules (as in the heart) → heal by fibrosis.

Clinical picture

A. Major criteria of Rheumatic fever

I- Arthritis (75%)

- Usually affect big joints (e.g. knee, ankles, wrist, elbow).
- Polyarticular, either simultaneous or successive.
- Migratory (fleeting) form one joint to another.
- Affected joint is: → red - hot – swollen
  → with absolute limitation of movement (severely tender)
- Dramatic response to salcylates.
- Resolve without residuals, even without treatment, over days to few weeks.

II- Carditis (50%)

Endocarditis:

•Valvulitis affecting commonly mitral valve with or without aortic valve:

1- Mitral valve:

- Leaflets oedema → transient mitral stenosis (Carey Combs murmer)
- Leaflets destruction → mitral regurge.

2- Aortic valve → aortic regurge.

Myocarditis:

1- Tachycardia out of proportion to age & fever(rarely bradycardia due to heart block)

2- Heart failure (with cardiomegaly , gallop rhythm, &muffled heart sounds) indicates severe carditis

Pericarditis:

1- Dry pericarditis:
- Stitching chest pain.
- Pericardial rub (on the bare area , unrelated to respiration).

2- Pericardial effusion:
- Uncommon.
- Dull aching pain.
- Dullness outside the apex.
- Distant heart sounds.
- Low voltage ECG.

N.B: Carditis may be silent **or** late onset (appear after 6 week – 6 months of onset)

III- Rheumatic chorea "Sydnham chorea" (10%)

- **Incidence** → more in girls 8-12 years (school age).
  → occur weeks **or** months after strept pharyngitis so, other criteria are usually lacking.
- **A/E:** Dsfunction of the basal ganglia due to antineuronal antibodies.
- **Manifestations:**
  1- Emotional lability and personality changes.
  2- Involuntary movements:
  - Spontaneous purposeless movements of limbs and facial grimace.
  - increase with emotional stress and decrease by sleep.
  - Last for months.
  3- Hypotonia.
- **Tests for chorea:**
  - Milk maid's grip: irregular contraction & relaxations while sequeezing examiner fingers
  - Extension of arm → spooning & pronation of hands. (*choreic hand*).
  - Wormian movements of tongue upon protrusion.
  - Evaluate hand writing.

IV- Erythema marginatum (< 5%)

- Site → on the trunk & proximal parts of the limbs.
- Criteria → large erythematous macules.
  → with pale centeres & serpiginous borders.
  → evanescent.
  → not pruritic

V- Subcutaneous nodules (< 1%)

- Site → over the extensor surfaces of tendons near bony prominences.
- Criteria → size about 1 cm.
  → firm, mobile, painless.
  → usually associated with severe carditis.

B. Minor criteria of Rheumatic fever

i. Clinical

1. Fever → usually between 38.4 – 40 °C
2. Arthralgia (can't be used as minor manifestation in presence of arthritis)

ii. Laboratory

3. Prolonged P-R interval (can't be used as minor manifestation in presence of carditis)
4. Elevated acute phase reactants (↑ ESR, ↑ C-reactive protein, leucocytosis)

Modified Jones criteria for rheumatic fever diagnosis (1993)

A. Two major criteria **or One** major & **Two** minor criteria **Plus**

B. Evidence of recent antecedent streptococcal infection ;

- Positive throat swab or
- ↑ ASO titer or
- ↑ Anti Deoxyribonuclase (DNase) β titre.

Exceptions to Jones criteria:

1- Rheumatic chorea

2- Late onset carditis

Each can diagnose acute rheumatic fever alone in absence of other criteria and evidence of recent strept infection but after active exclusion of other causes for both.

3- Occasionally, patients with rheumatic fever recurrences(rheumatic activity) may not fulfill Jones criteria so in patients with documented chronic rheumatic heart disease diagnosis of rheumatic activity can be made in absence of major criteria **i.e** minor criteria plus evidence of recent strept infection is enough to make the diagnosis.

Complications of rheumatic fever

1. Congestive heart failure:

1. Acute : due to myocarditis
2. Chronic : with episodes of acute failure precipitated by:
   - Rheumatic activity
   - Infective endocarditis
   - Chest infections

2. Cardiomegaly:

✧ Due to: carditis or heart failure or multivalvular lesions

✧ Detected by:

- Clinically : Precordial bulge, precordial and epigastric pulsations.
- Chest x ray.

3. Chronic valve lesions :

✧ Carditis ,especially in recurrences, can cause permanent organic valve lesions e.g. MS, MR , AS , AR or combined valve lesions.

✧ Organic valve lesions can be complicated with pulmonary hypertension, arrhythmia, infective endocarditis, thromboembolism & shortened life span.

4. Rheumatic activity (Recurrences):

✧ Suggested by:

- Fever with arthritis or arthralgia.
- Change in character of already existing murmur
- Appearance of new murmurs.
- Carditis with heart failure.
- Pericardial involvement.

✧ Clinical value: it can diagnose rheumatic fever attack in presence of evidence of recent antecedent streptococcal infection

5. Pulmonary hypertension:

✧ Due to long standing mitral valve lesions

✧ Symptoms: dyspnea, fatigue, may be syncope

✧ Signs:

- Pulmonary pulsations(diastolic shock)
- Dull pulmonary area
- Accentuated P2
- Soft ejection systolic murmur over pulmonary area.

✧ Chest x ray: Dense hilar shadows& RVH.

Differential diagnosis

1. Other causes of arthritis
   - Rheumatoid arthritis:
     - Chronic arthritis ;last at least for 6 weeks.
     - Can involve small peripheral joints.
     - Non migratory
     - No evidence of recent strept. infection.
     - No response to salcylates within 48 hours.
     - Deformities are common.
   - Infections : viral, bacterial, tuberculous
   - Hematologic e.g. Acute leukemia , hemophelia.
   - Immunologic e.g. Systemic lupus erythematosis& Henoch Schonlein purpura
2. Other causes of carditis e.g.:
   - Vial carditis.
   - Infective endocarditis.
   - Drug induced.
3. Other causes of chorea e.g.:
   - Wilson disease.
   - Huntington chorea
   - Cerebral palsy.

Prognosis

1- Arthritis sub side within days to weeks even without treatment.

2- Chorea subside within few months without residuals.

Treatment of acute Rheumatic fever:

1- Prophylactic:

1ry prevention:

- Hygienic housing.
- Treat streptococcal pharyngitis: penicillin **or** erythromycin for 10 days.

2ry prevention:

- Prevent recurrence of Rheumatic fever by:
  - * Long acting penicillin (Benzathine penicillin)
    - Dose : 1.2 million unit single injection, I.M every **3 - 4** weeks.
    - For at least 5 years after last episode for cases without carditis
    - For at least 10 years after last episode for cases with carditis without residuals
    - For life or till age of 40 for cases with carditis with residuals
  - * Alternatives: daily oral penicillin V or erythromycin (250 mg twice daily)

2- Treatment of acute attack:

1. Bed rest: needed mainly for cases with carditis & heart failure till heart failure is controlled & ESR is normalized
2. Diet: light, low salt in cases with heart failure.
3. Eradicate strept. infection by: A10 days course of oral penicillin V or single injection of Benthazine penicillin or Erythromycin (for penicillin sensitive).
4. Anti inflammatory drugs.

a- **Salcylates**

- ♂ Indications: - Rheumatic arthritis
  - Mild rheumatic carditis without heart failure.
  - During steroid withdrawal
- ♂ Dose: **100** mg/kg/day (max = 6 gram /day); in four devided doses.
  - For 3-5 days **then 75** mg/kg/d for 4 weeks,then
  - Gradual withdrawal monitored by decline in ESR & CRP
- ♂ Side effect: - Toxicity (early symptoms are tinnitus, hyperventilation)
  - Others :Gastritis , Reye's syndrome

b- **Corticosteroids (Prednisone)**

- * Indications: - Moderate to severe carditis
  - Heart failure.
- * Dose: 2 mg/kg/d (max = 60 mg/day); in divided doses for 2-3 weeks , then
  - Taper the dose by reducing 5 mg (one tablet) every 2-3 days.
  - With tapering , aspirin is started with dose 75 mg/kg/d for 6 weeks.

5- Treatment of rheumatic chorea:

- * Avoid emotional stress.
- * Control abnormal movements:
  - Phenobarbitone 15-30 mg / 8 hours oral.
  - Alternative: Haloperidole (Safinase tablet) 0.01-0.03 mg/kg.
- * Long acting penicillin prophylaxis.

6- Treatment of: - heart failure (diuretics-vasodilators–Digoxin used cautiously).
- Infective endocarditis.

Infective Endocarditis

Definition: Infection of the valvular & mural endocardium.

Pathogenesis: Two factors are essential:

i- Presence of structural abnormality in the heart with significant pressure gradient.

ii- Bacteraemia; even transient.

Commonest causative organisms:

1- Streptococcus viridans (50%): Follows dental surgery & dental caries.

2- Staphylococcus aureus (30%): Mainly postoperative.

3- Enterococci: Follow GIT & genitourinary surgery or instrumentation.

4- Pseudomonas & serratia in I.V. drug users.

5- Fungal in immunodeficient & post open heart surgery.

6- HACEK group: Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella.

Pathology: Implantation of the organism in the diseased endocardium → Local inflammation & formation of friable vegetations composed of platelets, fibrin, inflammatory cells, organisms

Risk factors:

- Congenital heart diseases except secondum ASD
- Previous bacterial endocarditis
- Prosthetic valves
- Pulmonary - systemic shunts or conduit
- Acquired valve dysfunction (rheumatic heart diseases, collagen vascular diseases)
- Hypertrophic cardiomyopathy
- Mitral valve prolapse with mitral regurge

Clinical picture:

i- General manifestations:

1- Fever (pyrexia).

2- Poor appetite → weight loss & malaise.

3- Palpable spleen (tender splenomegaly).

4- Pallor.

5- Purpura.

6- Pale clubbing.

7- Rare manifestations due to vasculitis (due to immune complexes):

- Osler nodules → firm, tender intradermal nodules in pads of fingers & toes.
- Janeway lesions → painless erythema in palms & soles
- Splinter hemorrhage → linear hemorrhagic streaks beneath nails.

ii- Cardiac manifestations:

- Appearance of new murmers
- Change in the character of previous murmers
- Sea gull murmer (musical) → due to rupture of valve leaflets.
- Heart failure.

III- Embolic manifestations:

1- Neurolgic: - Embolic stroke (seizures, hemiparesis).
- Cerebral abscess.
- Mycotic aneurysm → intracranial hemarrhage.

2- Retinal hemorrhages (Roth spots); oval with pale centers

3- Pulmonary embolism

4- Renal infarction → hematuria & renal failure.

5- Peripheral embolisation

Complications

1- Cardiac: - Toxic myocarditis.
- Myocardial abscess:

2- Immune complex lesions: - Acute glomerulonephritis.
- Arthritis.

3- Embolic manifestations.

4- Remote infections e.g.: - Meningitis
- Osteomyelitis.

Investigations

1- Blood culture: 3-5 blood samples before start of antibiotics(positive in 90 %)

2- Echocardiography:

Value: - Detect vegetations (but minute vegetations less than 3 mm^3 may be missed).
- May detect underlying cardiac lesions
- May predict embolization (fungating vegetation > 1 cm^3).

3- Complete blood count: Anemia & leucocytosis with shift to the left

4- ESR is increased unless there is polycythemia

5- Microscopic hematuria is found in 30% of patients

Treatment

I- Prophylaxis:

1- Oral and dental care

2- Patients with risk factors who will be exposed to surgical procedures must receive prophylactic antibiotics **as follow:**

Procedure	1 hr before surgery	6 hr after surgery
Oral & dental	Oral amoxycillin (50 mg/kg)	Oral amoxycillin (25 mg/kg)
GIT & Genitourinary	Parentral ampicillin (50 mg/kg) & gentamicin (2 mg/kg).	⇓ same

N.B: Erythromycin, Clindamycin & Vancomycin are alternatives for cases already receiving long acting penicillin prophylaxis **or** penicillin sensitives.

II- Curative:

Medical:

1- Hospitalization

2- Bed rest

3- Treat heart failure.

4- I.V. antibiotic combinations is started immediately while waiting for results of blood culture:

- Penicillin G 200.000 IU/kg/day → divided / 4 hours
- Gentamicin 7 mg / kg / day → divided / 8 hours.
- Cloxacillin 200 mg / kg / day **or** vancomycin 40 mg / kg / day
- Amphotricin B and 5- florocytosine for fungal endocarditis

- Duration of antibiotics: 4- 6 weeks.

Surgical:

- Indications: - Severe valve lesions with uncontrolled heart failure.
  - Fungal endocarditis.
  - Failed medical treatment
- Goal: - Remove vegetation.
  - May be valve replacement.

Prognosis: Very high mortality especially with staphylococcal & fungal endocarditis.

Heart Failure

Definition: Clinical syndrome in which the heart is unable to pump enough blood to meet body needs.

Causes

- Congenital heart diseases are the commonest causes in infancy (uncommon in ASD & Fallot tetralogy)	- Rheumatic valvular heart diseases (in school age)
- Myocarditis: - Viral (Coxachie A, B & Echo viruses) - Toxic (drugs, diphteria). - Protozoal (e.g. Chagas disease). - Dilated cardiomyopathy. - Infective endocarditis.	- Acute hypertension - Severe anemia
- Acute cor pulmonale - Broncho pulmonary dysplasia.	Arrythmia: - Supraventricular tachycardia - Complete heart block.
Nutritional: - Beri Beri - Kwashiorker.	- Carnitine deficiency - Keshan disease (Selenium deficiency)

Clinical features

i- Symptoms:

Infants: - Poor feeding: Tachypnea and cold sweating during feeding.
- Poor weight gain.

Older child: - Dyspnea on exertion.
- Effort intolerance.
- Ankle oedema.

ii- Signs:

a- Compensatory response to heart failure.

1- Tachycardia, gallop rhythm & weak pulse.
2- Cardiomegaly is almost always present.
3- Cold, sweaty skin (due to ↑sympathetic derive)

b- Pulmonary congestion

1- Tachypnea
2- Exertional dyspnea
- Infant → poor feeding.
- Child → dyspnea & orthopnea

3- Chest wheezes & fine crepitations.

c- Systemic congestion:

1- Enlarged tender liver (may be absent in early left sided failure).
2- Congested neck veins; hard to detect in infants due to short neck.
3- Oedema → generalized start in ankles (sacral in bed ridden)
4- Oedema in infants usually involve eye lids and the sacrum

Investigations (heart failure is clinical diagnosis)

1- Chest X-ray: - Cardiomegaly

2- Echo: - Confirm left ventricle dysfunction (decreased ejection fraction & increased ejection time).
- Confirm chamber enlargement.
- May detect cause of failure.

3- ECG: - Detect arrythmias.

Treatment

1- Hospitalization &

- Bed rest in semisitting position
- O_2 inhalation.
- Low salt diet (to avoid further salt & water retention).
- If parenteral fluids is indicated ; give restricted maintenance fluids

2- Diuretics (↓ cardiac pre-load)

1- Frosemide → I.V. = 1 mg / kg / dose.
→ oral = 2 mg / kg.
- Side effect: Hypokalemia & Alkalosis → may increase digitalis toxicity.

2- Spironolactone (k-sparing diuretic)
→ oral = 2 mg / kg.

3- Thiazide → oral = 20-40 mg / kg.

3- Digitalis:

Digoxin is the commonest.

- **Functions of digitalis :** -↑ myocardial contractility (inotropic drug)
- **Digitalization:**

1- Get baseline ECG & electrolytes (especially potassium)

2- Loading dose is given within 24 hours:
→ ½ the total digitalizing dose (TDD) immediate.
→ ¼ TDD after 8 hours → ¼ TDD after another 8 hours.

3- Maintenance dose (= ¼ TDD) is given in two divided doses after 12 hours.

	Oral TDD (mg/kg)	I.V. TDD (mg/kg)
Prematures	0.02	= 75% of oral T.DD.
Newborn	0.03	
Infants < 2 y	0.05	
Child > 2 y	0.03	

- **Absolute contraindications to digitalis :**
  - Hypertrophic cardiomyopathy.
  - Heart block.
  - Fallot's tetralogy.

- **Digitalis toxicity**

1- Causes:
- Accidental over dose.
- Renal impairment.
- Increased myocardial sensitivity e.g.: hypokalemia & rheumatic carditis.
- Drug interactions.

2- Signs:
- Anorexia, vomiting
- Drowsiness & visual disturbance in older child.
- Bradycardia
- Worsening of heart failure.
- Arrythmias (supraventricular arrythmia & heart block).
- Serum digitalis level > 2 ng/ml.

3- Treatment:
- Continuous ECG monitoring.
- Stop digitalis
- Correct hypokalemia
- Correct arrythmias by: a- Atropine 0.01 mg/kg/6 hours for heart block.
  b- lidocaine for ventricular arrythmia
- Increase excretion of digoxin by Digoxin immune Fab (Digibind), slow I.V.

4- VasoDilators:

Role: - Act by ↓ cardiac after load → increase stroke volume.
- Useful in:
  - hypertensive heart failure.
  - Dilated cardiomyopathy.
  - Large left to right shunt.
  - Severe MR and AR.

Types: - ACE inhibitors e.g. Captopril, Enalapril
- Hydralazine.
- Nitroglycerine I.V. infusion (used in acute pulmonary oedema).

5- Sedation → morphine subcutaneous in severe excitation.

6- Severe heart failure with acute pulmonary oedema → Aminophylline i.v. infusion is added.

7- Search for & treat the cause e.g.:
- Rheumatic carditis → steroids.
- Renal failure → dialysis.
- Surgery e.g. for congenital heart diseases.

Systemic Hypertension

Definition: Systolic and or diastolic pressure levels greater than 95th percentile for age & gender on at least three occasions.

* Normal blood pressure at birth 70/50 (↑ 10 systolic & 5 diastolic every 3 years).
* Incidence → 1-3 % of pediatric age group.
* Degrees of hypertension: (according to increase above normal range for age)
  1- Mild hypertension: systole increase by **10** mmHg
  or diastole increase by **5** mmHg
  2- Moderate hypertension: systole increase by **20** mmHg
  or diastole increase by **10** mmHg
  3- Severe hypertension: systole increase by ≥ **40** mmHg
  or diastole increase by ≥ **20** mmHg

Causes

1- Essential (primary) hypertension → **rare** in children; common in adults.
* Associations → obesity, hereditary factors, increased sensitivity to salt intake.

2- Secondary → **more common:**

A/E	Acute	Chronic
Renal	- Acute glomerulonephritis. - Acute renal failure. - Hemolytic uremic syndrome.	- Renal tumors, hypoplasia, dysplasia. - Chronic pyelonephritis - Hydronephrosis/reflux nephropathy. - Renovascular: • Renal artery stenosis, thrombosis, Polyarteritis. • Renal vein thrombosis.
Endocrine		- Cushing syndrome - Hyperaldosteronism - Congenital adrenal hyperplasia. - hyperparathyroidism (hypercalcemia)
Tumors		- Neuroblastoma - Wilm's tumor. - Pheochromocytoma
Cardiac		- Coarctation of aorta
Neurologic	- Acute ↑ intra cranial tension. - Guillian Barre syndrome - Poliomyelitis.	
Drugs	- Sympathomimitics.	- Steroids - NSAIDs

Possible mechanisms in 2ry hypertension:

1- Stimulation of Renin-Angiotensin-Aldosterone system e.g. renal hypertension.
2- Salt & water retention e.g. Cushing & hyperaldosteronism.
3- Stimulation of vasomotor center e.g. neurologic hypertension.
4- Vasoconstriction due to: - ↑ release of catecholamines e.g. pheochromocytoma
- Sympathomimitc drugs.

Presentation

1- Usually asymptomatic.
2- May be → headache, irritability, blurr of vision (in severe cases)
3- Complications::
   1- Hypertensive heart failure.
   2- Acute pulmonary oedema.
   3- Hypertensive encephalopathy manifested by severe bursting headache, vomiting, irritability, convulsions and coma.
   - Fundus examination: Vasospasm,papilloedema & retinal hemorrhage.

Investigations: Mainly for 2^{ry} causes.

1- **Renal:** - Urine analysis, urine culture, renal function tests.
- Abdominal ultrasound.
- Renal Doppler.
- Renal scanning.
- Renin level; total & selective (renal vein level)
- Renal angiography.

2- **Endocrinal:**- Electrolytes (potassium & sodium).
- Night time blood or salivary cortisole level →↑ in Cushing.
- Aldosterone level.

3- **Cardiac** - Chest X-ray & Echocardiography.

4- **Tumors:** - 24 hr urine vallynile mandilic acid (VMA); (metabolite of catecholamines) →↑ in pheochromocytoma & Neuroblastoma.
- Abdominal ultrasound & CT.

Treatment

A- Chronic hypertension:

I. Essential hypertension

1. Non pharmacologic:
- Weight reduction may result in a 5-10 mmHg reduction in systolic pressure
- Low salt , potassium rich diet
- Dynamic aerobic exercises and physical fitness
- Avoid smoking and oral contraceptives

2. Drug therapy:

Indications:
- Family history of early complications of hypertension
- Target organ damage(ocular, cardiac, renal, neurologic)
- Symptomatic hypertension

Stepped care approach:
- Step 1: A small dose of single antihypertensive drug either diuretic or an adrenergic inhibitor
- Step 2: If the first drug ineffective a second drug is added to or substitute the initial drug starting with small dose then proceed to a full dose.
- Step 3: If blood pressure is still high a third drug ; usually a vsodilator, is added

Drugs	Daily dose(mg/kg)
Diuretics:	
- Hydrochlorothiazide	1-2
- Chlorothiazide	0.5-2
- Spironolactone	1-2
Adrenergic inhibitor:	
- Propranolol	1-3
- Atenolol	1-2
- Prazocin	0.1 per dose /6-12 hours
Vasodilator	
- Hydralazine	1-5
- ACE inhibitors:	
* Captopril	0.05-0.5 (if < 6 months)
	0.5-2 (if > 6 months)
* Enalapril	0.2- 1 (2.5- 5 in adolescents)
- Calcium channel blockers:	
* Nifedipine	0.25- 2
* Amelodipine	2.5-5 (above 6 years)

II. Secondary hypertension :

1. Treat the cause whenever possible
2. Drug therapy as in essential hypertension

B- Acute hypertension:

1- Ensure adequate airway , breathing and circulation(ABC)

2- Slow reduction of blood pressure is mandatory.

3- Drugs useful in acute hypertension:

- Esmolol 100-200 μ g/kg/minute I.V. infusion
- Hydralazine: I.V.(used with a diuretic & β-blocker).
- Labetalol (α and β blocker): I.V. bolus then I.V. infusion.
- Nicardipine 1-3 μ g/kg/minute I.V. infusion.
- Na nitroprusside: 0.5-10 μ g/kg/minute I.V. infusion.
- Duiretics (e.g. frosemide 0.5-2 mg/kg).
- Diazoxide: I.V. push.
- Captopril: Sublingual(nifidipine sublingual is no more used)

4-Treat the cause (in 2^{ry} hypertension).

5- After adequate control of acute hypertension shift to oral antihypertensives.

Shock

Definition

Acute circulatory failure characterized by hypoperfusion of tissues with subsequent impaired oxygen delivery interfering with metabolic demands of vital organs and tissues

Mechanisms: hypoperfusion can result from;

1. Decreased blood volume(hypovolemic shock)
2. Decreased myocardial contractions(cardiogenic shock)
3. Obstruction to blood flow(obstructive shock)
4. Venular and arteriolar dilatation(distributive shock)
5. Combination of factors(septic shock)

Causes

S: Septic shock due to severe sepsis.

H: Hypovolemic shock due to hemorrhage , burn , dehydration, polyuria.

O: Obstructive shock due to critical coarctation, pulmonary or aortic stenosis and tension pneumothorax or massive pulmonary embolism.

C: Cardiogenic: acute heart failure, acute cardiac tamponade, dysrrhythmias,post cardiac surgery

K: Kinetic or distributive shock due to shift of intravascular fluid to extracellualr space: Anaphylactic ,neurogenic, septic

Stages of shock

1. **Early shock**(compensated) peripheral hypoperfusion with:
   - Tachycardia, weak thready pulse.
   - Cold extremities
   - Slow capillary refill(>5 seconds)
   - Skin mottling and peripheral cyanosis.
   - In septic shock there is warm extremities initially(warm shock)
2. **Established shock** (Decompensated) :
   - Progressive shock with arterial hypotension
   - Oliguria/anuria.
3. **Advanced shock**: established shock progressing to **Multiple Organ System Failure**:
   - Brain: disturbed consciousness
   - Heart : serious dysrrhythmia
   - Lungs: adult respiratory distress syndrome
   - Kidneys: acute renal failure
   - GIT: stress ulcers
   - Blood: DIC

Management

A- General measures

1. Positioning: supine elevated legs to help redistributing blood to more vital areas.
2. Ensure ABC
   - ⊕ Airway: clear ,secure airways with or without intubation
   - ⊕ Breathing O2 with or without assisted ventilation
   - ⊕ Circulation : - Obtain vascular access if failed, intraeosseous route is performed
     - Fluids: give isotonic fluid boluses
3. Treat the cause e.g. stop bleeding, antibiotics, arrythmias,.....
4. Medications: inotropics e.g. dopamine, dobutamine, isoproternol or epinephrine.

B- Specific treatment

1- Hypoveolemic shock:

- Start with saline or Ringer's lactate 20 ml/kg.
- Can be repeated
- If > 60 ml is required consider using colloid solution as albumin or blood.

2- Septic shock:

- Aggressive volume replacement
- Intropic medications
- Antibiotics

3- Cardiogenic shock:

- Intropic medications
- Minimal volume support.

4- Specific treatment :for anaphylaxis , neurogenic shock, tension pneumothorax & pericardial tamponade

C- Supportive treatment:- For multiple organ system failure

Hematology

Introduction

- Intrauterine hematopoesis passes into 3 stages:

1st 8 weeks	8th week → 6th month	6th month → onwards
↓	↓	↓
in yolk sac	in the liver	in bone marrow

- Exposure to **hematologic stress** (e.g. chronic hemolysis) → ++ bone marrow then ++ extramedullary hematopoiesis in the spleen & the liver.

- **Active Bone marrow contain:**
  - Erythroid cells → give → RBCs.
  - Myeloid cells → give → WBCs.
  - Megakaryocytic cells → give → platelets.

- Normally: Myeloid / Erythroid ratio (M/E) equals 2/1.
  - In Erythroid hyperplasia (e.g. hemolytic anemia.) → M/E ratio < 2/1.
  - In Erythroid hypoplasia → M/E ratio > 10/1.

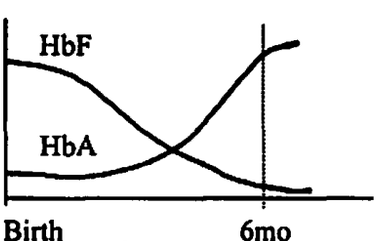
Hemoglobin (Hb) composition

Hb molecule is composed of Heme groups (ferrous iron containing) attached to 4 polypeptide chains which define the type of Hb.

Types

Emberyonic Hb.	Foetal Hb.	Adult Hb.
- Gower 1	Hb F (α_2, γ_2)	- Hb A (α_2, β_2)
- Gower 2	(has high affinity to O_2)	- Hb A_2 (α_2, Δ_2)
- Portland		

	Intrauterine	At Birth	> 6 month
Hb F	Dominant	70 %	< 0.5%
Hb A	--	30 %	97%
Hb A_2	--	Trace	2.5%



* At the 3rd – 6th month ➠ normal switch from γ to β chain production occurs

Blood indices

i- Hemoglobin content:
- in 1st 2 weeks → 14-20 gm/dl (intrauterine hypoxia →↑ erythropiotin).
- in infancy → 10-14 gm/dl (higher in males due to androgen).

ii- RBCs count:
- in newborn → 6 million / mm^3.
- afterwards → 4-6 million / mm^3.

iii- Hematocrite value (Ht. value) = packed red cell volume.
= percent of RBCs volume in 100 ml blood ≈ 40-50%.

iv- Mean corpuscular volume (MCV)

$$= \frac{\text{Ht.value} \times 10}{\text{RBCs count}} = 72 - 79 \text{ femtolitre.}$$

- if < 70 → RBCs are small (Microcytes).
- if > 85 → RBCs are big (Macrocytes)

(Reference: Manual of Pediatric Hematology and Oncology; page 4, 2005)

v- Mean corpuscular hemoglobin (MCH)

$$= \frac{\text{Hb content} \times 10}{\text{RBCs count}} = 30 \text{ pg.}$$

- if < 25 pg → RBCs are hypochromic.

vi- Mean corpuscular hemoglobin concentration (MCHC)

→ concentration of Hb. In an erythrocyte

$$= \frac{\text{Hb content}}{\text{Ht. value}} \times 100 = 33\%$$

N.B: Mentzer index:

- Equals MCV/ RBCs count in millions
- Usually > 13 in iron deficiency anemia
- Usually < 13 in thalassemia due to higher RBCs count

vii- Platelet count = 150.000 – 400.000 / mm^3

viii- Reticulocytic count = 1 %.

Reticulocytosis occur in:

1- Hemolytic anemias.
2- Hemorrhage
3- Response to hematinics e.g. (iron, folic acid, B_{12})
4- Recovery of bone marrow from suppression.

Anemia

Definition: It is reduction of hemoglobin and/or RBCs count below average value for age and sex interfering with O_2 carrying capacity of the blood.

Sequalae of anemia

i- Compensatory mechanisms:

tissue hypoxia due to anemia leads to:

1- ↑ 2, 3 diphosphoglycerate:

↳ ↓ Hemoglobin affinity to O_2 →↑ O_2 delivery to tissues.

2- ↓ peripheral resistance & peripheral vasodilation → hyperdynamic circulation.

3- ↑ Erythropoietin.

4- At Hb < 6g/dl → redistribution of the blood to vital organs → Brain, heart and kidneys.

ii- General features of anemia:

- **Symptoms**
  1- Anorexia → weight Loss.
  2- Easy fatiguability
  3- Headache, tinitus, sweating.
  4- Fainting.
- **Signs**
  1- Pallor
  2- Tachycardia (palpitation)
  3- Hemic murmers. (functional, systolic).
  4- Heart Failure in severe anemia (with hemoglobin < 4 gm/dl).

Causes of anemia

A. Decreased production:

Decreased erythroid cells in bone marrow (Bone marrow failure)	Decreased production despite normal RBCs precursors	Specific factor defeciency (Dyshemopiotic anemia)
* Pure red cell anemia. * Aplastic anemia * Marrow infiltration e.g.: - Leukemia - Myelofibrosis	* Anemia of chronic disease: - Chronic inflammation. - Chronic infection - Chronic renal failure.	* Iron deficiency. * Folic acid & B12 deficiency. * Protein deficiency.

B. Increased destruction (hemolytic Anemia)

A. Intra corpuscular causes

1- Membrane defects
- Hereditary spherocytosis
- Hereditary elliptocytosis.
- Paroxysmal nocturnal hemoglobinuria.

2- Hemoglobinopathy
- α thalassemia
- β thalassemia.
- Sickle cell disease

3- Enzymatic defects
- G6PD deficiency
- pyruvate kinase deficiency.

B. Extra corpuscular causes

Immunologic (Coombs +ve)

Isoimmune hemolytic anemia (passively acquired antibodies)

1- Hemolytic disease of newborn.
2- Incompatible blood transfusion.

Autoimmune hemolytic anemia (actively formed antibodies)

Non immunologic (Coombs –ve)

1- Microangiopathic hemolytic Anemia (MAHA)
- DIC
- Hemolytic uremic synd (HUS).
- Renal vein thrombosis (RVT).
- Intracardiac prosthesis

2- Septicaemia (Staph strept., clostridia)
3- Malaria.
4- Wilson disease.
5- Drugs & heavy metals.
6- Hypersplenism.

C. Hemorrhagic anemia:
- Acute hemorrhage
- chronic hemorrhage.

Bone Marrow Failure

A. Trilineage failure

Criteria

- Failure of the 3 cell lines with pancytopenia
- No organomegaly nor lymphadenopathy.

Causes

a. Congenital
- Fanconi anemia
- Familial aplastic anemia
- Dyskeratosis congenita.

b. Acquired
- Idiopathic (70%)
- Secondary (30%)

B. One cell line failure

1. Red cells (hypoplastic anemia;pure red cell anemia)

a. Congenital
- Diamond Blackfan anemia
- Congenital dyserythropeoitic anemia

b. Acquired
* Idiopathic
* Secondary:
  - Drugs
  - Infections
  - Parvo B19 in chronic hemolytic anemia.
  - Malnutrition

2. White cells

1. Schwashman Diamond syndrome: autosomal recessive disorder with :
   - Exocrine pancreatic dysfunction
   - Bone marrow failure
   - Metaphyseal dysostosis
2. Genetic agranulocytosis(Kostmann disease;severe congenital neutropenia)
3. Reticular dysgenesis

3. Platelets

1. Congenital amegakaryocytic thrombocytopenia
2. TAR syndrome(thrombocytopenia absenr radii syndrome)

Pure Red Cell Anemia

i- Congenital pure red cell anemia
(Diamond Blackfan anemia)

Definition: Familial disease(AR or AD) due to decreased sensitivity of erythroid cells to erythropoietin → hypoplasia of RBCs precursors.

Clinical picture

1- Pallor: usually evident by the 2nd – 6th months.

2- Associated anomalies: - Abnormal thumbs; (triphalangeal thumb).
- Congenital heart diseases.
- Short stature

3- Hepatosplenomegaly, if present, is due to chronic transfusion therapy.

Investigations

1- CBC
- Macrocytic anemia & reticulocytopenia
- Normal platelets and WBCs.
- Increased erythrocyte adenosine deaminase activity (ADA)& hemoglobin F

2- BM
- Decreased erythroid cells.
- Normal myloid and megakaryocytic cells.

Treatment

1- Steroids: Give remission in 80%.

2- Chronic transfusion therapy (Packed RBCs) with iron chelation for steroid resistant cases

3- Bone marrow transplantation for steroid resistant, transfusion dependent cases.

Prognosis: There is risk of developing acute myeloid leukemia.

ii- Acquired pure red cell anemia

1- Auto antibodies against erythroid cells.

2- Parvo B19 infection may cause hypoplasia in children with chronic hemolytic anemia.

3- **Transient erythroblastopenia of childhood;**

Differs from Diamond Blackfan anemia in:

a- Anemia occur between 6month-3years.

b- RBCs volume, hemoglobin F, ADA are normal for age.

c- No anomalies.

d- Due to transient immunologic suppression of RBCs synthesis.

e- Usually need no treatment (recover within 1-2 months).

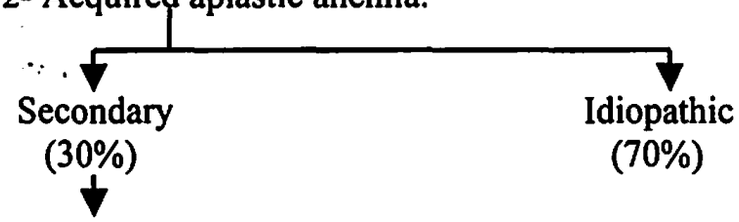
Aplastic Anemia

Definition: Marked decrease **or** absence of blood forming elements in bone marrow with peripheral pancytopenia (decreased RBCs, WBCs and platelets).

Etiology

1- Congenital aplastic anemia: e.g. Fanconi anemia

2- Acquired aplastic anemia.



- Irradiation
- Insecticides
- Infections → Ebstein Barr virus, hepatitis B virus, hepatitis C virus.
- Drugs → Predictable bone marrow depression by chemotherapy.
  → Occasional (idiosyncratic) bone marrow depression by:
  - Antibiotics → chloramphenicol.
  - Anticonvulsants → carbamazepine.
  - Antithyroid → carbimazole.
  - Antimalarial → quinacrine
- Diseases → paroxysmal nocturnal hemoglobinuria &myelodysplastic syndromes.

Pathogenesis: Altered stem cells proteins in the bone marrow by drugs or infection → stimulate T lymphocytes → secretes interferon γ → suppress stem cells → pancytopenia.

Clinical picture

* Anemia → pallor.
* Thrombocytopenia → purpura.
* Lecuopenia → recurrent infections resisting antibiotics.
* No organomegaly (no hepatosplenomegaly nor lymphadenopathy).

*** In Fanconi anemia**

Inheritance: Mainly autosomal recessive ; 11 mutant genes have been cloned.

Clinical features:

- Skin pigmentation (café au lait spots) mainly over neck and trunk
- Short stature with short trunk(growth hormone or hypothyriodism may exist).
- Skeletal :Abnormal thumb (absent or hypoplastic), absent radii
- Microcephaly & mental retardation (in 10 %)
- Malignancy risk is high including acute myeloid leukemia and solid cancers
- Anomalies of eye , ears , cardiac , renal and genital
- Pancytopenia :- Typically starts with thrombocytopenia or leukopenia
  - Present between 4th – 12th years (but may be earlier or later).

Investigations

a- CBC → pancytopenia and reticulocytopenia.(with macrocytic anemia)
b- BM → hypocellular replaced by fibrofatty tissue.
c- Cytogenitics of blood lymphocytes shows increased chromosomal breakages and rearrangements induced by mutagen(e.g. Diepoxy butane) in Fanconi anemia.
d- Elevated α feto protein can be used as rapid screening test in Fanconi anemia.

Differential diagnosis

1- From other causes of pancytopenia:
- Bone marrow failure e.g. leukemia, osteopetrosis.
- Hypersplenism (pancytopenia with compensatory bone marrow hyerplasia).

2- From other causes of purpura e.g. Idiopathic thrombocytopenic purpura.

Differentiation requires complete blood count and bone marrow examination.

Treatment

1. Supportive

i- Control infections via:
- Oral hygiene
- Intravenous antibiotics according to culture & sensitivity tests.
- In cases with granulocytopania (neutrophils < 500 cell /mm^3).give:
  a- Granulocyte colony stimulating factor (G-CSF) Or granulocyte monocyte colony stimulating factor (GM-CSF).
  b- Granulocyte transfusion

ii- Control bleeding : - Avoid IM injections
- Platelet transfusion if platelets count < 20.000 /mm^3.

iii- Control anemia : - Erythropiotin subcutaneous.
- Packed red cells if hemoglobin fall below 7 gm/dl.

2. Specific treatment : Indicated in severe aplastic anemia with:
- Absolute neutrophil count < 500/mm^3 with serious *infections*
- Platelet count < 20.000/mm^3 with significant bleeding
- Corrected reticulocyte count < 1% or absolute count < 40.000/mm^3
- Hypocellular (<25%of normal) bone marrow biopsy

a. For Fanconi anemia

1- Oral prednisone (2 mg/kg/d) with or without Androgen (Oxymethalone)
2- Bone marrow transplantation from HLA matched donor ; after testing donor lymphocytes for chromosomal breakages.

b. For acquired aplastic anemia

1- Bone marrow transplantation from HLA matched donor.
2- If HLA matched donor unavailable use: - Anti thymocyte globulin
- Cyclosporin A

Prognosis

- Long term survival after early bone marrow transplantation is greater than 80 %
- Sustained remssion may be seen in 65-80 % after immunosuppressive therapy

Iron Deficiency Anemia

Incidence: The most common cause of anemia in pediatrics.

Iron metabolism

- Most of dietary iron present in ferric state.
- Iron changes to ferrous by combined action of HCL & vitamin C.
- Only **10%** of dietary iron is absorbed from the jejnum (So daily need = 10 mg/day)
- Absorbed iron is bound to serum **transferrin.**
  ↳ and stored as **ferrittin** to be used in:
  a. In bone marrow → RBCs
  b. In cell enzymes e.g. Catalase, peroxidase, mono amine oxidase (MAO).

Causes

i- Decrease intake: Common in ages 6-24 months due to:
- Prolonged breast feeding with out supplementation (delayed weaning).
- Cow milk feeders (↓ iron, ↓ lactoferrin, heat labile protein may induce occult blood loss).

ii- Decrease iron absorption:
- Malabsorption syndrome.
- Excess tea, phytate & antiacids.

iii- Decrease iron stores
- Iron deficient pregnant
- Perinatal Blood loss.
- Preterm.

iv- Increase requirements due to:
- Rapid rate of growth in twins, preterm, infants, adolescence.
- Congenital cyanotic heart diseases(due to polycythemia)

v- Increase loss: Common in ages > 2 years.
1- Overt blood loss e.g hematuria, epistaxis,heamodialysis,.....
2- Occult blood loss due to - Ankylostoma
- Peptic ulcer, polyps, gastro esophageal reflux
- Cow milk protein allergy
- Meckle's diverticulum.

Clinical picture

1- Mild anemia is asymptomatic.
2- Manifestations of anemia (anorexia, pallor,...) vary with severity of iron deficiency.
3- Irritability, decreased alertness, learning & concentration span (due to ↓ iron containing cellular enzymes).
4- Other rare manifestations:
* Atrophic glossitis (pale & smooth).
* Pica (Geophagia) desire to ingest unusual substances e.g. dirts
* Nails ⇒ longitudinal ridges, flattening and spooning (koilonychia)
* Palpable spleen in about 15% of cases.

Investigations

1- For diagnosis:

1 - CBC : Anemia → Hypochromic, Microcytic

↓ ↓ ↓

↓ Hb% MCH < 27 Pg MCV < 70 fl

↓ RBCs count MCHC < 30% Increased RDW

2- Iron indices:

Index	Iron deficiency	Normal (age dependent)
* Serum Iron.	< 30 µg / dl	60 - 120 µg / dl
* Transferrin saturation.	< 15%	33%
* Soluble serum transferrin receptors.	increased	
* Total iron binding capacity (TIBC).	> 350 µg / dl	250-350 µg / dl
* Serum ferrittin. (index of iron stores)	< 10 ng / ml	25-140 ng/ml

2- For the cause: - Stool analysis for parasites & occult blood tests (Gauiac test)

- GIT barium study, and endoscopy .

Differential diagnosis: Other causes of hypochromic microcytic anemia

I- Defective globin synthesis:

1- β thalassemia trait

2- β thalassemia major: Easily excluded by full blown picture of chronic hemolysis.

3- α thalassemia trait

4- Hemoglobin H disease

(*For full details , see page 243*)

II- Defective Heme synthesis:

1-Anemia of chronic disease:

in:

- Chronic inflammation e.g. lupus, rheumatoid arthritis.
- Chronic infections e.g. bronchiactasis, infective endocarditis.
- Chronic renal failure.

Criteria: Defective iron utilization results in:

- Occasional microcytic anemia (usually normocytic).
- Low serum iron & iron binding capacity.
- Normal or high serum ferrittin.
- Normal soluble serum transferrin receptors.

2- Chronic lead poisoning (plumbism):

Criteria:

- Basophilic stippling of RBCs.
- High serum lead.
- Increased protoporphrins in urine.

3- Sidroblastic anemia:

- Impaired heme synthesis → iron retention in mitochondria → ringed sidroblasts in RBCs precursors in bone marrow.
- High serum iron and ferrittin.
- May respond to vitamin B_6.

Treatment

i- Prophylaxis:

Oral iron given at 4th – 6th months (2mg/kg/d) for breast and cow milk feeders.

ii- Curative:

1- Treat the cause.

2- Diet → Rich in vitamin C, meat, fish
→ Limit amount of cow milk & tea.

3- Iron preparation:

- Oral Iron:
  - Ferrous sulphate, gluconate or fumarate.
  - Dose: 6 mg/kg/d. elemental iron inbetween meals.
  - For: 8 weeks after blood values are normalized.
  - Side effects: GIT upset & dark stool.
- Parentral Iron
  - Iron Dextran (I.M), **or** iron hydroxide sucrose complex ;*Venofer* (I.V).
  - For malabsorption **or** Intolerance to oral iron.
  - Side effect → staining, abscess,anaphylaxis.

4- Packed red cell transfusion:

- in: - Severe anemia (Hb < 4gm/dl).
  - Anemic heart failure.
  - Infection interfering with iron therapy.

Response to iron therapy:

Time after iron administration	Response
By 1st day	Replaced cellular enzymes → ↓ irritability with increased appetite.
By 2nd day	Erythroid hyperplasia in bone marrow.
By 3rd day	Reticulocytosis peaking at 5-7 days (good therapeutic test).
By 1st month	Increase hemoglobin at rate of 0.25 – 0.5 gm/dl/day
1 – 3 months	Repletion of stores.

Causes of failure of iron therapy:

- Non compliance.
- Continuing use of cow milk
- Continuing blood loss
- Coexisting diseases(renal,infection)
- Impaired absorption
- Incorrect diagnosis.

Megaloblastic Anemia

Definition: Anemia with megaloblasts in BM and macrocytes in peripheral blood.

Causes: i- Vitamin B_{12} (cobalamin) deficiency ii- Folic Acid deficiency.

Pathogenesis

Folic acid & B_{12} are essential for DNA synthesis in stem cells of RBCs, platelets and WBCs.

so

nucleus can't devide ⇓ ↓ RBCs production

while RNA is normal ⇓ ↑↑ cytoplasm. ⇓ ↑ megalobasts in BM

macrocytes in blood ⇓ trapped in the spleen ⇓ extramedullary lysis

can't leave BM. ⇓ Intramedullary lysis

Metabolism

Vitamin B_{12}	Folic acid
Sources: animal origin only e.g. milk, meat.	- animal & plant (green leaves, fruits)
Requirements: 5-20 mcg./day	20-50 mcg./day
Absorption: gastric parietal cells release intrinsic factor (IF) which binds to B_{12} → B_{12}/IF complex then absorbed from terminal ileum	absorbed from proximal jejunum (need vitamin C)

Causes of B_{12} & folic acid deficiency

	Vitamin B_{12}	Folic acid
↓Intake	very rare except breast feeders of vegetarian mothers	❁ Uncommon; may occur in infants fed on: Goat's milk
↓ Absorption	1-Generalized malabsorption 2- Pernicious anemia: - congenital: no or abnormal IF - Juvenile: antibodies against IF & parietal cells. 3-B_{12} /IF consumption by Diphyllobothrium latum **or** bacterial overgrowth. 4- Ileal disease. **Or** resection	❁ same ❁ vit C deficiency **↓ Metabolism** ❁cytotoxic drugs→ methotrexate ❁anticonvulsant → phenytoin → valproate
Others	Defective transport: transcobalamin II deficiency.	❁ increase requirements: e.g. - prematures (↓stores) - chronic hemolyis

Clinical picture

a. Anemia (Anorexia, pallor, ...) with slight jaundice.

b. GIT manifestations esp. in folate deficiency:

- Red glazed tongue & glossitis.
- Abdominal pain and chronic diarrhea.

c. Neurologic manifestations: subacute combined degeneration (SCD)

- May occur Only with vitamin B_{12} deficiency:
  1- Posterior column degeneration → sensory ataxia
  2- Pyramidal tract degeneration → delayed motor milestones
  3- Peripheral Nerve degeneration → paraesthesia.

Investigations

1- Is it megaloblastic anemia?

- CBC: - Anemia → Macrocytic, Normochromic
  ⇓ ⇓ ⇓
  ↓ Hb% & Ht value MCV > 100 fl. MCHC = normal
  - Hypersegmented neutrophils (contain 4-5 lobes; early finding).
  - WBCs and platelets moderately reduced in advanced cases.
- BM: - Megaloblastic

2- What is the cause?

I- Folic acid deficiency:

1- Low serum folic acid < 3 ng/ml (normal 5-20 ng/ml).
2- FIGLU test: oral load with histadine → ↑ FIGLU secretion in urine.

II- B12 deficiency:

1- Low serum vit B_{12} < 100 pg/ml.
2- Schilling test:
- Small amount of radioactive B_{12} is given orally
- 1 mg non radioactive B_{12} is given IM to saturate B_{12} binding proteins.
- Normally 10-30% of oral B_{12} excreted in urine.
  - in B_{12} malabsorption → < 2% is excreted.
  - If the test is corrected by oral IF → consider IF deficiency.
  - If the test is not corrected by IF → consider ileal disease.

3- Others: Gastric function tests, IF antibodies, small bowel biopsy.

Treatment

1- Folic acid deficiency:

- Folic acid tablet 0.5 – 1 mg/day for 3-4 weeks.
- If diagnosis of folic acid deficiency is doubtful use smaller dose 0.1 mg/day for a week & look for reticulcytosis (therapeutic test).

(large dose of folic acid worsen neurologic manifestation of vitamin B_{12} deficiency)

2- Vitamin B12 deficiency:

1- Without SCD: B_{12} 1 mg IM monthly for life.
2- With SCD: B_{12} 1mg IM daily for 2 weeks then 1 mg IM monthly for life.

* With successful treatment ; reticulocytosis is seen in 2- 4 days

Hemolytic Anemia

Definition: Anemia resulting from increased RBCs destruction exceeding bone marrow capacity for compansation.

- Normal RBCs life span 110-120 days.

Acute Hemolytic Anemia

Causes

i- Intra corpuscular causes

- Enzymatic defects: G6PD deficiency

ii- Extra corpuscular causes

Immunologic (Coombs +ve)

- Isoimmune hemolytic anemia
  - 1- Hemolytic disease of newborn.
  - 2- Incompatible blood transfusion.
- Autoimmune hemolytic anemia

Non immunologic (Coombs –ve)

1- Microangiopathic hemolytic Anemia (MAHA)
   - DIC
   - Hemolytic uremic syndrome (HUS).
   - Renal vein thrombosis (RVT).
   - Intracardiac prosthesis
2- Septicaemia (Staph strept., clostridia)
3- Malaria.
4- Wilson disease.
5- Drugs & heavy metals.

General clinical features

1- Acute pallor.
2- Tinge of jaundice.
3- Dark colored urine (hemoglobinuria)
4- Pyrexia & rigors.
5- Loin pain.

General Investigations

1- Anemia: low Hb% and Ht. value.
2- Decreased RBCs Survival
   - ↑ Plasma hemoglobin.
   - ↓ Haptoglobin & hemopexin.
   - ↑ Unconjugated bilirubin.
   - Hemoglobinuria.
3- Increased erythropioesis
   - ↑ Reticulocytic count > **5-15%** (up to **50%**)
   - ↑ Normoblasts.

Specific investigation

1- Coombs test: Diagnose Immunologic hemolytic anemia.

2- Blood film for:

- Heinz bodies in G6PD deficiency.
- Microangiopathic hemolytic anemia: - Fragmented RBCs (schistocytes).
  - Thrombocytopenia.
- Malaria.

3- Blood culture for septicemia.

Glucose - 6 - Phosphate Dehydrogenase Deficiency

(G6PD Deficiency)

Etiology

* Hemolytic anemia due to age labile Glucose - 6 - Phosphate Dehydrogenase enzyme
* Sex linked recessive disorder
* Being sex linked it occurs mainly in males
* May occur in females if homozygous or heterozygous with random inactivation of the normal X chromosome (Lyon hypothesis).

Pathogenesis

* G6PD enzyme is key enzyme of Hexose Mono Phosphate (HMP) shunt which produce reduced glutathione.
* Reduced glutathione protects the red cells against oxidizing agents.
* In G6PD deficiency → ↓ reduced glutathione → impaired elemination of oxidants → oxidation of Hb → methemoglobin → precipitate inside RBCs → acute hemolysis.

Oxidizing agents include:

* Food → Fava beans (favism)
* Infections → Viral or bacterial
* Drugs → Anti pyretics e.g. - Acetyle salicylic acid
  - Metamisol
  - Phenacetin

  → Anti microbial e.g.- Sulpha
  - Chloramphenical
  - Nitrofurantion

  → Anti malarial e.g. primaquine

Genetic variants:

* Types A^+ & B^+ → Normal variants.
* Type A^- → American type (enzyme activity = 5-15%).
* Mediterranean type → Severe deficiency (enzyme activity < 5%).
* Canton type.

Clinical picture

A. Acute hemolytic anemia:

- Features of acute hemolysis without organomegaly(*see before*).
- Occur 24- 48 hours after exposure to the oxidants.
- Degree of hemolysis varies with triggering agent, amount ingested and severity of enzyme deficiency
- Episodes usually brief as newly produced young RBCs have higher enzyme activity (more abundant and stable)
- May occur in neonatal peroid → neonatal anemia & jaundice.

B. Chronic non spherocytic hemolytic anemia:

- Extremely rare.
- Pallor, tinge of jaundice & mild splenomegaly.

Investigations

1. For **anemia** → Low Hb% and Ht value.
2. For **acute hemolysis** → ↓ RBCs survival & ↑ Erythropiosis.
3. For **the cause**:
   - Blood film → Fragmented RBCs
     → Heinz bodies (intracellular inclusion bodies).
   - Enzyme assay → done **2-3** months after the attack (during the attack, bone marrow produce juvenile RBCs with higher enzymatic activity which may give false normal results).

Treatment

i. Prophylactic:

- Avoid oxidant food & drugs.
- Anti oxidant → vitamin E.
- Anti pyretics in fever → paracetamol **or** ibubrufen.

ii. During the attack:

- Stop the oxidant agent.
- Packed RBCs transfusion (5-10 ml/kg) → can be repeated in severe attack.

Paroxysmal Nocturnal Hemoglobinuria

Definition: - Red cell wall susceptable to lysis with serum complement → severe intravascular hemolysis during sleep → morning hemoglobinuria

- Associations: -Thromboembolism.
  - Pancytopenia.
  - Iron deficiency.

Treatment

- Oral iron.
- Anticoagulants.
- Bone marrow transplantation.

Chronic Hemolytic Anemia

Causes

i- **Intra corpuscular causes**

1- Membrane defects: - Hereditary spherocytosis
- Hereditary elliptocytosis.

2- Hemoglobinopathy. - α thalassemia
- β thalassemia.
- Sickle cell disease

3- Enzymatic defects: - Pyruvate kinase deficiency.

ii- **Extra corpuscular causes**

1- Immunologic (Coombs +ve): Autoimmune hemolytic anemia (Warm type).

2- Non immunologic (Coombs –ve): Hypersplenism.

General clinical features

1- Features of anemia (pallor, ...)

2- Tinge of jaundice.

3- Splenohepatomegaly due to extramedullary hematopioesis & hemosiderosis

4- Skeletal changes due to bone marrow expansion:

* Head (= mongloid features): - Macrocephaly.
- Depressed nasal bridge.
- Prominent maxillae.
- Prognathism.

* Generalized osteoporosis.

5- Gall bladder stones (Calcium bilirubinate stones) in chronic hemolysis for > 4 years.

6- Hematologic crisesis:

* Aplastic crisis:- Transient sudden bone marrow hypoplasia.
- Due to parvo-B19 infection (infect erythroid cells).
- Presentation → increased pallor without deepening of jaundice
→ reticulocytopenia.

* Hemolytic crisis: Increased pallor, jaundice & reticulocytic count.
* Megaloblastic crisis due to folate deficiency.
* Hyperhemolytic crisis due to associated G6PD deficiency.

General Investigations

1- Anemia: low Hb% and Ht value

2- Decreased RBCs survival:
- ↑Unconjugated bilirubin (usually < 5 mg/dl).
- ↑ Fecal stercobilinogen.

3- Increased erythropioesis:
- ↑ Reticulocytic count between **3-15%**
- Skull X-ray: marrow space expansion → macrocephally & wide diploic space (hair on end appearance).

4- ↓ Chromium (^{51}Cr) labelled RBCs survival

Hereditary Spherocytosis

Pathogenesis

* Autosomal dominant disorder
* Due to deficiency of red cell wall skeleton protein "Spectrin or Ankyrin" → ↑ cell wall permeability to Na^+ → ↑ intracellular Na^+ influx.

↑water content inside RBCs → Cells become spherical with rigid cell wall

Over work of Na/k pump to keep Na out the cell (↑ ATP & glucose consumption) → premature RBCs aging

RBCs are trapped & destroyed in the spleen.

Clinical picture

* Positive family history usually present (may be absent)

1- Features of anemia
2- Features of chronic hemolysis

} starting early in life; **50%** present by neonatal anemia and jaundice.

3- Gall stones occur in **50%** of unsplenctomized cases by 4-5 years

Investigations

1. For **anemia** → ↓Hb% and ↓Ht value(usually normocytic , hyperchromic anemia)
   → Most patients have mild anemia with hemoglobin level of 9-12 g/dl
2. For **chronic hemolysis** → ↓ RBCs survival & ↑ erythropioesis.
3. For **the cause**:
   a. Blood film → RBCs are small, rounded without central pallor = spherocytes.
   b. Osmotic fragility test: There's increased osmotic fragility of RBCs
      * Idea of the test:
        - Normally exposure of RBCs to hypotonic solutions cause it to swell and rupture
        - Spherocytes (already swollen cells) lyse more readily than normal biconcave cells in hypotonic solutions
      * Red cell lysis is accentaued by depriving cells of glucose for 24 hours at 37 ^{0}C (Incubated osmotic fragility test) which is more characterstic
   c. Recent; more sensitive tests: Cryohemolysis test &osmotic gradient ektacytometry
   d. Negative Coomb ś test (rules out auto immune hemolytic anemia)

Treatment

1- Supportive → folic acid 1mg/day (till splenectomy is done).
2- Slight anemia (Hb > 10 gm/dl and reticulocytic count < 10%) → No treatment.
3- Severe anemia need packed red cells transfusions.
4- **Splenectomy:**
   * Indication? → Severe anemia with frequent crises, poor growth or cardiomegaly
   * Value? Clinical cure → prevent hemolysis, crises and gall bladder stones
   * Timing , precautions and complications ? → See Thalasemia

Thalassemia

Definition: Autosomal recessive disorders due to defective globin chain production

1. α thalassemia syndromes:

✧ Impaired α chain production

✧ Due to deletion of one or more of the 4 α globin genes on chromosome 16

A. One gene deletion → **Silent carrier**

- Asymptomatic without any hematologic abnormalities.
- Electrophoresis in neonatal period shows <3 % Bart's hemoglobin (4 γ globin chains) which disappear few months later.

B. Two gene deletion → **α thalassemia trait**

- Familial microcytic anemia ; commonly mistaken as iron deficiency
- Normal iron indices
- Electrophoresis shows:
  * 3-8 % Bart's hemoglobin in neonatal period which disappear by childhood
  * Normal levels of Hb F & Hb A_2 for age.
- Diagnosed by exclusion; to confirm → DNA analysis.

C. Three genes deletion → **Hemoglobin H disease**

- Mild to moderate microcytic hemolytic anemia at birth
- Evidence of chronic hemolysis
- Electrophoresis shows:
  * 15-30 % Bart's hemoglobin in neonatal period
  * Hb H (4β chains).

D. Four genes deletion → **Fetal hydropes**

- Severe intra uterine anemia and anemic heart failure
- Resulting in intrauterine fetal death , still birth or early neonatal death
- Electrophoresis shows: Dominant Bart's hemoglobin with complete absence of normal fetal and adult hemoglobin (i.e require BMT)

2. β-thalassemia syndromes :

✧ Impaired β chains production

✧ Due to mutation of one or more of the 2 β globin genes on chromosome 11

A. One gene mutation → **β thalassemia trait** (Heterozygous β-thalassemia)

- Most patients have short RBCs survival without evidence of overt hemolysis.
- Microcytic anemia
- Differentiated from iron deficiency anemia by:
  - Normal iron indices.
  - Increased RBCs count in contrast to iron deficiency (Mentzer index >13)
  - Electrophoresis: - ↑ Hb A_2 up to 3-7% in over 90% of cases.(diagnostic)
    - ↑ HbF up to 1-3% in only 50% of cases.

B. Two genes mutation → **β thalassemia major**

β Thalassemia Major

(Cooley's anemia)

The commonest cause of chronic hemolytic anemia in Egypt & Mediterranean areas.

Pathogenesis **1- Impiared β chain production**

↓ production of HbA ($\alpha_2 B_2$)

Deposition of excess unmatched α chain inside the RBCs → hemolysis → Anemia

Compensatory production of other Hb containing non Beta chains especially Hb F ($\alpha_2\gamma_2$) → ↑ Level of HbF (↑O_2 affinity)

→ Tissue hypoxia → Compensatory ↑RBCs production

- Medullary hematopoeisis → Bone marrow expansion **(Skeletal changes)**
- Extramedullary hematopoeisis → **Splenomegaly (± hepatomegaly)** ± hypersplenism

2- Iron overload due to:

- Chronic hemolysis.
- ↑ Iron absorption.
- Repeated blood transfusion.

→ Iron deposition in various organs → hemosiderosis.

Clinical picture

1- Features of anemia
2- Features of chronic hemolysis

} Starting after the 6th month of age when switch from γ to β chain production normally occur.

3- Hemosiderosis → Iron deposition in:

- ✧ Skin → bronzed color
- ✧ Heart → cardiomyopathy.
- ✧ Pancreas → diabetes mellitus.
- ✧ Liver → cirrhosis.
- ✧ Pituitary → growth retardation & hypogonadism.

Investigations

i- For **anemia** → Low Hb% and Ht. value.

ii- For **chronic hemolysis** →↓ RBCs survival & ↑ erythropioesis.

iii- For **the cause**

1- Blood film → hypochromic, microcytic anemia with target cells.

2- Alkaline denaturation test → Hb F resist denaturation by alkali

3- Hemoglobin electrophoresis :

- β^0 **Homozygous:** ↑↑ Hb F (98%),↑ Hb A_2 (2%), no Hb A (no detectable β chains)
- β^+ **Homozygous:** ↑↑ Hb F, ↑ Hb A_2 , some Hb A (reduced β chains synthesis)

4- Prenatal diagnosis is possible by chorionic villous sampling (CVS)

Complications and cause of death

1- Heart failure may be due to:
- Under transfusion → anemic Heart failure.
- Over transfusion → volume overload.
- Cardiomyopathy due to hemosiderosis.

2- Hemosiderosis:
- Diabetes mellitus → Diabetic ketoacidosis.
- Liver cirrhosis → Liver cell failure.

3- Hazards of frequent blood transfusion:
- Allergic reactions.
- Pyrexial reactions.
- Incompatible blood transfusion.
- Disease transmission (HBV, HCV, AIDS)

4- Hypersplenism → pancytopenia

5- Splenectomy → Sepsis.

Treatment

1- Chronic transfusion therapy (Regular packed RBCS transfusion)
- Started when hemoglobin fall below 7gm/dl.
- Aim: To keep Hb between **9.5-12** gm/dl post transfusion (hypertransfusion protocol).
- Dose: 10-15 ml/kg packed RBCs every **3-4** weeks.
- Benefit → allow normal growth
  → ↓ bone marrow activity → ↓ skeletal changes.
  → ↓ extramedullary hematopoeisis → ↓ organomegaly.
- Recently : young red cells transfusions → help reduce iron overload

2- Iron chelation therapy:
- Started when serum ferrittin exceeds **1000** ng/ml.
- Aim: avoid hemosiderosis(keep serum ferrittin close to **1000** ng/ml) .
- Drugs used:

i- Desferroxamine (Desferal):
- Dose: 40-60 mg/kg/day
- Route: IM, IV or by continous SC pump for 10 hours, 5 nights per week.
- Side effect: local reactions ,anaphylaxis, ototoxicity, ocular toxicity & growth retardation (rickets like changes)

ii- Recent drugs:

1- Deferiprone(L1) oral: 75 mg/kg. (better used combined with desferal)
Value: Reduce cardiac iron overload.
Side effects: - Neutropenia & polyarthropathy.
- Possible adverse redistribution of iron .

2- ICL-670 oral : As effective as desferal but with longer half life

- Monitoring? Check serum ferrittin /3-6 months.

3- Supportive treatment:

1- ↓ Iron in diet

2- Folic acid 1mg/day (prevent megaloblastic crisis).

3- Endorcine support as necessary.

4- Hepatitis B vaccine

5- Calcitonin (Miacalcin) and calcium carbonate for osteoporosis.

6- Cardiac support:

- L carnitine.
- Treat heart failure:diuretics,digoxin,desferal infusion 15 mg /kg/hr.

4- Splenectomy:

Indications:

- Hypersplenism suggested by:
  - Increasing need for transfusion by ≥50% than usual for more than 6 monthes.
  - Annual packed RBCs > 250 ml/kg/year in face of uncontrolled iron overload.
  - Severe leucopenia and / or thrombocytopenia.
- Huge spleen with pain or pressure symptoms.

When: Preferably after the 5th year.

Risk : Overwhelming sepsis (esp. if done < 5 years)

Precautions:

- Two weeks before splenectomy → immunize the patient against:
  - Hemophilus influenzae
  - Pneumococci
  - Meningeococci
- After splenectomy → oral penicillin 250 mg twice daily till adulthood.

5- Recent treatment:

- Hydroxyurea → induction of Hb F. → ↓unmatched α chain accumulation → ↓ hemolysis (of limited value due to serious side effects).
- Bone marrow transplantation → best for patient less than 3 years.
- Gene therapy is under research.

N.B : Tools for measurement of body iron

1. Serum ferritin
2. Hepatic iron concentration by biopsy (The gold standard tool ; but invasive)
3. Superconducting quantum interface device: SQUID (Noninvasive)
4. Magnetic resonance imaging

Sickle Cell Disease

Etiology

✧ Autosomal recessive disorder.

✧ Due to single amino acid substitution in the number 6 position of the β-chains (valine for glutamic) resulting in new Hb → HbS ($\alpha_2\beta_2^{6glut.}$ → $\alpha_2\beta_2^{6val.}$ = HbS).

Pathogenesis

HbS can't withstand hypoxia → if exposed to low O_2 tensions → HbS polymerize→ RBCs distortion → intra vascular sickling with subsequent :

1. Aggregation → vascular occlusion
2. Trapping and hemolysis in reticulo endothelial system in the spleen & liver

Forms: - Sickle cell anemia (homozygous)
- Sickle cell trait (heterozygous)

Clinical picture

✧ Common in negroes

✧ Earliest manifestations:

- Mild hemolysis is evident by 3 months of age with Hb of 7-10 and reticulocytic count of 10-20%
- Hyposplenism can occur as early as 5 months of age and initial splenomegaly can be detected after 6 months of age
- The first crisis detected between 6-12 months of age in about 50% of cases.

✧ Features of anemia
✧ Features of chronic hemolysis
] Starting after the 6th month of age

✧ Renal disorders → proteinuria, nephrotic syndrome, chronic renal failure.

✧ **Crisises**

1. Aplastic 2. Hemolytic 3. Megaloblastic 4. Hyperhemolytic (as before)
5. **Vaso occlusive crisis (painful crisis)**

Due to : invivo sickling → vascular occlusion → ischaemia ± infarction.
Precipitating factors : fever, acidosis, dehydration, infection & hypoxia.
Clinically:

* Cerebrovascular stroke(esp. middle cerebral artery)
* Pulmonary infarction → hemoptysis
* Acute chest syndrome :
  - Chest pain, fever, leucocytosis and lung infilterates→ fatal in 20%
  - Due to pulmonary emboli of necrotic bone marrow (fat emboli)
* Hand and foot syndrome: Ischemia of metacrapal & metatarsal bones → symmetric bone pain & swelling
* Renal infarction → hematuria
* Priapsim (sustained, painful purposeless erection)
* Leg ulcers

6. Sequestration crisis:

Sudden pooling of the blood in the spleen ± the liver; precipitated by dehydration

Clinically: - Acute pallor with hypovolaemic shock.

- Acute abdominal pain with massive splenomegaly (± hepatomegaly)

7. Infectious crisis: due to hyposplenism (↓Antibodies, ↓opsonins, ↓phagocytosis)

Common organisms: usually encapsulated

Site: - Meningitis (Pneumococci & H.influenzae)

- Pneumonia (Pneumococci)
- Osteomyelitis (Salmonella)

Investigations

1- For **anemia** → Low Hb% & Ht value.

2- For **chronic hemolysis** →↓ RBCs survival & ↑ erythropioesis.

3- For **the cause:**

- Blood film: - detect sickle cells in peripheral blood. If not detected, sickling can be enhanced by adding sodium metabisulfite (Sickling test).
  - Howell–Jolly bodies (nuclear reminants) and Submembraneous pits in RBCs may be seen indicating hyposplenism.
- Hemoglobin electrophoresis: Show HbS (90%) & Hb F (2-10%).
- Neonatal screening allows early detection , adequate care and longer survival

Treatment

1- Chronic transfusion therapy & iron chelation.

Indications: patients with strokes,splenic sequestration crises, repeated episodes of acute chest syndrome.

2- Treatment of crisises:

✧ Supportive care: Ensure ABC & remove precipitating factors(e.g. infections)

⌖ Vaso oclusive
- Hydration at 1.5-2 maintenance & alklinization.
- Analgesics (paracetamol, ibuprofen, opiates)
- If refractory → partial exchange transfusion.

⌖ Sequestration
- Blood transfusion.
- Exchange transfusion(keep sickle cells<30%)
- If refractory → emergency splenectomy.

⌖ Aplastic / hemolytic → Blood transfusion

3- Control of infection:
- Prophylactic penicillin (up to 6 years)
- Immunize against: Pneumococci & H. influenzae

4- Recent treatment:
- Hydroxyurea → induction of Hb F.
- Bone marrow transplantation.

N.B: Sickle cell trait: Heterozygous form

- The patient's blood contains mixture of (HbS = 30%) and (HbA).
- Asymptomatic but severe hypoxia may lead to ⇉ vaso occlusive crisis.
- Patients are resistant to falciparum malaria.

Auto Immune Hemolytic Anemia (AIHA)

Definition: Hemolytic anemia due to circulating antibodies against patients own RBCs.

Explanation

- Altered immune response (not recognise self antigens).
- Altered RBCs antigenicity by infection or drugs.

Clinical types: According to type of antibodies

	Warm antibodies	Cold antibodies
Causes:		
• Idiopathic	• Idiopathic	• Idiopathic
• Secondary to:		
- Infection	- Cytomegalo virus, Hepatits B virus.	- Mycoplasma, Ebstein Barr virus.
- Vaccination	- DPT, MMR	- MMR
- Disease:	- Lymphoma.	- Lymphoma
	- Systemic lupus erythmatosis	
- Drugs	- Aldomet, penicillin.	
Criteria of Antibodies	- IgG. - active at 37°C	- IgM - active below 37°C

Clinical picture

i- AIHA due to warm antibodies:

1- Acute transient type	2- Chronic type
- in child 2-12 year. - may follow respiratory infection. - acute hemolytic anemia with splenomegaly. - respond to steroids → recover within 3 months.	- in child < 2 or > 12 years - may be underlying systemic disease e.g. lymphoma. - chronic hemolytic anemia. - variable response to steroids.

ii- AIHA due to cold antibodies:

1- Cold agglutinin disease:

⇒ Cold antibodies may present with low titre

↓

infection with mycoplasma or Ebstein Barr virus.

↓

↑↑ antibody titre $\xrightarrow[\text{cold}]{\text{exposure to}}$ acute hemolytic anemia

2- Paroxysmal cold hemoglobinuria:

- Due to Donath landsteiner antibody (IgG which can activate complement)
- Association: 1- infection with mycoplasma , Ebstein Barr virus,Cytomegalo virus
  2- Congenital or acquired syphilis.
- Course: Mild, resolve with infection resolution.

Investigations

i- For **anemia** → Low Hb % & ↓ Ht value.

ii- For **acute hemolysis.**
iii- For **chronic hemolysis** } ↓ RBCs survival & ↑ erythropioesis

iv- For **the cause.**

1- CBC: - Micro spherocytes.
- AIHA plus autoimmune thrombocytopenia → **Evan's Syndrome.**

2- Coombs test.
- Direct: Detects high titre of autoantibodies coating the RBCs
- Indirect: Detects the free autoantibodies in patient serum

Complications

- Anemia may be severe enough to cause cardiovascular collapse
- Severe intra vascular hemolysis may be associated with DIC
- Complications of associated underlying disease e.g. Systemic lupus erythmatosis and immunodeficeincy

Treatment

1- Treat the underlying cause and avoid exposure to cold.

2- Blood transfusion:
- Value: Correct severe anemia.
- Use: Small volume of packed RBCs starting with a test dose.
- Disadvantage:- hard to find totally compatible blood.
- transient effect.

3- Steroids: - Effective in warm type.
- Dose 2 - 4 mg/kg/d
- Larger dose (6 mg/kg) may be needed to control hemolysis.

4- Plasmapharesis: effective in severe cold type.

5- I.V. immunoglobulin 1 gm/kg for 2 days

6- Splenectomy for resistant warm type cases.

7- Cyclosporin A and Monoclonal antibodies which target B lymphocytes.

Approach to a Case of Anemia

A. History

* Onset: - Neonatal e.g. G6PD, spherocytosis
  - After 6 month e.g. β thalassemia, sickle cell anemia.
* Past history:
  - Hemorrhage
  - Drugs which may induce (aplasia, acute hemolysis in G6PD deficiency).
  - Infection or fava beans → G6PD deficiency.
  - Family history → similar cases & consanguinity for inherited causes.

B. Clinical approach

- Features of bone marrow failure(pallor,purpura,pyrexia)
- Features of hemolytic anemia: - Acute hemolysis(see page 219)
  - Chronic hemolysis(see page 222)
- Anemia with congenital anomalies: - Fanconi anemia.
  - Diammond Blackfan anemia.
- Anemia with: - GIT upset → Folic acid deficiency
  - Neurologic disorders → B_{12} deficiency

C. Laboratory approach

1. Confirm Anemia → ↓ Hb% & ↓ RBCs count.

2. Anemia with other hematologic abnormalities(e.g.purpura):

Consider: - Aplastic anemia
- Leukemia
- Other bone marrow replacement disorders.

3. Anemia without other hematologic abnormalities⇒Assess reticulcytic count

a. Low / normal reticulocytic count ⇒ check RBCs size :

- MCV < 70 fl→ **microcytic anemia** (for differential diagnosis ;see page 215)
- MCV > 85 fl → **macrocytic anemia;**

Causes:

With megaloblastic changes	Without megaloblastic changes
- Folic acid and B12 deficiency	- Normal newborn
- Thiamine responsive megaloblastic anemia	- Reticulocytosis
	- Postsplenectomy
- Orotic aciduria	- Aplastic anemia
- Lesch Nyhan syndrome	- Diamond Blackfan syndrome
	- Liver disease
	- Hypothyroidism
	- Paroxysmal nocturnal hemoglobinuria.

✧Normal MCV(72-79 fL) → **normocytic anemia**

Causes: - Acute blood loss
- Bone marrow infilteration
- Anemia of chronic disease(infection,connective tissue disorder)
- Chronic renal failure
- Hemolysis(enzyme deficiency,membrane defect)

b. High reticulocytic count ⇒ check for serum bilirubin:

✧ Normal → hemorrhagic anemia

✧ High → hemolytic anemias

4- Cases with hemolytic anemia is subjected to Coomb's test:

✧ Positive Coomb's test: Immune hemolytic anemia .

✧ Negative Coomb's test : Other causes of hemolytic anemia(see page 210)

5- Detailed peripheral blood smear :

⌖Sherocytosis:
- Hereditary sherocytosis
- Pyruvate kinase deficiency
- Auto immune hemolytic anemia
- ABO incompitability
- Microangiopathic hemolytic anemia
- Hypersplenism
- Burn
- Sickle cell disease
- Severe hypophosphatemia

⌖Target cells:
- Thalassemia
- Severe iron deficiency
- Hyposplenism
- Hemoglobinopathy; Hb SC, Hb E

⌖Blister cells(area under membrane free of hemoglobin): G6PD deficiency .

Hemorrhagic Disorders

Hemostasis is the mechanisms of stoppage of bleeding after injury of a blood vessele; different factors are involved:

1- Vascular factor :

Role: - Reflex vasoconstriction at the site of bleeding.
- Damaged endothelium activate F XII

Assessment

1- Bleeding time → normal = 4-8 min.

2- Hess test (capillary fragility test) → cuff of sphygmomanometer is inflated between systole & diastole for 5 min.→ if > 5 petechiae appear within 5 cm circle in the forearm → +ve test.

2- Platelets:

Role

1- Adhesion to exposed collagen fibers (Von Willbrand factor is essential).

2- Aggregation; platelets accumulate at injured site helped by adenosine diphosphate (ADP) & thromboxane A_2

3- Release of: - Thromoxane A2 →↑ platelet aggregation.
- Serotinine →↑ vasoconstriction
- Platelet factor 3 (PF_3) → enhance clotting
- Thrombasthinine →↑ clot retraction.

4- Platelet plug formation

Assessment:

1- Bleeding time.

2- Hess test.

3- Platelet count (N = 150 – 400.000 /mm^3)

4- Platelet function tests: → assess platelet adhesiveness.
→ assess aggregation by aggregometer
→ assay of PF3 level.
→ clot retraction test.

3- Coagulation factors:

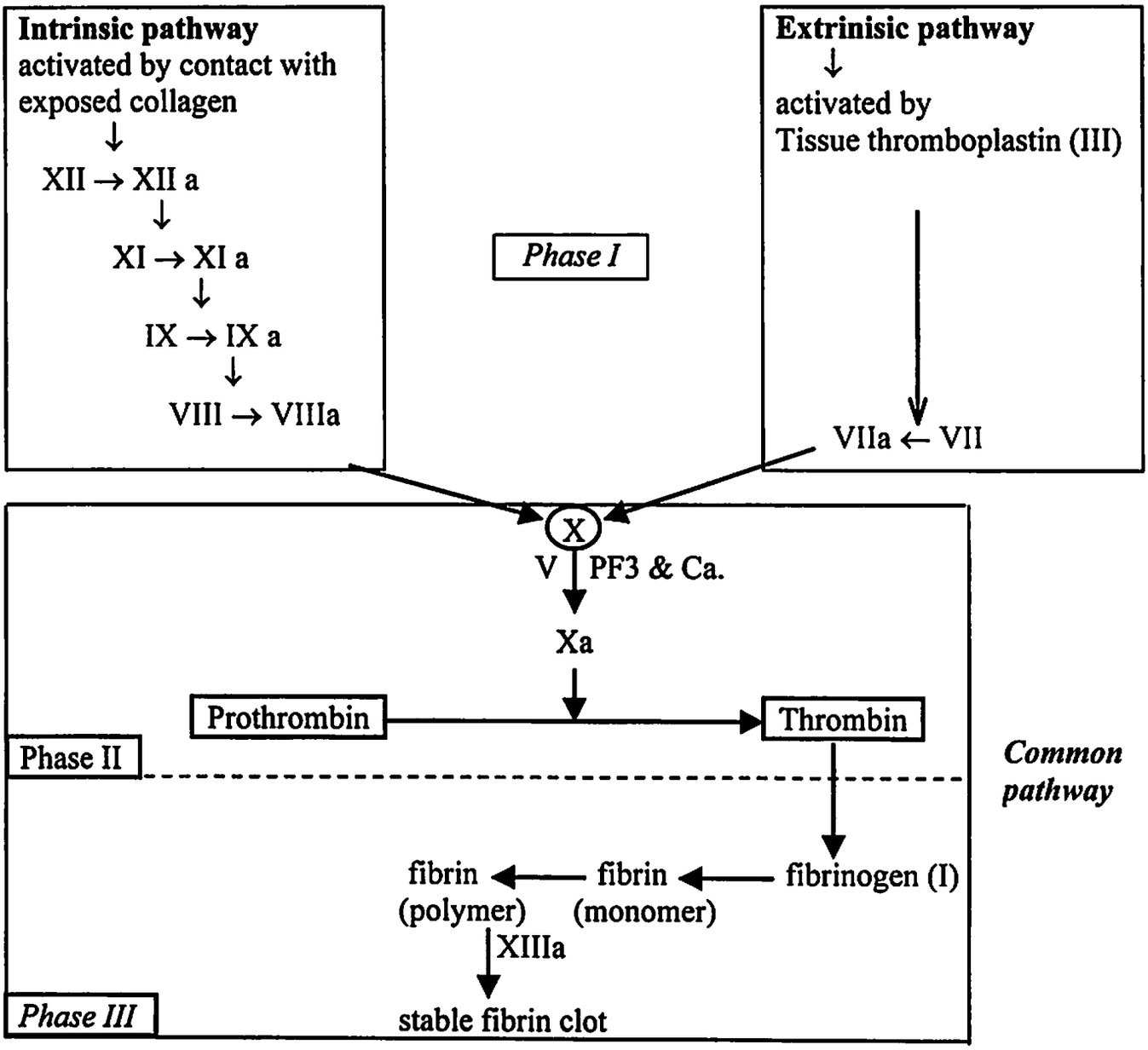
Names

I	Fibrinogen	II	Prothrombin
III	Tissue thromboplastin	IV	Calcium
V	Labile factor	VII	Stable factor
VIII	Antihemophilic factor	IX	Chrismas factor
X	Stuart prower factor	XI	Plasma thromboplastin antecedent
XII	Hageman factor	XIII	Fibrin stabilizing factor

Criteria

- Most coagulation factors are formed in the liver except F VIII is formed by endothelial cells.
- Vitamin K dependent factors → II, VII, IX, X.
- Factor VIII is composed of clotting part = F VIIIc & antigenic part = F VIIIa, normally → $\frac{\text{F VIIIc}}{\text{F VIIIa}} = 1$

Activation: Coagulation factors are present in inactive form activated in a cascade.



Control of coagulation factors:

1- Fibrinolytic system: Plasmin splitt fibrin network into fibrin degradations products.

2- Natural coagulation inhibitors (Antithrombin III, Protein C & Protein S).

Assessment:

1- Clotting time ➽ normal = 8-12 **min.**
rough test → prolonged with defects in any phase

2- Thrombin time (TT) ➽ normal = 15-20 Sec.
- time needed to plasma to clot after addition of bovine thrombin
- prolonged in fibrinogen deficiency.

3- Prothrombin time (PT) ➽ normal = 12-14 Sec.
- time needed to plasma to clot after addition of thromboplastin & Ca.
- Test extrinsic & common pathways.

4- Partial thromboplastin time (PTT) ➽ normal = 25-40 Sec.
- time needed for plasma to clot after addition of kaolin, Ca & platelets.
- Test intrinsic & common pathways.

Interpretation

Defect in	PT	PTT	Specific
Common pathway (X, V, II, I)	Prolonged	Prolonged	Specific factor assay
Extrinsic pathway (VII)	Prolonged	Normal	
Intrinsic pathway (XII, XI ,IX, VIII)	Normal	Prolonged	

N.B.: Prolonged both PT & PTT also occur in multiple factors deficiency e.g. liver cell failure, vitamin K deficiency & DIC.

Purpura

Definition

1- Multiple, spontaneous hemorrhages in the skin & mucous membranes.
2- Range from pin point (petechiae) to several centimeters (ecchymosis)
3- Purple in color, not elevated, not blanch on pressure, not pruritic.

Causes

I- Non thrombocytopenic purpura: (normal platelet count)

1- Vascular purpura:
- **i-** Hereditary: e.g. Ehler Danlos Syndrome
  - Defect in type III collagen in connective tissue.
  - Clinical picture → hypermobile joints + purpura.
- **ii-** Acquired:
  - HSP
  - Scurvy (vitamin C ↓↓) → defective connective tissue collagen.
  - Infective endocarditis.
  - Sepsis (meningeococcal)

2- Thrombasthenia = platelet dysfunction
- **i-** Hereditary: - Defective adhesion = Von Willbrand disease.
  - Defective aggregation = Glanzmann disease.
- **ii-** Acquired: - Chronic renal failure.
  - Aspirin →↓ ADP & thromboxan A2.

II- Thrombocytopenic purpura: (↓ platelet count)

1- Decreased production

Congenital	Acquired
- Fanconi anemia. - Thrombocytopenia absent radii (TAR) syndrome (thrombocytopenia & absent or hypoplastic radii). - Wiskott – Aldrich syndrome (thrombocytopenia, eczema, immunodeficiency) - Osteopetrosis.	- A plastic anemia. - Bone marrow infiltration e.g. Leukemia. - Megaloblastic Anemia.

2- Increased destruction

Antibody-Mediated	Non- immunologic
- Idiopathic thrombocytopenic purpura . - Imunologic diseases e.g. systemic lupus. - Drug induced e.g. phenytion, sulpha.	- Microangiopathic hemolytic anemia - Sepsis. - Hypersplenism. - Trapping in giant cavernous hemangioma (Merrit – Kasabach syndrome)..

Immune Thrombocytopenic Purpura

(Idiopathic Thrombocytopenic Purpura ;ITP)

Definition: Purpura characterized by:

1- Shortened platelets survival(^{51}Cr labeled platelets life span = few minutes to 1-4 hrs)

2- Due to antiplatelet antibodies .

3- Thrombocytopenia (< 100.000 /mm^3).

4- Increased megakaryocytes in bone marrow.

5- Absence of other identifiable thrombocytopenic disorders (diagnosis of exclusion).

Etiology: Antiplatelet antibodies triggered by preceeding viral infection (in most cases).

Spleen is the primary site for antibody production & platelets destruction.

Clinical picture

I- Bleeding → usually spontaneous but may follow minor trauma
- Purpura.
- External bleeding e.g. epistaxis, oral bleeding, ...
- Rarely; internal bleeding e.g. intra cranial hemorrhage.

II- No significant organomegaly: Tip of spleen is palpable in < 10%.

III- No pallor except with significant bleeding **or** with Evans syndrome

Outcome

☆ Spontaneous recovery occur in 70- 80% of acute ITP over 6 months.

☆ 10-20% go onto chronic ITP :
- Defined as persistent thrombocytopenia for more than 6 months.
- Incidence is higher in:
  - Older females children & adolescents.
  - May be a manifestation of a systemic illness as SLE or chronic HIV.

Investigations

• ITP is still clinical diagnosis: thrombocytopenia in well appearing child with normal CBC(Platelets antibodies tests are still unreliable to confirm or exclude diagnosis)

i- Bleeding time: - Prolonged.

ii- CBC : - Platelet count → always < 100.000 / mm^3.
- Normal WBCs. & RBCs.

iii- BM. ex.: - Megakaryocytes hyperplasia
- Normal myeloid & erythroid cells (exclude aplasia & leukemia).

Differential Diagnosis

From other causes of **purpura** by clinical picture , CBC &BM. examination.

Treatment

1. Observation:

- For asymptomatic case without bleeding with platelet count >20.000/mm^3.
- Avoid trauma, aspirin, contact sports.

2. Steroids:

Value - ↓ Platelet antibodies production.
- ↓ Phagocytosis of antibody coated platelets

Indications - Bleeding orifices
- Count < 20.000/mm^3
- Extensive eruption.
- Persistent > 2 weeks

Dose - 2 mg/kg/day for 3 weeks course with gradual tapering .

3. Intravenous Immunoglobulin:

Value - Block phagocytes Fc receptors → protect platelets from destruction

Indications - Alternative to steroids (can be used together)
- Used in acute and chronic ITP

Dose - 0.8 – 1 gm/kg for 1-2 days

4. Intravenous Anti D (Win Rho):

Value - Coat RBCs → block phagocytes Fc receptors → platelet escape destruction with transient mild hemolysis

Indications - Chronic ITP
(Patient must be Rh positive , unsplenctomized with Hb % > 9 gm/dl)

Dose - 50 μgm/kg per dose

5. Splenectomy:

Indications - Acute ITP with life threatening bleeding unresponsive to platelet transfusion, steroids and intravenous immunoglobulin
- Chronic ITP in older patient ; uncontrolled medically

6. Other therapies for resistant cases:

1. Rituximab: - Nature: Anti CD20 monoclonal antibody
   - Role : Eleminate autoreactive B cells
   - Dose : 375 mg/kg/m^2 IV weekly for 4 weeks
2. Cytotoxic drugs
3. Plasmapharesis

Treatment of life threatening bleeding episode:

1- Adequate resuscitation(ABC; including blood transfusion if needed)
2- Platelet transfusion (especially if platelets count < 20.000/mm^3).
3- I.V. methyleprednisolone.
4- I.V. immunoglobulin.
5- Emergency splenectomy.

Anaphylactoid Purpura (Henoch Schonlein Purpura)

Definition

- Vasculitis of small blood vesseles affecting children 2-8y; more in males.
- Most common vasculitis of children
- May follow upper respiratory infection → viral or bacterial.

Pathogenesis

- ♦ Antigenic stimulation→ elevated IgA levels → IgA mediated small vessels vasculitis
- ♦ Supposed antigens may include:
  - ⊕ Infections: - Bacterial: mycoplasma ,hemophillus parainfleunza,yersinia.
    - Viral: adenovirus, parvo virus, ebstein barr virus.
  - ⊕ Allergens: - Drugs(penicillin,erythromycin)
    - Foods
    - Insect bites
  - ⊕ Post vaccination for:measles,typhoid,yellow fever

Clinical picture

i- Skin rash: in 100 % of cases

1- Where? over the buttocks & extensor surfaces.
of upper and lower limbs usually sparing the trunk.

2- Pattern?
- Start as erythematous maculopapular rash.
- Then become purpuric (petechiae)
- Elevated
- May be pruritic.
- May be erythema multifome

3- Association? Non pitting angioedema of lips, scalp, hands & feet.

ii- Arthritis: in 75 % of cases.

1- Where? usually in large joints e.g. ankle & knee, rarely wrists &fingers.

2- Presentation? swollen, hot, tender, limited mobility but without effusion.

3- Fate? resolution within few days without residuals but may recur in the same illness.

iii- GIT: in 50 % of cases.

1. Usually follow onset of rash and arthritis

2- Presentation:

- ☆ Colicky abdominal pain with vomiting
- ☆ Bleeding : - Gross or occult blood in stool
  - Hematemesis
- ☆ Complications:
  - Intussusception (may be due to submucosal hematoma)
  - Bowel infarction and perforation
  - May be hepatomegaly and pancreatitis

iv- Renal:

☆In 50 % of cases; develop within 3 months of onset of the skin rash.

☆Renal affection is more likely with:

Gastrointestinal involvement
Rash persisting for 2-3 months
Episodic purpura

☆Presentations

Mainly	Rarely
- Hematuria (microscopic or gross)	- Proteinuria
- Acute nephritis.	- Nephrotic syndrome.
- Normal renal function	- End stage renal disease

v- Others: - CNS → siezures, paresis.
- Testis → Hemorrhage.

Investigations: (diagnosis of HSP is clinical mainly).

1. **Biopsy:** Skin biopsy from involved skin show leukocytoclastic vasculitis with deposits of IgA(serum IgA is elevated in 50% of cases)
2. **For purpura :**
   - Normal platelet count & function (may be thrombocytosis) .
   - Normal coagulation profile.
3. **For renal lesions :**
   - ✧ Urine analysis for → RBCs, RBCs casts, protenuria
   - ✧ Renal function tests
   - ✧ Renal biopsy show:
     - Hypercellular glomeruli with focal and segmental proliferation
     - In severe cases;cresentic glomerulopathy
     - In complicated cases;segmental sclerosis
     - In electron microscopy:diffuse IgA deposits
4. **For GIT lesions** → stool examination for gross **or** occult blood
   → abdominal ultrasound & abdominal C.T.

Treatment

1. **Supportive:** adequate care for renal and gastrointestinal disturbances.
2. **Monitoring**: weekly in the 1st month, biweekly in the2nd month then at end of 3rd month
3. **Medications :**
   - **i-** NSAIDs (Salicylates)for arthritis
   - **ii-** Steroids (**2** mg/kg/d for **1** wk)for :
     - GIT problems(pain,hemorrhage)
     - Neurologic problems.
     - Testicular swelling
     - Presence of more than 50% crescents in renal biopsy
     - Intrapulmonary hemorrhage

N.B Steroids is not recommended for skin rash nor for arthritis

Coagulation Disorders

A. Hereditary:

1- Intrinsic pathway disorders:

- Factor VIII deficiency (Hemophilia A)
- Factor IX deficiency (Hemophilia B or Christmas disease).
- Factor XI deficiency (Hemophilia C).
- Factor XII deficiency
- Von Willbrand disease (Vascular hemophilia) ⇒ commonest disorder.

2- Extrinsic pathway disorders:

- Factor VII deficiency

3- Common pathway disorders:

- Factors II, X deficiency
- Factors V (Para Hemophilia)
- Fibrinogen deficiency:
  - Congenital afibrinogenaemia.
  - Congenital dysfibrinogenaemia
- Factor XIII deficiency

B. Acquired:

1- Vitamin K deficiency

2- Liver cell failure

3- DIC.

Hemophelia A

(Classic hemophelia)

Definition

- Sex-linked recessive coagulation defect due to deficiency of F **VIIIc**
- 20% of cases are new mutations.
- Hemophilia A represents 85% of all hemophilias

Pattern of deficiency

- Hemostatic level of factor VIII is >30-40U/L(30-40%); below this level bleeding occur
- Plasma level of Factor VIII in carrier females is between 40-60%

Clinical picture

The severity of bleeding depends on plasma level of factor VIII& severity of trauma .

	Severe	Moderate	Mild
F VIIIc	< 1%	1-5%	6-30%
Bleeding	spontaneously	with mild trauma	with severe trauma

1- At birth : unusual bleeding from the umbilicus or circumcision site

2- Later:

- ✧ External bleeding : epistaxis, dental bleeding ,hematuria, gastrointestinal
- ✧ Internal bleeding e.g.: intracranial hemorrhage, muscle hematoma
- ✧ Skin → ecchymosis & hematoma (**no** petechiae)
- ✧ Hemarthrosis → mainly in big joints of lower limbs:
  - Joint become swollen, red,hot, tender with limited mobility.
  - Later on → fibrosis & ankylosis

Investigations

1. Diagnostic:

1- Coagulation profile

Prolonged Clotting time — Normal Bleeding time

Prolonged PTT — Normal PT

⇓

Time is corrected by barium sulphate adsorbed plasma (contain F8 & F11) **not** by serum (contain F9 & F11)

2- F VIIIc assay → low

2. Carrier detection by:

- Direct gene mutation analysis
- F VIII/vWF ratio (<1.0)

3. Prenatal diagnosis:

- CVS or amniocentesis & DNA analysis.
- Fetal blood sample at 18-20 weeks

Treatment

1- Prophylactic treatment

- Regular F VIII replacement 20 unit/kg 3 times a week.
- Hepatitis B vaccine.
- Avoid trauma, I.M. injections & aspirin.

2- During bleeding attacks

A. Factor VIII replacement:

1- Recombinant factor VIII ⇒ dose = 25-50 unit/kg according to severity.
Calculated dose(IU) = % desired (rise in F VIII) x Body weight(kg) x 0.5

2- Others: - Fresh frozen plasma.
- Cryopreciptate
- Factor VIII concentrate.

B. Adjuvant drugs:

1- Desmopressin (DDAVP) →↑ plasma F VIII by 4 folds.

2- Antifibrinolytics → inhibit fibrinolysis → stabilize the clot e.g. .
* Tranexamic acid.
* ξ-AminoCaproic Acid (EACA).
Indications: - Mucosal bleeding(oral bleeding, epistaxis).
- Menorrhagia

3- Prednisone (short course) in hemarthrosis & hematuria (minimize fibrosis).

C. Special cases:

1- Intracranial Hemorrhage: High dose of F VIII (50–75 unit/kg) for 2 weeks.

2- Hemarthrosis: - Local → cold compresses.
- F VIII replacement + prednisone (short course)
- Rest for 48 hr then physiotherapy to avoid ankylosis

Complications

a. Of bleeding:

- Severe blood loss→ hypovolemic shock
- Severe intracranial hemorrhage.
- Hemophilic arthropathy→joint stiffness(joint MRI show ↑ iron deposition)
- Muscle atroply

b. Of treatment:

1- Complications of transfusion (*See page 245*)

2- Factor VIII inhibitors:

✧ About 5-10 % of hemophilics develop antibodies against factor VIII. So, become refractory to treatment. Antibody titre is measured by Bethaseda units

✧ Treatment options:

- High dose of factor VIII(100-200 unit/kg)
- Activated prothrombin complex concentrate(*aPCC*)
- Recombinant activated F VII (*Novo Seven*)→ activate extrensic pathway.
- Others : Desensitization , Rituximab

Hemophelia B (Chrismas disease)

- Factor IX deficiency.
- Incidence:1 out of 50.000(in contrast to hemophelia A which is 1 out of 10.000)
- Sex-linked recessive disorder.
- As hemophelia A. **but** milder.
- Treated by: Recombinant factor IX or factor IX concentrate given/24 hours.

Hemophelia C

- Factor XI deficiency.
- Autosomal recessive disorder so can affect both sexes.
- Very mild disease.
- Treated by fresh frozen plasma given / 48 hours.

Vascular hemophelia (Von Willbrand disease)

☆ Von Willbrand factor (VWF) is essential for:

1- Platelet adhesion.

2- Carrier for F VIII protecting it from proteolysis

☆ Deficiency of Von Willbrand factor result in: Platelet dysfunction and decrease plasma F VIII.

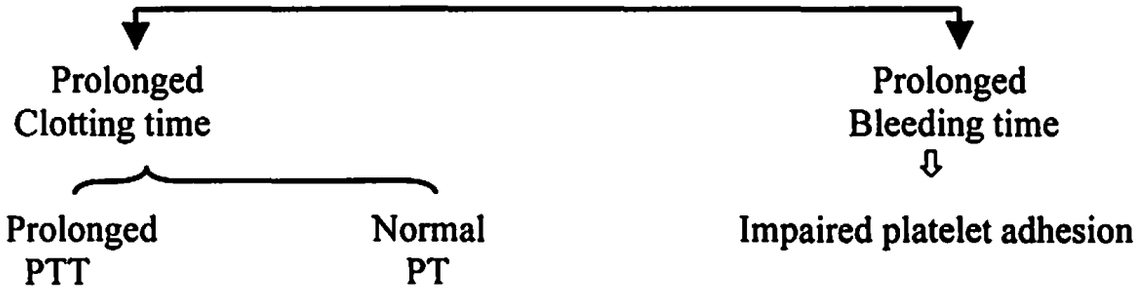
☆ In Von Willbrand disease: Von Willbrand factor may be low or abnormal or absent.

Clinical picture

- Inherited mainly as autosomal dominant disorder
- The commonest hereditary bleeding disoredr (3-4 out of 100.000)
- Mild bleeding: - Commonly epistaxis, gum bleeding &menorrhagia.
  - May be post operative bleeding
  - Very rarely purpura or hemarthrosis

Investigations

1- Coagulation profile



2- F VIII assay → low (both F VIIIa & F VIIIc are decreased)

3- VWF assay → low (type 1) or abnormal (type 2) or absent (type 3).

Treatment

1. Desmopressin (i.v. or intranasal) → effective especially in type 1 & some of type 2.
2. Factor VIII concentrate (contain F VIII & VWF):
   - For severe bleeding episodes.
   - The only effective treatment in type 3.
3. Cryoprecipitate & fresh frozen plasma may be used.
4. Antifibrinolytics (e.g EACA) → as adjuvant treatment in oral bleeding.

N.B. VWF is formed & stored in endothelial cells & platelets.

Dissiminated Intravascular Coagulation (DIC)

Definition: Wide spread activation of clotting factors allover the body resulting in:

1- Thrombosis and ischaemia of different vessels.
2- Consumption of coagulation factors → bleeding.
3- Microangiopathic hemolytic anemia & thrombocytopenia.

Predisposing factors

1- Severe tissue damage in → shock, dehydration, burn, hyperthermia.
2- Sepsis : meningeococcal, rickettsia,malaria,viral
3- Tumors e.g. AML, dissiminated malignancy e.g. neuroblastoma
4- Incompatible blood transfusion.
5- Severe hepatitis , pancreatitis or severe collagen vascular disease
6- Snake bites , insect bites.

Clinical picture

1- Manifestations of **the cause.**
2- Hemorrhagic manifestations: (bleeding from puncture sites, ecchymosis , purpura).
3- Thrombotic manifestations: gangerene in the skin, subcutaneous tissues, extremities or infarction of the kidney.
4- Uncontrollable severe bleeding and severe anemia → Shock

Investigations

1- Investigations for the cause.
2- Consumption of coagulation factors (defective all phases of coagulation esp. prolonged PT , PTT, thrombin time, and low fibrinogen).
3- ↑ Fibrin degradation products (FDPs) & D-dimer assay.
4- Anemia →↓ Hb%, ↓ RBCs count & fragmented RBCs (schistocytes).
5- Thrombocytopenia →↓ platelet count & ↑ bleeding time.

Treatment

1- Aggressive management of **the cause.**
2- Plasma **or** whole blood transfusion.
3- Heparin used only in: - AML.
   - Purpura fulminans.
   - Severe ischemic manifestations.

Prognosis

- Generally bad ,depending on the cause and the extent of spread of coagulations.

Leukemia

Definition

- Group of malignant diseases of hematopiotic cells in bone marrow
- Giving rise to uncontrolled clonal proliferation of cells
- With arrest of maturation at different stages
- With subsequent marrow failure.

Risk factors:multifactorial disease

1- Genetic predisposition is strongly suggested by high incidence in twin of children with leukemia
2- Chromosomal anomalies. e.g. Down, Klinefelter syndromes.
3- Chromosomal breakage disorders Fanconi anemia, Bloom syndrome ,Ataxia telangiectasia
4- Immunodeficiency states e.g., Wiskott Aldrich syndrome
5- Ionizing irradiation which either:
   - Diagnostic irradiation
   - Therapeutic irradiation
   - Atom bomb irradiation
6- Chemical carcinogens :
   - Benzene
   - Pesticide
   - Herbicide
   - Chemotherapeutic drugs specially alkylating agents.
7- Viral infections

Classification

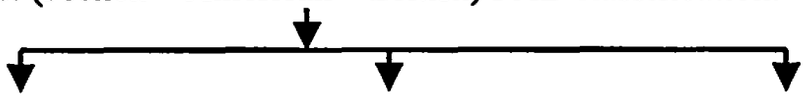
- Acute leukemia (95%)
  - Acute lymphoblastic leukemia (75%)
  - Acute non lymphoblastic leukemia (20%)
- Chronic leukemia
  - ↓
  - Philadeliphia chromosome (t 9;22) positive.
  - Juvenile myelomonocytic leukemia.

Acute Lymphoblastic Leukemia (ALL)

Incidence: Peak age = 2-5 y. , more in males (♀: ♂ = 1.4)&in whites

Classifications

1- Morphologic: (French – American – British) FAB classification.



L1	L2	L3
- Small cell	- Larger cell	- Large cell
- Small cytoplasm	- Larger cytoplasm	- Vaculated cytoplasm
- Best prognosis	- Prominent nucleoli	- Worst prognosis.
	- Poor prognosis	

2- Immunophenotyping ⇒ determine subtypes of ALL:

⇒ Classify ALL according to blast cell membrane & cytoplasmic markers.

	1. Early pre B (common ALL)	2. T cell type	3. B cell type
Percent	75%	20%	<5%
Age	2-5 years	Teenagers	Teenagers
WBCs	Not elevated	Elevated	Elevated
Remote infilterations	Not frequent	Commonly mediastinal mass	Not frequent
Prognosis	Best	Poor	Worst

4- Others e.g Pre B type

Clinical picture

I- Manifestations of hypercatabolic state:

- Anorexia → weight loss.
- Prolonged fever
- Bone aches.

II- Manifestations of bone marrow infilteration:

- Anemia → pallor
- Thrombocytopenia → purpura.
- Neutropenia → persistent infections & prolonged pyrexia.

III- Manifestations of organ infiltration:

1- Generalized lymphadenopathy

2- Hepatosplenomegaly (HSM)

3- Mediastinal mass (common with T ALL).

4- CNS leukemia: may manifest with:

- Raised intracranial tension→ headache, vomiting, coma or
- Focal lesion → fits, paresis,cranial nerve paralysis.

8- Testis → painless swelling.

7- Kidneys → hematuria, renal failure.

5- Bone swellings (subperiosteal hemorrhage or infiltration).

6- Arthritis

Investigations

A. For diagnosis:

1- CBC

- WBCs: → Count may be normal, low or high.
  → Blood smear show blast cells > 2%, but absence of blasts doesn't exclude leukemia.
- RBCs: → Normocytic normochromic anemia.
- Platelets: →Thrombocytopenia

2- B.M. examination

- Light microscopy: Marrow is replaced by > 25% blasts (up to 80-100% blasts) all with malignant features

Blast cells must be subjected to:

1- Cytochemical examination of blast cells show: - Absent peroxidase +ve granules
- Positive PAS (in clumps)

2- Immunophenotyping.

3- Cytogenetic studies.

Blast cells in BM is normally less than **5%** & never detected in peripheral blood

B. To detect infilterations:

- Cerebro spinal fluid examination & CT scan
- Chest X-ray & CT scan.
- Abdominal sonogram
- Renal & liver function tests -electrolytes.
- Bone survey.

Differential diagnosis

1- Infections

1- Typhoid & Brucellosis:
- ✧ Cause prolonged fever
- ✧ Excluded by blood culture & antibody titre

2- Infectious mononucleosis:
- ✧ Cause fever ,organomegaly,purpura
- ✧ Excluded by:no blast cells
  - Monospot test
  - Positive IgM anti EBV

3- Perussis:
- ✧ Cause fever and leukemoid reaction (WBCs count > 50.000/mm^3).
- ✧ Excluded by:
  - No organomegaly
  - WBCs are mature lymphocytes
  - Normal RBCs, platelet & bone marrow

2- Aplastic anemia

- ✧ Cause pallor,purpura,pyrexia (due to infections)
- ✧ Excluded by: no organomegaly and hypocellular bone marrow

3- Causes of purpura: e.g.ITP

✧ Excluded by: - Very good general condition
- Normal Hb &bone marrow

4- Rheumatic fever

✧ Cause fever & arthritis

✧ Excluded by:

- In leukemia joint pain is so severe & profound out of proportion to degree of objective arthritis.
- No hematologic abnormalities

5- Acute myeloid leukemia

- Myeloblasts have: - Peroxidase +ve granules.
- Positive PAS (diffuse reaction).
- Immunophenotyping.

6- Malignancy with bone marrow infilteration: e.g. Neuroblastoma.

Prognosis

	Favorable (low risk)	Unfavorable (high risk)
Initial WBCs count	< 50.000 /mm^3	> 50.000 /mm^3
Age	> 1 yr & < 10 yrs	< 1 yr & > 10 yrs
Sex	Female	Male
FAB	L_1	L_3
Immunophenotyping	Common ALL	B - cell ALL
Cytogenetics	Polypliody	- Hypopliody - Translocations e.g. (t 9; 22) (t 4; 11)
Response to initial therapy	Rapid	Slow
Others		- CNS leukemia. - Large tumor burden. - Mediastinal mass.

Treatment of ALL

A. Supportive:

1. Psychological & nutritional support

2. Control infections by

- Oral hygiene (Mycostatin for candida)
- Intravenous antibiotics according to culture & sensitivity tests.
- In cases with granulocytopenia (neutrophils < 500 cell /mm^3) give:
  - a- Granulocyte colony stimulating factor (G-CSF) Or granulocyte monocyte colony stimulating factor (GM-CSF).
  - b- Granulocyte transfusion
- Pneumocytis carnii prophylaxis with Trimethoprim/Sulphmethoxazole.

3. Control bleeding by

- Avoid IM injections.
- Platelet transfusion if platelets count < 20.000 /mm^3.

4. Control anemia by

- Erythropiotin (subcutaneous).
- Packed red cells if hemoglobin fall below 7 gm/dl.

5. **If blasts > 50.000/mm3** give → Allopurinol
→ Superhydration.
→ Na bicarbonate.
} to guard against tumor lysis syndrome & uric acid overload

B. Specific treatment:

1. Induction of remission

Aim → Eradicate malignant cells in bone marrow (i.e. attain remission).
Duration → 4 weeks
Drugs
- Vincristine 1 mg /m^2 weekly iv.
- Prednisone 60 mg//m^2 daily oral.
- L-Asparganase (9 doses).
- Intrathecal methotrexate & Ara-C.
- Adriamycin weekly added for high risk

Criteria of remission:
* Clinical → No organomegaly nor detectable extramedullary disease
* CBC → Near normal platelets & WBCs.
→ No blast cells in peripheral blood
* BM → Balsts < 5%, none have frank malignant features

2. CNS prophylaxis (CNS therapy)

Aim → Prevent later CNS relapses for cases with lymphoblasts in CSF
Duration → 4 weeks
Drugs
- Intrathecal methotrexate.
- Intensive systemic chemotherapy
- Cranio spinal irradiation

3. Consolidation therapy

- Intensified treatment immediate after remission
- Mainly for high risk patients specially T cell leukemia
- Minimize development of drug cross resistance

4. Maintenance phase

Aim → Maintain remission and avoid relapse
Duration → 2-3 years
Drugs
- Daily 6 mercaptopurine.
- Weekly oral methotrexate.
- Intermittent doses of vincristine & steroids

C. Bone marrow transplantation: Done in the first remission for high risk patients.

Complications

A. Complications of chemotherapy

- Bone marrow depression → pancytopenia.
- Tumor lysis syndrome (hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia) may occur with intial WBCs counts > 50.000 /mm^3.
- Vincristine → neuritis.
- Methotrexate → renal toxicity.
- Adriamycin → Cardiomyopathy.

B. Relapse

Defined by any of the following:

a- Progressive marrow repopulation with > 5% blasts.

or b- More than 25% lymphoblasts in bone marrow & > 2% in peripheral blood.

or c- Leukemic cell infiltration in CNS or testis.

Possible causes:

- Persistence of leukemic cells in hidden sites(CNS,testes)
- Less susceptible cells to chemotherapy due to G0 phase of cell cycle
- Biochemical drug resistance

Decision: - Intensive chemotherapy.
- Local irradiation

C. Late effects: e.g.

- Secondary malignancy specially secondary ANLL
- Gonadal toxicity
- Neurologic disorders

Acute Myloid Leukemia (ANLL)

- More in older children with equal sex incidence.

Risk factors

- Chromosomal anomalies e.g. Down, Fanconi anemia, Bloom syndrome.
- Anti neoplastic drugs.

FAB classification

1- M1 Myeloblasts with **No.** maturation.
2- M2 Myeloblasts with **some** maturation (chloroma is common → proptosis)
3- M3 Pro myelocytic (DIC is common).
4- M4 Myelomonocytic
5- M5 Monocytic (gingival hyperplasia is common)
6- M6 Erythroleukemia.
7- M7 Megakaryocytic

Clinical picture: As ALL (other features may be present in M2, M3 & M5)

Investigation: Bone marrow show myeloblasts which have:
- Peroxidase +ve granules.
- Positive PAS (diffuse reaction).

Treatment

1. Chemotherapy: **DCTER** regimen;
   Dexamethasone + Cytararbine + Thioguanine + Etoposide + Rubidomycin
2- Bone marrow transplantation after successful remission.
3- Other therapies:
   1. High dose Ara C &L Asparginase regimen (Capizzi regimen)
      - Indication: for refractory or recurrent cases
   2. Monoclonal antibody targeted therapy(Gemtuzumab;Myelotarg)
      - Indication: for relapsed AML prior to allogenic stem cell transplantation
   3. *trans* Retinoic acid.Indication: for M3 (induce differentiation of promyelocytes)

Lymphoma

Definition: Malignant tumors of lymph nodes (LN) & extranodal lymphoid tissue.
1- Hodgkin disease(HD): Mainly nodal
2- Non Hodgkin lymphoma(NHL): Mainly extranodal

Hodgkin Disease

Peak age → bimodal 15-30 & > 60 y (rare before 5 years).
Histologic classification:
1- Nodular sclerosing →↑ Fibrosis + ↓ cells.
2- Mixed cellularity →↑ lymphocytes + plasma cells + Reed – Sternberg cells.
3- Lymphocyte predominance →↑ lymphocytes + ↓ Reed – Sternberg cells.
4- Lymphocyte depletion type.

Staging → (Ann – Arbor staging)
Stage **I** : One L.N. group or single extra lymphatic organ.
Stage **II** : > one LN group on one side of the diaphragm.
Stage **III**: As stage II but on both sides of the diaphragm.
Stage **IV**: Wide spread involvement: A- No systemic symptoms.
B- With systemic symptoms.

Clinical picture

1. **Non specific manifestations**
   - Intermittent fever (Pel Ebstein fever).
   - Night sweating.
   - Anorexia → weight loss.
2. **Lymphadenopathy**

Sites	Criteria	Effects
- Cervical	- variable size	- Mediastinal syndrome: cough, dyspnea, dysphagia, face oedema
- Supraclavicular	- Painless	
- Mediastinal	- Rubbry	- Mesentric: - Abdominal mass.
- Mesentric	- Discrete	- may be intestinal obstruction

3. **Extra nodal manifestation** (rare)
   - Hepatosplenomegaly.
   - Bone marrow failure.
   - Spinal cord compression.

Diagnosis: lymph node biopsy and histologic examination.

Treatment

Radiotherapy (3500 – 4000 Rad).
Chemotherapy:
- ABVD = Adriamycin + Bleomycin + Vinblastine + Decarbazine
- MOPP = Mechlorethamine + Oncovin + Procarbazine + Prednisone

Prognosis: 90% achieve initial remission (more in stages I & II).

Non Hodgkin Lymphoma

Classification

A. Histologic	B. Immunolgic
- Lymphoblastic type (usually of T cell origin). - Large cell type. - Small non cleaved cell type: Burkitt and non Burkitt types.	- T. Cell - B. Cell - Non B, Non T.

Incidence

- 3 times common than Hodgkin
- Peak age=5-15 y
- ♂:♀ ratio = 3:1

Clinical picture

i- Abdominal lymphoma (35%)

- Mainly B cell type.
- Start in appendix, ileocaecal region **or** ascending colon.
- Presentation:
  1- Rapidly enlarging Abdominal mass with abdominal pain and vomiting.
  2- May be: - Ascites.
  - Intussusception.
  - Hepatosplenomegaly.
  - Obstructive jaundice.

ii- Anterior mediastinal mass: (25%)

- Mainly T. cell type.
- Presentation:
  1- Mediastinal syndrome (cough, dyspnea, dysphagia, face oedema).
  2-- May be: - Pleural effusion.
  - Pericardial effusion.

iii- Others

- Lymphadenopathy in head & neck (15%).
- Bone marrow infiltration→ pancytopenia (occur in advanced lymphoma).
- Bone pain.
- CNS infiltration →↑ ICT **or** focal signs.

Diagnosis

- Biopsy & immunophenotyping & cytogenitic studies.
- Cytologic examination of ascitic fluid, pleural fluid, B.M.

N.B.: Burkitt lymphoma

Nature: B-cell type.
Histology: Starry sky appearance.
Cytogenetics: May be (t 8; 14).

Types	Endemic	Sporadic
Distribution	African	World wide
Age	Children	Young adults
Site	Jaw, Ovary	Abdomen, Marrow
Association with Ebstein Barr virus	In > 97%.	In < 30%.

Treatment

1. Supportive ;specially for life threatening complications:

Complication	Action
1. Superior vena cava syndrome or upper airway obstruction by mediastinal mass(often with lymphoblastic lymphoma)	Corticosteriods with or without limited radiation field
2. Tumor lysis syndrome ; often with Burkitt lymphoma	- Allopurinol - Superhydration. - Na bicarbonate

2. Surgery: Only for *small,easily,totally* resectable tumors e.g.localized bowel disease

3. Chemotherapy : Protocols differs according to :

- Staging(localized or advanced)
- Immunophenotyping

e.g. High dose methotrexate(2-3 gm/m^2) I.V along with folonic acid in advanced cases

Wilms' Tumor

(Nephroblastoma)

Incidence

- 2nd common abodmianl tumor
- 4th most common childhood malignancy in USA.
- Age: usually occurs in children < 5 ys .
- Sex: both are affected(♂ : ♀ = 1:1)

Types

1. Sporadic form (common)

- Majority of cases.
- Usually unilateral.
- Median age: 39 months

2. Familial form Rare (10%)

- Usually bilateral.
- Tumor suppressor genes are identified.
- Median age :26 months

3. Associations:

A. Congenital anomalies:

- Congenital aniridia .
- Hemihypertrophy.
- Genito-urinary anomalies (Hypospadius, cryptorchidism).

B. Syndromes:

- WAGR syndrome : Wilms', aniridia, genito-urinary anomalies, mental retardation.
- Denys-Drash syndrome :Wilms'tumor, renal disease, pseudo hermaphroditism.
- Beckwith Wiedemann syndrome .

Pathology

Variable proportions of three cell types in form of cellular , supporting stroma & epithelial tubules .

Clinical picture

1. Abdominal mass (the most common presentation):

- Asymptomatic: discovered accidentally .
- Abdominal mass:
  - Firm, smooth surface, asymmetrical.
  - Never cross midline (enlarged vertically)
  - Bilateral in 5-10%
- Association: Microscopic hematuria.

2. Hypertension :

Due to: -Renin-producing tumor.

- Renal ischemia by compression .

3. Others:

- Polycythemia: occasional .
- Metastasis:
  - Lungs (commonest) → cannon-ball lesions.
  - Others: Liver, lymph nodes, brain .

Investigations

i. Detect the tumor:

1. Abdominal ultrasonography.
2. Abdominal CT:
   - Exclude neuroblastoma.
   - Evaluate contralateral kidney.
   - Evaluate metastasis.
3. Biopsy.

ii- Detect metastasis: as for leukemia.

Staging: Based on operative findings

Stage	Tumor extent
I	Limited to kidney & is completely excised
II	Extends beyond the kidney but is completely excised
III	Non-hematogenous spread with residual abdominal extension (LN, vital structures, peritoneal surface).
IV	Hematogenous spread to lungs, liver, bone,…
V	Bilateral renal involvement at time of diagnosis

Differential diagnosis: Causes of abdominal mass

1. Neuroblastoma.
2. Hydronephrosis.
3. Renal cyst.
4. Others: Hypernephroma, Clear cell sarcoma, mesoblastic nephroma

Treatment

1. Surgical: Radical nephrectomy

2. Chemotherapy:

☆ Combination of: - Actinomycin D.
- Doxorubicin.
- Vincristine.

☆ Used for 18 – 24 wks.

3. Radiotherapy: Used according to stage & histology

Neuroblastoma

- It is a malignant tumor originating from neural crest cells that give rise to adrenal gland & sympathetic ganglia.

Characters

1. Occurs early in life (infancy).
2. Multiple clinical presentations.
3. Highly malignant.
4. Highly metastasizing (70% presented in stage IV).
5. High spontaneous resolution.
6. Prognosis depends on age not stage.

Incidence

-It accounts 8-10% of all childhood malignancies.

- Age: Children < 3ys (commonest malignancy in 1st year of life & may occur in fetal life → maternal hypertension & sweating).

Pathology

♦Site: The tumor originate from any site of sympathetic nervous system

1. Adrenal medulla (35%).
2. Sympathetic chain: - Abdomen 35%.
   - Thoracic 25%.
   - Cervical 5%.

♦Microscopic: The tumor consists of Primitive neuroblastoma cells (→ rosette shaped cells)& ganglion cells

Staging

Stage	
I	- The tumor is confined to site of origin with complete excision.
II	- The tumor extend beyond site of origin but not cross midline
III	- Unresectable unilateral tumor crossing midline with or without regional lymph node. - Localized tumor with contralateral regional lymph node involvement.
IV	- Remote disease .
IVs	- Stage I or II + involvement of skin, liver and/or BM .

Clinical picture

1. Abdominal mass (commonest)

♦Origin → adrenal medulla or abdominal sympathetic chain.

♦Mass: Hard with irregular surface, located in upper quadrant of abdomen & may cross midline as it enlarges horizontally.

2. Mediastinal or cervival mass

♦Origin: Thoracic or cervical sympathetic chain.

♦Manifestations:

i. Dyspnea & SVC obstruction (→ congested face , dilated veins)

ii. Horner syndrome (unilateral ptosis, enophthalmos, meiosis & anhydrosis).

3. Spinal cord compression

- ♦Origin → sympathetic chain.
- ♦Manifestations:
  - Localized back pain and tenderness (most common & early feature)
  - Paraparesis or paraplegia.
  - Sphincteric dysfunction.

4. Metastatic neuroblastoma

- ♦BM (70%) → pancytopenia.
- ♦Bone → Bone pains, limping or refusal to walk.
  → Skull bones → mouth eaten appearance in dipolic space.
- ♦Liver → huge hepatomegaly.
- ♦Orbit→ Proptosis (unilateral or bilateral) with ecchymotic discoloration of upper & lower eye lids → *Raccoon like appearance.*
- ♦Skin → multiple firm purple skin nodules (blue-berry muffin lesions).

5. Para-neoplastic syndromes

i- Excessive catecholamines secretion :

- Intermittent attacks of sweating, palpitation, hypertension , flushing, polyuria & polydipsia .

ii- VIP secretion : (Kerner -Morison syndrome)

- Intractable watery diarrhea ,abdominal distension and hypokalemia

iii- Acute myoclonic encephalopathy syndrome (dancing eyes syndrome):

- Consist of Opsclonus and Myoclonus.
- Opsclonus:bursts of rapid involuntary eye movements in all directions
- Treatment: - Dexamethazone& high dose IVIG.
  - Chemotherapy for the neuroblastoma

Diagnosis

1. Detect origin of 1^{ry} site (adrenal, sympathetic chain)
   - Abdominal ultrasonography & CT.
   - Chest x ray & CT.
   - Myelography or MRI spine.
   - Biopsy (if histopathology is equivocal → cytogenetics)
   - MIBG (meta-iodo benzyl guanidine) scan
2. Screening for urinary catecholamines: -Vallinyl mandelic acid & Homovanillic acid

Treatment

Vary according to age ,cytogenetics and stage

1. Supportive care
2. Surgery
3. Combination chemotherapy(platinum based)
4. Irradiation
5. BMT

Gastro enterology And Hepatology

Causes of Vomiting

i- Acute vomiting

Acute infections	Metabolic	Acute intestinal obstruction
- CNS infections - Labrinthitis - Pulmonary infections - Sepsis - Gastroenteritis - Acute pancreatitis - Acute pyelonephritis	- Intoxication - Rye's syndrome - Diabetic keto acidosis - Renal failure - Adrenal failure - drugs: chemotherapy , erythromycin,..	* Functional: Paralytic ileus * Organic: - Intussusception - Volvulous

ii- Chronic vomiting

- Over feeding - Cow milk intolerance - Celiac disease - Castro-Esophageal reflux - Peptic ulcers. - Congenital pyloric stenosis	- Chronic renal failure - Inborn errors of metabolism - Metabolic acidosis - Psychogenic

Causes of Abdominal pain

i- Acute abdominal pain

Acute infections	Acute medical conditions	Acute intestinal obstruction
- Strept. Pharyngitis (mesenteric adenitis) - Acute hepatitis. - Acute pancreatitis - Acute pyelonephritis - Acute appendicitis. - Acute peritonitis.	- Intoxications - Pneumonia - Rheumatic fever - Henoch schonlein purpura. - Familial mediterranean fever. - Diabetic keto acidosis - Porphyria	

ii- Chronic (recurrent) abdominal pain

- Irritable bowel syndrome - School phobia - Angioedema - Abdominal migraine - Chronic lead poisoning	- Chronic hepatitis - Intestinal parasites e.g. Giardiasis - Chronic diarrhea (and malabosorption) - Stones (urinary, biliary) - Chronic constipation - Inflammatory bowel disease

The following might suggest an organic origin of abdominal pain:

1. Pain awakens the child at night
2. Pain localized away from the umbilicus
3. Nonintestinal symptoms, e.g. rash, fever, joint pain, dysuria
4. Blood in stools (guaiac-positive)
5. Pain associated with change in bowel habits, particularly diarrhea, constipation, or nocturnal bowel movements
6. Perirectal abnormalities, e.g. fissure, ulceration
7. Anemia / Elevated erythrocyte sedimentation rate (ESR)
8. Weight loss or growth deceleration

Gastro- Esophageal Reflux Disease

(GERD),(Chalasia)

Definition: Abnormal retrograde of gastric contents into oesphagus due to persistent relaxation of lower oesphageal sphincter (LES).

Incidence: - Mainly in neonates & young infants
- 60% improve with age (resolve by 6 mo-2years).

Clinical picture

A. Uncomplicated cases

1- Vomiting:
- At the end of the feed.
- From the 1st week of life.
- Increase with lying flat
- May be bile stained.

2- Sandifer syndrome: abnormal head posture and opisthotonus in attempt to protect airways.

3- Substernal pain and dysphagia in older child

B. Complicated cases

1- Oesphagitis → GIT bleeding

2- Recurrent aspirations → recurrent aspiration pneumonia in 30% of cases.

3- Chronic cough & chest wheezes.

4- Growth retardation

5- May be laryngospasm and apnea

6- May be sudden infant death syndrome.

Investigations

1- Diagnostic:
- Radiologic → barium swallow under screen → retrograde of the dye
- Endoscopic → low LES pressure by manometry **and** low pH (< 4).

2- For complications → detect occult blood in stool

Treatment

Medical:
- Feeding → solids or thick formula.
- Position → upright for 30 min after feeding.
- Drugs → domperidone **or** metoclopramide.
- Avoid methylexanthines → it lowers LES tone

Surgical:

Operation: - Fundo plication.

Indications: - Failed medical treatment.
- Complications.
- Growth retardation.

Congenital Hypertrophic Pyloric Stenosis

Definition: Progressive hypertrophy of circular muscles fibers of the pylorus with subsequent pyloric narrowing and gastric outflow obstruction.

Clinical picture

Incidence: - Males (especially first born) affected than females.
- Positive family history may exist.

Symptoms

1- Vomiting:
- Occur short after feeding.
- Usually start between the 2nd – 6th weeks of life (Rarely before or after)
- Initially non projectile then projectile
- Non bile stained.
- Baby is hungery after vomiting.

2- Constipation.

3- Indirect hyperbilirubenmia in 5% of newborns may be due to decreased glucoronyle transferase enzyme activity & increased enterohepatic circulation.

Examination

1- Baby is marasmic & dehydrated.

2- Visible peristalsis from the left to the right.

3- Palpaple mass (olive mass) in the right hypochondrium; mobile & non tender.

4- Progressive vomiting result in metabolic alkalosis

Investigations

1- **For diagnosis**

i- Barium meal: May show
- Elongated narrow pyloric canal
- Bulge of pyloric muscle into antrum (shoulder sign).
- Parallel streaks of barium (double tract sign).

ii- Abdominal ultrasound: Confirm diagnosis & can diagnose early cases.

2- **For complications**

* Hypochloremic metabolic alkalosis (↑pH, ↓CL)
* Hyponatremia & hypokalemia

Differential Diagnosis: From causes of vomiting in neonates and early infancy e.g. GERD, inborn errors of metabolism, adrenal insufficiency, pyloric membrane.

Treatment

1- **Surgical:** Ramstedt's pyloromyotomy.
- Pre operative → correct electrolytes disturbance and dehydration.
- Post operative → start small feeds → gradually increasing.

2- **Medical:** Not efficient, includes.
- Antispasmodic before feeds.
- Small, thick, frequent feeds.

Congenital Aganglionic Megacolon

(Hirschsprung Disease)

Definition

- Functional obstruction of the colon due to absence of ganglion cells in bowel wall starting from anus for variable length proximally.
- Aganglionic segment is limited to rectosegmoid in 75% & involve entire colon in 10%.

Incidence: - 1 / 5000
- Male: Females = 4 : 1 (positive family history may be present).

Clinical picture

1- Presentation may be:

Neonatal (80%): - Delayed passage of meconium beyond 48 hours.
- May be acute obstruction.

In older child: - Chronic constipation and abdominal distension.
- Large fecal mass felt in left lower abdomen with empty rectum

2- Complicated cases:

- Enterocolitis: - Infection with clostridia difficile, staph aureus and anaerobes.
  - Presented with bloody diarrhea & toxemia.
- Intermittent attacks of intestinal obstruction.
- Failure to thrive due to protein losing enteropathy.

Investigations

1- Anorectal manometry :

- Normally rectal distension result in reflex decline of internal anal sphincter pressure.
- In Hirschsprung disease, distending the rectum fail to drop the pressure at the internal anal sphincter.

2- Rectal suction biopsy (from narrow segment) reveal absent ganglia.

3- Barium enema:

- Narrow aganglionic segment (funnel shaped).
- Distended proximal colon.

Treatment

1- Surgical repair.

2- Preparation before surgery:

- Regular evacuation of rectum.
- Antibiotics.

Q Causes of constipation ?

- Hypothriodism
- Spina bifida
- Dehydration
- Psychomotor retardation
- Medications(narcotics)

Achalazia

Definition

Achalzia is esophageal motility disorder characterized by:

- ✧ Incomplete relaxation of lower esophageal sphincter
- ✧ Lack of primary or secondary esophageal propulsive peristaltic waves
- ✧ Increased lower esophageal sphincter pressure
- ✧ Number of ganglion cells in esophagus may be reduced
- ✧ Incidence in children < 5 years is 5 %.

Clinical picture

1. Difficult swallowing
2. Regurgitation of food
3. Cough due to overflow of fluids into trachea (frequent aspiration).
4. Failure to gain weight
5. Recurrent chest infections

Diagnosis

1. Upright chest x ray show air fluid level in dilated esophagus
2. Barium swallow show massive dilatation of the esophagus at the gastric end (peaking)
3. Esophageal manometry is diagnostic

Treatment

- Can be relieved by intra sphincteric injection of botulism toxin (for 6 months)
- Nifedipine improve emptying
- Heller myotomy: surgical division of muscles at gastroesophgeal junction induce permanent relief

Hepatology

Functions of the liver

1- Synthesis of all proteins (except gamma globulin and F VIII)
2- Synthesis and excretion of Bile.
3- Synthesis and excretion of cholestrol.
4- Carbohydrate: - Post prandial → convert glucose to glycogen.
- Fasting → convert glycogen to glucose.
5- Detoxication e.g. convert ammonia to urea.

N.B. Hepatic enzymes:

❶ Intra cellular; (Markedly raised in hepatitis):
- Alanine aminotransferase (ALT); more specific to the liver.
- Aspartate aminotransferase (AST).

❷ Intra canalicular → Alkaline phosphatase, Gamma glutamyle transferase, 5 Nucleotidase ⇒ markedly raised in cholestaisis.

Hepatitis

Causes

Metabolic
With some inborn errors of metabolism e.g.
1- Glactosemia
2- Wilson disease
3- α1 antitrypsin deficiency.
4- Tyrosinemia.

Toxic
- Drug e.g.: - INH, rifampicin
- Paracetamol overdose
- Toxins e.g.: Mush-Room.

Infections

Bacterial ⇓
- Septicaemia
- Enteric fever
- Brucellosis

Protozoa ⇓
- Malaria
- Toxoplasma

Parasitic ⇓
- Bilharsiasis
- Hydatid cyst.

Viral

Hepatotropic
Viruses attack the liver mainly

Enteral transmitted ⇓
- Hepatitis A virus (HAV)
- Hepatitis E virus (HEV)

Parentral transmitted ⇓
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)

Non hepatotropic
Viruses may cause hepatitis during its course
e.g.
- CMV
- Herpes viruses
- EBV
- Rubella

Acute Viral Hepatitis

1- Enteral viruses ⇒ Hepatitis A & E viruses

Criteria:

- Execreted only in stool (not in body fluids) so infection occur by faeco-oral route via contaminated water & food.
- Non enveloped RNA viruses.
- Incubation period is short (4 weeks).
- Infectivity: During incubation period & 1st week of jaundice.
- Epidemiology:-
  - Occur in epidemics or sporadic.
  - Mainly in low socioeconomics.
  - HAV is the commonest cause of acute viral hepatitis especially in school age.
  - HEV is rare in children.
- Outcome: - Complete recovery is the rule; no carrier state nor chronic hepatitis.
  - Fulminant hepatic failure may rarely occur.
  - HEV has high fatality in pregnant women.

2- Parenteral viruses ⇒ Hepatitis B, C & D viruses

Criteria

	HBV	HCV	HDV (Delta virus)
Nature	Enveloped DNA virus.	Non enveloped RNA virus.	Non enveloped RNA virus → need HBV coat to be infective (defective virus; dependent on HBs Ag).
Route	- Parenteral - Contaminated blood products. - Perinatal. - Sexual.	As HBV, (mainly post transfusion).	As HBV.
Incubation period	2-6 months	1-4 months	1-4 months
Epidmiology	- Occur sporadic **not** in epidemics. - High risk groups → chronic blood products receivers → hemodialysis patients → drug abusers.		
Outcome	Complications may occur: 1- Carrier state 2- Chronic hepatitis (20% in HBV, 50% in HCV) may be complicated with: - Cirrhosis & liver cell failure. - Hepatocellular Carcinoma 3- Fulminant hepatic failure (FHF) → may occur in 1-3% of cases.		

Pathology : Hepatocyte injury can be due to:

- Cytopathic effects (by all viruses except HBV).
- Immune mediated cell lysis (by HBV & HCV)

Clinical picture of acute hepatitis

1- Many cases of viral hepatitis pass asymptomatic.

2- Symptomatic cases pass in following phases:

I- **Pre-icteric phase** (2 – 4 weeks)

- Fever, malaise
- Anorexia, nausea, vomiting.
- Abdominal pain.

II- **Icteric phase** (2-4 weeks)

- Improved previous symptoms with appearance of:
  - Jaundice
  - Tender hepatomegaly.
  - Dark urine + pale stool
- Splenomegaly & lymphadenopathy are common with HBV.

III- **Convalescent phase:**

- Complete resolution (especially in HAV & HEV)
- Other types (HBV,HCV, HDV) may pass into chronic hepatitis or carrier state

Complications: As before plus:

i- **Extrahepatic manifestations:** due to circulating immune complexes; mainly in HBV & HCV:

Common presentations:

- Arthralgia
- Aplastic anemia

Rare presentation:

- Myocarditis
- Acute pancreatitis
- Glomerulonephritis.
- Vasculitis.

ii- **Fulminant hepatic failure:**

Incidence:

- Common with HBV especially if there's co-infection or superinfection with HDV
- Uncommon with HCV.
- Very rare with HAV.

Clinically:

- Deep progressive jaundice
- Bleeding tendency (↓ coagulation factors).
- Generalized oedema with ascites.
- Disturbed sleep rhythm, astrixis., stupor & coma.

Fate:

- Mortality rate about 30%
- Definitive treatment is liver transplantation.

Investigations

I- To prove acute hepatitis:

1- Liver function tests:

- ALT & AST → very high.
- Serum bilirubin → moderate ↑↑ (mainly conjugated).
- Alkaline phosphatase → mild↑.
- Albumin → usually normal.

2- Urine: - Dark color due to ↑ cholebilirubin

3- Stool: - Pale color due to ↓ stercobilinogen.

In fulminant hepatitis:

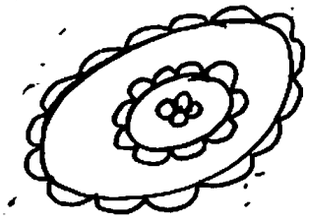
- ALT & AST rise initially then decline.
- Rising bilirubin.
- Prolonged prothrombin time.
- Low albumin.
- Hypoglycemia & hyperammonemia.

II- For the cause → viral serology:

1- HAV markers

Marker	Significance
Anti – HAV (IgM)	Recent HAV infection.
Anti – HAV (IgG)	Previous HAV infection or HAV vaccination.

2- HBV markers



HBs Ag (surface antigen)
Hbe Ag (envelope antigen)
HBc Ag (core antigen)

Marker	Significance
HBs Ag	- Acute infection. - If persist > 6 months → indicate chronic hepatitis
Hbe Ag	- Acute infection (high infectivity).
IgM anti HBc – Ag IgG anti HBc – Ag	- Acute infection (reliable single marker) - Infection acute or chronic
Anit HBs – Ag	- If present alone, it indicate previous vaccination. - If present with anti-HBc Ag → resolved infections.

N.B. HBc – Ag is present only in hepatocytes.

Hbe – Ag is not structural antigen but it is produced by self-cleavage of core antigen.

3- For HCV, HDV, HEV infection

- Detect specific RNA by PCR.
- Detect specific antibodies.

Prevention

1- For enteral viruses (A & E) :
- Food & water hygiene
- Isolation of hepatitis A patients till one week after clinical jaundice.
- Insist on hand washing after defecation or dealing with infected child
- Sterilization of toilet after use.

2- For parentral viruses (B, C, D) ⇒ Blood donation screening

3- HAV immunization:
- Passive: HAV immunoglobulin given for contacts within 2 weeks of exposure.
- Active: HAV vaccine (Havrix):
  - Nature: Inactivated
  - Time: Above 2 years.
  - Dose: 2 doses 6 months apart, IM.

4- HBV immunization:
- Passive ⇒ HBV immunoglobulin given either
  - Infant born to HB sAg + ve mothers 0.5 ml IM, within 12 hr after birth with the first dose of HBV vaccine (which given as 0, 1, 6).
  - Post exposure → 0.06 ml/kg within 24 hrs
- Active ⇒ HBV vaccine:
  - Nature: Recombinant DNA vaccine.
  - Time: 3 doses, IM at 2, 4, 6 months

Treatment of Acute Hepatitis

1- Supportive → bed rest + high carbohydrate diet + multivitamins.
→ Avoid hepatotoxic drugs

2- Treatment of complications.

Chronic Hepatitis

Definition: an inflammatory process of the liver lasting longer than **6** months.

Recently → continuing hepatic inflammatory process manifested with severe liver disease **or** features of chronicity (shorter time can be employed)

Chronic persistent hepatitis	Chronic active hepatitis
Causes Viral → HBV, HCV	1- Auto immune → the commonest; may be due to imbalance between CD_4-CD_8 T lymphocytes 2- Viral → HBV, HCV, Delta virus. 3- Metabolic → e.g. Wilson disease.
Pathology - Inflammation limited to the portal zone - Little or no fibrosis. - No cirrhosis.	- Erosions of the limiting plate. - Piecemeal necrosis of hepatocytes. - If severe → birdging necrosis → fibrous septa
Clinical picture - Asymptomatic - May be non specific: malaise, anorexia - May be tender hepatomegaly.	1- Most cases have: - Hepatosplenomegaly (HSM) - Liver cell failure (LCF) 2- In auto immune; type there may be also: - Iridocyclitis - Thyroiditis - Vasculitis → nephritis - Serositis → arthritis , pleurisy - Immune hemolytic anemia - Clubbing
Complications Very uncommon	Common:-Cirrhosis→ portal hypertension -Fulminant hepatic failure.
Investigations 1- Is it hepatitis? **Yes.** - ALT & AST → mild increase. - Bilirubin → No or slight increase. 2- Is there liver decompansation? **No** - Albumin → Normal. - Prothrombine time → normal. 3- What is the cause? - HBV & HCV markers.	**Yes** → High (Usually < 1000 iu/L) → High. (2-10 mg/dl – mainly direct). **Yes** → Low → Prolonged 1- Viral markers. 2- For auto immunity: - Anit nuclear antibody (ANA). - Anti – smooth muscle antibody. - Anti liver kidney microsomal antibody - Anti soluble liver antigen antibody.
- Liver biopsy → diagnostic	

Treatment

i- Supportive as in acute hepatitis

ii- Follow up → clinical (for signs of decompensation) and laboratory.

iii- Specific:

1- Auto immune hepatitis :

- Steroids 1-2 mg / kg /day till ALT & AST less than twice high normal then taper slowly over 4-6 weeks to reach maintenance dose of 0.2 – 0.3 mg/kg/day
- If steroids were poorly effective or have side effects → Azathioprine is added in a dose of 1-5 mg/kg/day.

2- Post viral → Interferon α for HBV & HCV.

3- Cirrhosis & fulminant hepatic failure → liver transplant.

Reye's syndrome

Definition : Acute encephalopathy with fatty degeneration of the liver.

Clinical picture

1. Occur in previously healthy child
2. Association: Asprin treatment & viral infection
3. Prodromal viral URTI in 90 % of cases or chicken pox infection in 6 %.
4. Severe profound vomiting 5-7 days following viral infection
5. Hepatomegaly without jaundice.
6. Evidence of increased ICT : - Delirium and stupor
   - Generalized fits → coma→ may be death
   - CSF is normal but with raised pressure..

Diagnosis

1- Liver function tests → impaired + ↑↑ ammonia & hypoglycemia.

2- CT brain → brain oedema.

3- Liver biopsy → diagnostic:

- Light microscopy: Microvesicular fatty infilteration.
- Electron microscopy: Mitochondrial damage.

Treatment: Supportive (liver support & care of coma).

Wilson diseases

AR defect in ceruloplasmin (Copper carrying protein) → Copper accumulate in:

- Liver → Hepatitis and cirrhosis
- Basal ganglia → Behavior & speech disorder
- Cornea → Kayser Flisher ring
- Renal tubules → Tubular defects (Fanconi like).
- Red blood cells → Hemolytic anemia

Diagnostic triad: - ↓ Serum ceruloplasmin
- ↑ Urinary copper after loading dose of D-penicillamine
- Liver biopsy → excess copper deposition.

Treatment : - D-penicillamine (Copper chelating agent).
- Liver transplant

Liver Cirrhosis

Definition: Chronic liver disease with triad of:
- Hepatocytes necrosis.
- Regeneration nodules.
- Lost hepatic architecture.

Causes:
- Post hepatitic.
- Metabolic: e.g. Wilson & hemochromatosis.
- Biliary: 1ry or 2ry to bile flow obstruction.
- Chronic hepatic congestion: cardiac cirrhosis.

Clinical picture

1- Compansated : Clinical picture of the cause.

2- Decompansated: Features of liver cell failure

1- Jaundice.

2- Bleeding tendency: - Skin bruises.
- GIT bleeding → Hematemesis & melena.

3- Ascites & generalized edema.

4- Hepatic encephalopathy:
- Due to increased ammonia and neurotoxins (false neurotransmitters).
- Manifested by: Disturbed sleep rhythm, flapping tremor, coma.

5- Hepato-renal syndrome: Functional renal failure in patients with end stage liver disease due to intense renal vasoconstriction with systemic vasodilatation → renal hypoperfusion→ pre renal failure

6- Hepato pulmonary syndrome: - Intrapulmonary vascular dilatation → right to left shunting of blood → hypoxemia, dyspnea, cyanosis & clubbing.

7- Others:
- Feotor hepaticus.
- Palmar erythema.
- Spider nevi.
- Muscle wasting.

Diagnosis

1- To prove cirrhosis: - Abdominal ultrasound & MRI.
- Liver Biopsy → diagnostic (but avoided in decompansated)

2- For the cause: e.g. viral markers.

3- For complications:
- Liver functions tests → bilirubin, prothrombin time, albumin.
- Portal hypertension → **see later.**

Treatment

1- Supportive → Carbohydrates and vitamins rich diet
→ Low salt diet (for cases with edema)
→ Limit protein (for cases prone to encephalopathy)

2- Antifibrotic: Colchicine.

3- Treatment of complications.

4- Liver transplant.

Portal Hypertension

Definition: ↑ portal vein pressure > 10 mmHg (normal about 7 mmHg) due to extrahepatic or intrahepatic obstruction to flow of portal blood.

Causes

i. Extrahepatic portal hypertension:

1- Portal vein or splenic vein thrombosis due to:
- Umbilical infection with or without catheterization.
- Neonatal sepsis & dehydration.
- Hypercoagulable states e.g. protein S & protein C deficiency.
- Intra abdominal infections e.g. peritonitis.

2- Increased portal flow due to arterio venous fistula.

ii. Intrahepatic portal hypertension:

1- Pre sinusiodal:
- Chronic hepatitis.
- Congenital hepatic fibrosis.
- Schistosomiasis.
- Portal tract infiltrations.

2- Sinusiodal:
- Cirrhosis (the commonest cause).

3- Post sinusoidal:
- Venooculsive disease.
- Budd-Chiari syndrome.

Clinical picture

1- Splenomegaly

2- Ascites

3- Opened collaterals:
- Oesphageal varices → heamatemesis & melena.
- Caput medusae
- Heamorrhoids

4- Liver is:
- Shrunken in cirrhosis.
- Enlarged tender in post sinusoidal causes
- Normal clinically and biochemically in extrahepatic portal hypertesion.

Investigations

1- Abdominal ultrasound → for liver, spleen, ascites.

2- Measure portal vein pressure by ultrasound Doppler.

3- Search for the cause.

Treatment

i- Emergency treatment (Control bleeding osphageal varices):

1- Take blood sample for investigation & ask for blood.

2- Fresh blood transfusion.

3- Correct coagulopathy by:
- Vitamin K I.V.
- Fresh frozen plasma.

4- Place nasogastric tube → to monitor ongoing bleeding.

5- H_2 receptor blocker (I.V. Ranitidine) → avoid stress ulcers.
6- Vasopression or somatostatin analog (Octreotide) I.V infusion → ↓ splanchnic flow.
7- Sengstaken – Blackmore tube → compress osphageal & gastric varices.
8- Endoscopic sclerotherapy with ethanolamine or band ligation of varices.

ii- Prophylactic (Prevent subsequent bleeding):
1- Propranolol 0.5 – 4 mg/kg/day → ↓ portal pressure.
2- Porto-systemic Shunt operation.
3- Trans jugular intrahepatic porto systemic shunt (TIPS).

iii- Orthotopic liver transplantation for cases with intrahepatic portal hypertension.

Ascites

Definition.: Accumulation of fluid in peritoneal cavity.

Transudate	Exudate	Bloody	Chylous
- Clear - ↓proteins (<3gm/dl) - ↓ Cells - ↓Specific gravity. - No organisms.	- Turbid - > 3 gm / dl - ↑ cells (PMNL) - ↑ (> 1018) - may be organisms.	Bloody with RBCs on mic. ex.	Milky white
Causes: 1 - Renal e.g.: - nephrotic syndrome 2 - Cardiac e.g.: - Heart failure - Constrictive pericarditis. 3 - Hepatic e.g.: - Liver cell failure. - Cirrhosis with portal hypertension. - Budd chiarri.syndrome. - Veno occlusive disease.	- Septic peritonitis - T.B. peritonitis - Non microbial: • systemic lupus • Metastasis • B-cell lymphoma	- Trauma - Tumors - Bleeding disorders - Acute hemorrhagic pancreatitis	Rupture thoracic duct due to trauma. Or obstruction.

Other causes: Bilious, urinary

Diagnosis

1-Ascites or not?

Inspection
- ↑ Abdominal girth.
- Full flanks
- Umbilical protrusion

Percussion
- Massive (tense) → transmitted thrills.
- Moderate → bilateral shifting dullness.
- Mild → percussion in knee-chest position.

2- For the cause

Organ functions + Paracentesis & analysis

Deferential diagnosis: of ascites (fluid)
- Flatulance (gases) e.g. intestinal obst.
- Full bladder.
- Foreign body (cysts or tumors)

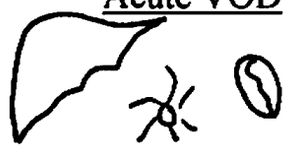
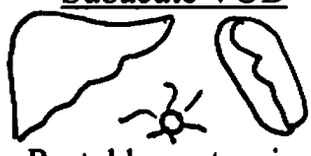
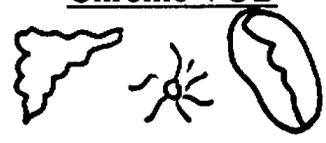
Treatment of ascites: Depends on the underlying cause e.g.:

Treatment of hepatic ascites:

1- Liver support (vitamins, avoids hepato toxic drugs, high carbohydrate diet).
2- Low salt and protein diet.
3- Diuretic: Aldactone.
4- Albumin or plasma infusion.
5- Therapeutic paracentesis provided:
   - Tense ascites.
   - Prothrombin concentration > 40%.
   - Bilirubin < 10 mg/dl.
   - Platelets > 40.000/mm^3.
   - Creatinine < 3 mg/dl.
   - Aspirated volume not more than 20ml/kg/setting.

Veno Occlusive Disease
(VOD)

Definition : Intrahepatic obstruction of hepatic veins.
Causes : Unknown, may be toxic injury by herbal teas or drugs.
Clinical picture

Acute VOD	Subacute VOD	Chronic VOD
		
- Portal hypertension - Hepatomegaly. - No splenomegaly.	- Portal hypertension - Hepatomegaly - Splenomegaly	- Portal hypertension - Cirrhotic liver - Huge Splenomegaly

Diagnosis

1- As for portal hypertension .
2- Liver biopsy → diagnostic.

Treatment: Supportive.

Budd Chiari Syndrome

Definition.: obstruction of the main hepatic veins.
Causes : 1ry or 2ry to polycythaemia, trauma, **or** hypercoagulable states.

Clinical picture

Acute stage	Chronic stage.
- Acute hepatomegaly - Acute abdominal pain & vomiting. - Acute ascites	- Hepatomegaly. - Portal hypertension.

Gastrointestinal Bleeding

Causes

- **Upper GIT bleeding:**

  Bleeding from above the ligament of Treitz:

  a. Eosphageal:
  - GERD
  - Varices
  - Tumors.

  b. Gastric ulcers.

  c. Duodenal ulcers.

- **Lower GIT bleeding:**

  Bleeding below the ligament of Treitz:
  - Inflammatory bowel disease.
  - Intestinal obstruction (intussusception & volvulous)
  - Meckles diverticulum.
  - Gastroenteritis.
  - Anal fissure.

- **Hemorrhagic blood disease:**

  Result in either upper or lower GIT bleeding e.g.
  - Hemophelias.
  - Purpura
  - DIC.

Common causes according to age:

Infant	Child	Adolescent
←	• Bacterial enteritis	→
	• Anal fissure • Intussusception	• Inflammatory bowel diseases
• Protein milk allergy • Swallowed maternal Blood.	• Colonic polyps • Peptic ulcer & gastritis • Mallory Weiss syndrome	

Management

1- Emergency treatment as **(see bleeding esophageal varcies).**

2- Search **for the cause:**

a- History of:
- Bleeding disorder.
- Liver disease.
- Gastroenteritis.
- Pattern of bleeding (melena or fresh blood)

b- Examination:

- Skin for → Signs of chronic liver disease.
  → Signs of coagulopathy (e.g. purpura & Bruises).
- Abdominal → Hepatosplenomegaly (in chronic liver disease & leukemia)
  → Distension (intestinal obstruction)
- P/R examination → For perianal ulcers & polyps.

c- Investigations:

- Rule out hemorrhagic blood diseases by → CBC.
  → Coagulation profile.
  → Liver function tests.
- Abdominal X-ray and ultrasound → for obstructions & organomegaly.
- Stool analysis → For gastro enteritis & enterocolitis.
- Endoscopy → for varices, ulcers, polyps.
- Specific tests → e.g. Meckles scan.

Treatment: of the cause

Medical for	Surgical for
- Hemorrhagic blood diseases.	- Varices.
- Peptic ulcers.	- Polyps.
- Enterocolitis.	

Pulmonology

Acute Pharyngitis

It include acute tonsillitis, pharyngitis or tonsillopharyngitis.

Causes: - Viral
- Bacterial (mainly by group A β heamolytic strept.).

Clinical picture

General	Local
- Headache - Fever (++ in bacterial) - Anorexia and malaise	- Dysphagia - Sore throat(red , congested) - Inflamed tonsils with white or yellow exudates. - Enlarged tender lymph nodes on the front of the neck.
Specific features: - Adeno virus: associated fever and conjunctivitis(pharyngoconjunctival fever) - Coxachie virus: associated minute pharyngeal vesicles and ulcers (herpangia) - Ebstein Barr virus: associated fatigue, rash, large tonsils and hepatosplenomegaly	

Complications: as that of scarlet fever + mesenteric adenitis (→ abdominal pain).

Treatment

* Symptomatic for fever.
* Specific: e.g. in strept infection 10 days oral penicillin V or amoxicillin or single IM injection of benthazine penicillin (600.000-1.2 million units)
* Surgical: Tonsillectomy if there's:
  - Peritonsillar abscess (Quinsy)
  - Obstructive sleep apnea (☞ tonsilloadenoidectomy).
  - Frequent tonsillitis.

Acute Otitis Media

Risk factors :Eustachian tube obstruction by adenoids or inflammatory edema in upper respiratory infection

Causes

1. Viral
2. Bacterial:- pneumococci, hemophilus influenza, moraxilla catarrhalis, streptococci

Clinical picture

* Fever
* Severe earache (irritability & rubbing the ears in infants) ⇒ relieved after drum perforation.
* Otoscopic examination ⇒ drum is congested, bulging or perforated ± discharge.
* Complications: - Mastioditis: tender swelling behind the ear
  - Chronic ear infection: draining ears for 14 days or more

Treatment

* Symptomatic for pain & fever(paracetamol).
* Specific = antibiotics for 10 days → amoxycillin or cotrimoxazole
  → 2nd or 3rd generation cephalosporins.
* Surgical = myringotomy & drainage rarely needed.

Stridor

Definition: Harsh, continuous inspiratory sound due to partial obstruction in upper airways (larynx & trachea)

Causes

Acute:

Infectious	Non infectious
* Viral: - Laryngeotracheobronchitis (croup) - Acute laryngitis. - Spasmodic laryngitis. * Bacterial: - Acute epiglottitis. - Acute tracheitis (staph. aureus). - Diphteritic laryngitis.	- Laryngeal foreign body. - Laryngeospasm. - Laryngeal oedema. - Laryngeal compression.

Chronic:

Congenital	Acquired
- Laryngeomalacia - Laryngeal web or cyst. - Tracheomalacia. - Congenital vascular ring.	* Laryngeal - stenosis - tumors - paralysis * Tracheal stenosis

Acute Infectious Stridor

	1- Laryngo-tracheo–bronchitis	2- Acute laryngitis	3- Spasmodic laryngitis
Age	6 mo - 6 years.	1 - 3 years	1 - 3 years
Cause	- Viral esp para-influenza types 1,3 others: RSV, influenza, adenovirus	- Viral infection of the subglottic region	- Viral but may be *allergy* or *psychogenic*
C/P	- Preceded by upper respiratory cattarh (Rhinitis) - Moderate – severe - Croupy cough and hoarseness of voice - Moderate fever - Inspiratory and expiratory stridor. - Respiratory distress may occur. (may be substernal & suprasternal retractions) - Neck x ray in antero posterior view show sub glottic narrowing (Steeple sign)	- Mild – moderate - Croupy cough and hoarseness of voice. - Mild fever - Inspiratory stridor - Usually no respiratory distress	- Occurs *at night* - Mild – moderate - Croupy cough and hoarseness of voice. - No fever - Inspiratory stridor - Respiratory distress may occur - *Recurrence is common*
Ttt	1- Calm the baby. 2- Humidified O_2 & steam inhalation 3- Adrenaline nebulizer (0.25 ml epinephrine in 3ml saline) reduce need for intubation. 4- Corticosteroids (Dexamethazone oral or IM or Budesonide inhalation). 5- In severe cases: Mechanical ventilation or rarely tracheostomy.		

4- Acute Epiglottitis (Supraglottitis)

Infection of the epiglottis by hemophilus influenzae, rarely by staph or pneumococci or streptococci.

Clinical picture

1- Peak age = 2-7 years.

2- Toxic child with high fever

3- Drooling of saliva (due to severe dysphagia)

4- The child is severely exhausted :- Voice is muffled.
- Stridor is mild.
- Little or no cough
- The child prefer upright posture

5- Laryngeoscope show large "cherry red" swollen epiglottis but this procedures and any stressful procedures may precipitate complete airway obstruction.

Management

Medical emergency, once suspected, patient must be admitted to intensive care unit.

1- Artificial airway:
- Endotracheal tube (or less often tracheostomy) is indicated regardless degree of respiratory distress.
- The tube kept in place for 2-3 days.

2- O_2 inhalation.

3- Culture of blood and, if possible, epiglottic surface should be done.

4- Antibiotics:
- Start parenteral 3rd generation cephalosporin (Ceftriaxone or Cefotaxime) or ampicillin – sulbactam pending results of culture & sensitivity
- Continue antibiotics for 7-10 days.

N.B. Lateral X-ray of the neck may show swollen epiglottis (thumb sign)

Fate
- Severe condition with high mortality.
- Incidence declined in developed countries due to HiB vaccination.

Lower Respiratory Diseases

Chest Examination

	Pneumonia	Bronchopneumonia	Pleural effusion	Pneumothorax	Hydropneumothorax	Collapse
Inspection						
- Movement	Decreased	Decreased bilateral		Decreased		Decreased
- Shape	Normal	Normal		Bulge		Retraction
Palpation						
- Tracheal shift	Central	Central	Shifted to opposite side			To same side
- Tactile vocal fremitus	Increased	? normal	Decreased			Decreased
Percussion						
- Note	Impaired note	? impaired note	Stony dull	Hyperresonance	Shifting dullness	Dull
- Topography	Lobar	Bilateral	Rising to axilla	Allover the side	Transverse upper border	Lobar
Auscultation						
- Breath sounds	Diminished bronchial	? Normal vesicular	Markedly diminished vesicular			
- Adventitious sounds	Crepitations	Bilateral wheezes , Crepitations				
- Vocal resonance	Increased Bronchophony	May be normal	Decreased			
Special signs	--	--	Aegophony	Coin test	Succussion splash	--

Pneumonia

Definition: Inflammation of the lung parenchyma.

Etiology

A. Community acquired pneumonia : acquired outside the hospital

1- Bacterial: Pneumococci, group B and A strept are the most common

2- Viral: Respiratory syncytial virus (RSV), parainflenza , influenza & adenovirus

3- Mycoplasma pneumoniae & chlamydia pneumoniae .

4- Mycobacterial :tuberculosis and atypical mycobacteria

5- Aspiration of milk or food → oral anaerobic flora, with or without aerobes

6- Allergic e.g. Esinophilic pneumonia (Loffler's syndrome)

7- Rickettsial e.g. Coxiella Burnetii

B. Hospital acquired pneumonia :acquired in hospitalized cases

Risk factors:

- Microaspiration of bacteria that colonize the oropharynx and upper airways in seriously ill patients
- Contaminated equipments e.g. intubation with mechanical ventilation
- Impaired host defenses e.g. immunodeficiency or steroids
- Coexisting cardiac, pulmonary, hepatic, and renal insufficiency

Causes: Virulent organisms are involved

1- Gram-negative bacteria (the most common);
Enterobacter, Escherichia coli, Klebsiella, Proteus, Serratia marcescens, and Hemophilus influenzae ,Legionella and Pseudomonas

2- Gram-positive bacteria : Streptococcus pneumoniae and Staphylococcus aureus.

3- Opportunistic infections in immunosuppressed individuals:
- Fungal e.g Aspergellosis , Histoplasma , Cryptococcus, Candida
- Protozoal e.g. Pneumocystis carinii

* N.B : ***Atypical pneumonia syndrome*** is caused by: Mycoplasma pneumoniae , Chlamydia pneumoniae , Chlamydia psittaci , Legionella and Coxiella

Symptoms

* General: - Fever, malaise , poor general condition(worst in bronchopneumonia).
- May be abdominal pain: Referred from lower lobe pneumonia.
* Chest: - Cough (dry then productive)
- Dyspnea and grunting.

Signs

1- Signs of respiratory distress :

Tachypnea & working alae nasi , retractions (intercostal & subcostal), grunting and , in advanced cases , cyanosis and may be impaired consciousness.

2- Chest examination:

- Pneumonia
- Bronchopneumonia

} **See previous table**

- Interstitial pneumonia: → Minimal chest findings.
  → Prolonged expiration & wheezes are common

Investigations

A. Radiologic

1. Chest X-ray:
   * Lobar pneumonia : homogenous opacity in one or more lobes (usually bacterial)
   * Bronchopneumonia : scattered opacities in both lungs (viral or bacterial)
   * Insterstitial pneumonia : scattered bilateral perihilar pulmonary infiltrate, hyperinflation, and atelectasis (usually viral in origin)
   * Complications as abscess, effusion & pneumatoceles may indicate *S. aureus,* gram-negative, or complicated pneumococcal pneumonia.
   * In complicated cases, repeat chest radiograph 6 weeks later to verify resolution.
2. Ultrasonography:
   - Differentiate non fibrinopurulent effusion and fibrinopurulent effusion
   - Guide thoracentesis of a loculated effusion
3. Contrast CT scan: for complicated cases
4. CT or ultrasonography guided lung biopsy : diagnose infection with rare organisms

B. Laboratory

- Arterial blood gas: indicated with significant respiratory distress
- Acute phase reactants : leucocytosis with predominant granulocytes , ↑ ESR and positive C-reactive protein suggest bacterial rather than viral pneumonia.
- Blood, pleural fluid or tracheobronchial secretions aspirate culture and sensitivity.
- Cold agglutinins in 50% of mycoplasma pneumonia (non specific test).
- Detect the virus or viral antigens by immunoflorescence.

Complications

i. Respiratory

1- Pleural effusion
2- Empyema with or without bronchopleural fistula and pyopneumothorax
3- Lung abscess
4- Pneumatoceles.
5- Septic emboli in pulmonary veins

These complications are more common with staph and klebseilla pneumonia

ii. Systemic

1- Meningismus especially with right upper lobe pneumonia
2- Heart failure
3- Distant infections: Septicemia , meningitis, pericarditis, osteomyelitis, arthritis
4- Metastatic abscesses

Differential diagnosis

1- Viral pneumonia:

The commonest cause in pre-school children with peak at 2- 3 years

Causes: RSV, adenovirus, influenza and para influenza virus.

Clinically:

- Preceding upper respiratory tract infection.
- Fever & R.D. ⇒ milder than bacterial pneumonia.
- May be widespread wheezes and crepitations.

Diagnosis:

1- Chest X-ray:

- Scattered bilateral infiltrate (bronchopneumonia **or** interstitial pneumonia)
- Hyperinflation

2- CBC show normal or mildly elevated WBCs with predominant lymphocytes

3- Detect viral antigens by immunoflorescence.

2- Bacterial pneumonia:

Risk factors usually present e.g.:

- Respiratory viral infections(so more common in winter)
- Viral exanthemas
- Splenectomy and hyposplenism→ Pneumococcal & H. influenza pneumonia

	Pneumococcal	Streptococcal	Staphylococcal	H.influenzae	Klebsiella
Age	Commonest bacterial. pneummia below 4yr	Peak age 3-5 yr.	Peak age in infancy < 1 yr	Peak age < 3 yr	more in immunodeficient
C/P	- moderate - moderate fever - usually lobar - bronchopneumia in young infants	- moderate - high fever - usually bronchopneumonia	- severe - high fever - usually bronchopneumonia (may be lobar)	- gradual onset - Prolonged course - usually lobar.	- severe - high fever - usually lobar
ttt	Penicillin	Penicillin	Cloxacillin or vancomycin.	3rd generation cephalosporin	Amikacin

3- Mycoplasma pneumonia (1ry atypical pneumonia):

Common in school age (5-15 yr)

Clinically :

- Severe non productive **cough** without significant respiratory distress.
- Pharyngitis is common.
- Minimal physical signs (walking pneumonia).
- May be chest wheezes and inspiratory crepitations.

Diagnosis is mainly clinical.

1- Chest X-ray show:

- Scattered bilarteral perihilar pulmonary infilterate.
- Rarely: Lobar pneumonia ± effusion.

2- CBC is usually normal

3- Cold agglutinins may be detected.

Treatment of pneumonias

i. Supportive

- Bed rest.
- With severe respiratory distress → humidified O_2 inhalation & restricted I.V. fluids
- Symptomatic treatment e.g. antipyretics for fever.
- Treatment of complications e.g. Heart failure.
- Chest tube drainage for massive effusion or empyema .

ii. Specific treatment

1- Bacterial pneumonia ⇒ Antibiotics

Choice :

- As suggested by clinical picture & chest X-ray.
- According to culture & sensitivity if available.
- Antibiotic combination if the cause can not be detected.

Empirical therapy: For

* Mild cases: amoxicillin or cefuroxime or amoxicillin clavulanate
* Hospitalized cases:
  - Parenteral cefuroxime 75-150 mg/ kg/day
  - Add vancomycin or clindamycin if staphylococci is suspected
* Mycoplasma pneumonia : Erythromycin or azithromycin or clarithromycin

2- Viral pneumonia:

* Antibiotics may be used as coexisting bacterial infection exists in 30% of cases
* Antiviral (for immunodeficient): - Ribavirin for RSV.
  - Amantidine for influenza A virus

Recurrent pneumonia

Causes

1. In the same lobe: - local causes e.g. foreign body inhalation.
2. In any site:
   - Immunodeficiencies congenital or acquired
   - Obstructing endobronchial lesions e.g. foreign body, pulmonary sequestration
   - Decreased mucociliary clearance e.g. ciliary dyskinesia ,cystic fibrosis
   - Congenital heart diseases with left to right shunt.

Slowly Resolving Pneumonia

Definition

Persistent symptoms or radiographic abnormalities beyond the expected time course.

Expected course

☆ Clinical improvement:
- Uncomplicated bacterial pneumonia improves within 2– 4 days of antibiotics.

☆ Radiographic improvement
- Uncomplicated bacterial pneumonia improve within 4–6 wk
- Pneumococcal & chlamydial pneumonia require 1–3 mo
- Mycoplasma pneumoniae require 2 wk to 2 mo.
- Staphylococcal, legionella, and enteric gram-negative require 3–6 mo
- Viral pneumonia may require many months.

Causes

1. Inadequate therapy : inappropriate antibiotic choice, dose, or poor compliance
2. Development of resistant organisms
3. Immunodeficiencies : congenital or acquired
4. Obstructing endobronchial lesions e.g. foreign body, pulmonary sequestration
5. Decreased mucociliary clearance e.g. ciliary dyskinesia ,cystic fibrosis
6. Nonbacterial causes: Viruses, fungi, parasites, and Mycobacteria
7. Noninfectious causes: hypersensitivity pneumonitis, sarcoidosis and Wegener granulomatosis

Work up

☆ Identify the offending organism: Blood, sputum, pleural, bronchoalveolar lavage, or lung biopsy can provide tissue for Gram stain and/or culture and thereby guide antibiotic choice.

☆ Chest CT scans (thin-cut and /or high-resolution)

☆ Anti-neutrophil cytoplasmic antibodies [ANCA] for Wegener granulomatosis.

☆ Flexible fiberoptic bronchoscopy

☆ Lung biopsy

Acute Bronchiolitis

Definition: Acute inflammation of the bronchioles.

Causes

1. Respiratory syncytial virus (RSV) in 70% of cases.
2. Others: Metapneumovirus , Adenovirus, Para influenza virus, Rhinovirus.

Pathogenesis

Mucosa & submucosa of small bronchioles are invaded by the virus → acute inflammantion → bronchiolar obstruction by oedema, mucus & cellular debris. → impaired pulmonary gas exchange may occur; early hypoxemia occur with severe disease hypercapnia develops.

Incidence: - Age: during the 1st 2 years of life (peak age = 6 months).
- Season: more in winter & spring.

Clinical picture

Symptoms

- Upper respiratory catarrh (rhinitis & mild fever) for few days then
- Gradually occurring dyspnea, cough and wheezy chest
- Along with irritability and difficult feeding

Signs

1- Respiratory distress (tachypnea, retractions, grunting ± cyanosis)

2- Chest examination:

- Inspection → Hyperinflated chest + prolonged expiration.
- Palpation → May be palpable wheezes.
- Percussion → Bilateral hyper resonance.
- Auscultation → Diminished vesicular breath sounds.
  → prolonged expiration.
  → Bilateral expiratory wheezes.
  → Bilateral fine crepitations.

N.B. Liver & spleen may be ptosed due to hyperinflated chest (→ normal liver span).

Complications

1- Heart failure

2- Dehydration → due to tachypnea & anorexia.

3- Lung collapse or pneumothorax → sudden deterioration.

4- 2ry bacterial pneumonia

5- Recurrence.

Investigations: Diagnosis of acute bronchiolitis is mainly clinical

1- Chest X-ray → hyperinflated lung (horizontal ribs + flat diaphragm).
→ bilateral perihilar infiltrates.
→ may be areas of collapse.

2- ESR, CRP & white blood cell count → usually normal.

3- Detect RSV antigens in nasopharyngeal secretions by immunoflorescence.

4- Arterial blood gases to assess severity of the disease.

Differential diagnosis

A. From other causes of **wheezy chest** in infants e.g.:

1- Bronchial asthma: suggested by
- Recurrent attacks of wheezy chest without viral prodrome.
- Related to certain allergens or exercise.
- Respond to anti-asthma therapy.
- Relatives with atopy or asthma.

2- Congestive heart failure.
3- Foreign body inhalation.
4- Pulmonary T.B.
5- Cystic fibrosis.

B. Causes of paroxysmal cough e.g. Pertussis.

Treatment

A. Mild attack : without respiratory distress → follow up.

B. Severe attack:

✧ Hospitalization for:
- Infants younger than 6 months
- Intolerance to oral feedings
- Apnea
- Severe respiratory distress with resting rate > 60 /minutes
- PaO2< 65 mmHg

✧ Humidified cool O_2 inhalation.
✧ IV. Fluids to avoid the high risk of aspiration
✧ Inhaled bronchodilator → start with a trial dose & continue regarding the response
✧ Adrenaline nebulizer → temporary relief of bronchiolar obstruction.
✧ Treat complications → digoxin for heart failure.
→ mechanical ventilation for respiratory failure.
✧ Steroids → controversial

C. Antiviral: Ribavirin aerosol.

Indications: risky infants; with
- Age: younger than 6 weeks / prematures
- Bad condition with PaO_2< 65 mmHg or rising $PaCO_2$
- Chronic lung disease
- Congenital heart diseases.
- ImmunoDeficiency.

Side effect: controversial benefits and very costly

Prevention

- By: - RSV intravenous immunoglobulin (RespiGam).
  - Monoclonal antibody to RSV F protein (Palivizumab) I.M.
- Given before RSV season for prematures & patients with chronic lung disease.
- Avoided in congenital cyanotic heart diseases.

Prognosis: - The first 2-3 days are the most critical
- Mortality rate ≈ 1% due to: apnea , respiratory failure, dehydration.

Bronchial Asthma

Definition: Chronic inflammatory disease of lung airways characterized by:
Hyper reactivity of airways to various stimuli leading to variable, widespread episodic airflow obstruction which is reversible either spontaneous or with treatment.

Associations
- Family history of asthma may be present.
- Other allergies may be present as eczema , allergic rhinitis or food allergy
- Sinusitis & gastro esophageal reflux disease (GERD).

Risk factors
- Genetic predisposition.
- Early weaning from breast milk before 4 months.
- Urban life.

Pathogenesis of asthma (Atopy or type I hypersensitivity)

1- Exposure to asthma triggers →↑↑ IgE →increased activated mast cells, T-lymphocytes & easinophils → increased cytokines (IL4, IL5, IL13) in airways which result in:
- Early phase: Bronchoconstriction.
- Late phase: edema, ↑mucus, ↑chronic inflammatory cells

} Airways narrowing especially in expiration

2- Persistent airway inflammation leads to airway remodeling:
- Collagen deposition beneath basement membrane.
- Hypertrophy of muscles & glands.

} Persistent Airways narrowing

Asthma triggers
- Respiratory viral infections.
- Exercise.
- Inhalation of: - Air pollutants e.g. dust, smoke.
  - Pollens, mites, animal dander.
  - Cold air.
  - Fumes & strong odors.

Clinical picture: 80% of asthmatic children develop symptoms before 5th year of life.

1. **Symptoms**
   - Recurrent attacks of dry cough , dyspnea& wheezes (worse at night).
   - Attacks may be induced by certain triggers.
   - In between attacks → the patient is either free **or** wheezing
2. **General signs** (during the attack)
   - Irritability and restlessness.
   - Respiratory distress (tachypnea, retractions,.....)
3. **Chest signs** (during the attack)
   - Inspection → Hyper inflated chest and prolonged expiration.
   - Palpation → May be palpable wheezes.
   - Percussion → Bilateral hyperresonance.
   - Auscultation → Diminished vesicular breath sounds with prolonged expiration.
     → Bilateral expiratory wheezes.

Classification of severity of acute asthmatic attack (exacerbation):

	Mild	Moderate	Severe
- Dyspnea	while walking	while talking	at rest
- Respiratory distress	Mild	Moderate	Severe
- Pulse	< 100 / min.	100-120/min.	> 120/ min.
- Pulsus paradoxus.	<10 mmHg.	10-20 mmHg.	20-40 mmHg.
- Wheezes	end expiratory	throughout expiration	exp and inspiratory
- O_2 saturation	> 95%	90-95%	< 90%
- $PaCO_2$	< 45 mmHg	same.	> 45 mmHg. (respiratory acidosis)
- Peak expiratory flow rate (PEFR)	> 80%	50-80%	< 50%

Classification of asthma severity:

	Days with symptoms	Nights with symptoms	PEFR & FEV_1
Mild intermittent	< 2 / week. (no symptoms between attacks)	< 2 / month	> 80%
Mild persistent	> 2 / week.	> 2 / month	> 80%
Moderate persistent	Daily	> 1/ week	60- 80%
Severe persistent	Continual	frequent.	< 6 0%

Investigations

Diagnosis of bronchial asthma is mainly clinical

1. Immunologic:

- ↑ IgE and esinophils in blood & sputum.
- Skin testing

2. Chest X-ray (during the attack) may show

- Hyperinflation.
- Increased bronchovascular markings
- May detect complications.

3. lung function tests (the most useful)

- Low forced expiratory volume in 1st second (FEV_1)
- Improved FEV_1 by ≥ 12% after inhaled β_2 agonist.
- Worsening of FEV_1 by ≥ 15% after exercise challenge
- Peak expiratory flow morning to afternoon variation ≥ 20%

Differential diagnosis : Other causes of wheezy chest: See acute bronchiolitis

Complications

- In acute exacerbations : Pneumothorax , lung collapse, and acute respiratory failure
- Long term sequels : Chronic obstructive airway disease.

Treatment

I. Drugs used in bronchial asthma

1- Bronchodilators:

	Mechanism	Side effects.
Short acting bronchodilators (4-6hrs) 1- Salbutamol 2- Albuterol / Lev albuterol 3- Terbutaline	- Selective β_2 agonists.	- hypokalaemia - tremors - tachycardia.
Long acting bronchodilators (12hrs) 1- Salmeterol (for cases > 4yrs). 2- Formoterol (for cases > 6yrs).	- Selective β_2 agonist	As short acting
3- Theophylline (sustained release)	- ↑ cAMP in bronchial muscles	- convulsions - tachycardia - GIT upset
Ipratropium bromide	Parasympatholytic	mild atropine like

2- Anti inflammatory drugs:

	Action	Route
Steroids	- potent anti inflammatory - ↑expression of β-receptors in bronchial muscles	Inhalation: - Fluticazone. - Budesonide. - Beclomethazone. (side effects: very little, may be oral moniliasis and dysphonia) Oral: - Prednisone I.V : – Methyleprednisolone.
Na cromoglygate	Mast cell stabilizer	Inhalation (by spinhaler)
Montelukast (singulaire)	leukotriene receptor antagonist with a bronchodilator effect	Oral (chewable tablets or sachets)

II. Plan For Treatment

Step up, Step down approach

Asthma	1- Quick relief	2- Long term control
Mild intermittent	Inhaled short acting β_2 agonist as needed	No
Mild persistent	⇓ Same	One anti-inflammatory drug: - Inhaled steroid (low dose) **or** - Montelukast **or** - Na cromoglygate .
Moderate persistent	⇓ Same in addition to: Short course of steroids. (oral or I.V) for 3-10 days to prevent recurrence of symptoms.	1- Inhaled steroid (low dose) **and** 2- Long acting bronchodilator **or** Montelukast
Severe persistent		1- Inhaled steroid (high dose) **and** 2- Long acting bronchodilator **or** Montelukast **and** 3- Oral steroid (if needed).

Step down: Gradual stepwise reduction in control treatment is possible after 1-6 months.
Step up: If control is not maintained take step up(add on another medication).

Status asthmaticus:

Definition: increasing severe asthma not responding to quick reliefers within **24hrs.**

Clinical picture: → as severe acute asthma

→ may be signs suggesting immenent respiratory failure:

1. Drowsiness or confusion.
2. Bradycardia.
3. Absent pulsus paradoxus (respiratory muscles fatigue).
4. Paradoxical thoraco abdominal movement.
5. Absent wheezes.

Treatment

1- Admit patient to intensive care unit.

2- Monitor: - vital data & chest signs.
- arterial blood gases.

3- Exclude complications by chest X-ray (esp.pneumothorax & lung collapse).

4- Supportive: - Humidified O_2 inhalation.
- I.V. fluids & correct dehydration.
- Antibiotics for 2^{ry} infection(fast breathing or chest indrawing)

5- Specific: **i-** Bronchodilators: Short acting B_2 agonist & ipratropium bromide inhalation → every **20** minutes for 3 doses **then** hourly **or** continuous with cardiac monitoring

ii- Methyle prednisolone 1mg/kg/6 hr. I.V for 48 hrs

iii- Other bronchodilators may be used:
- Theophylline I.V. infusion 0.5- 1mg /kg /hr.
- Epinephrine subcutaneous

iv- Mechanical ventilation in: - respiratory failure.

3. Avoid exposure to triggering agents

1- Eliminate or reduce fumes, dust, smoke, animal danders

2- Avoid allergens as suggested by skin testing.

3- Treat sinusitis, GERD and rhinitis.

4- Give annual influenza vaccine unless egg allergic

5- In exercise induced asthma give:

- β_2 agonist inhalation.
or - Na cromoglygate inhalation } Before exercise
or - Montelukast oral

4. Regular follow up:

* Asthma check ups
  - Every 2-4 weeks until good control
  - 2- 4 per year to maintain good control
* Lung function monitoring

Prognosis

- Gradual decline of the attacks with age occurs in 2/3 rd of patients.
- Atopic patients and steroid dependent carry a poor prognosis.

Wheezy Chest

Definition: expiratory musical continuous sound due to partial obstruction of small bronchi & bronchioles.

Causes

In infants	In older child
Acute: - Acute bronchiolitis. - Pertussis - Tuberculosis - Foreign body inhalation - Heart failure(e.g. congenital heart diseases) **Chronic /recurrent:** - Heart failure - Recurrent aspiration - Airway obstruction: e.g. bronchomalacia, ,lymph nodes, foreign body	**Acute:** - Viral infection - Mycoplasma pneumonia - Foreign body inhalation. **Chronic /recurrent** - Bronchial asthma. - Bronchiactasis. - Tuberculosis - Cystic fibrosis

Foreign body aspiration

Clinical picture

History:

- ✧ Commonly in children 3months to 6 years
- ✧ History of sudden chocking or frank history of foreign body aspiration
- ✧ Triphasic history may be obtained:
  - Initial phase: cough ,chocking, stridor or gagging
  - Silent phase: if foreign body pass and impact in smaller airways
  - Phase of complications: recurrent pneumonia , abscess, bronchiactasis

Signs

- ✧ Fixed localized wheeze.
- ✧ Diminished breath sound over one lung, one lobe **or** one segment.
- ✧ Mediastinal shift.
- ✧ Same site recurrent pneumonia , abscess, bronchiactasis.

Chest X-ray

- Positive only in about **50%** of cases
- There may be obstructive collapse **or** obstructive emphysema in expiratory x ray film.

Treatment

1. Without respiratory distress→ bronchoscopic extraction

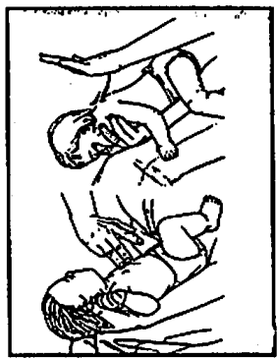
2. With respiratory distress:

A. If the child is breathing well:

- Let him attempt to clear the foreign body
- Encourage cough

B. If cough becomes ineffective :

- ✧ Try to assist expulsion of the foreign body
- ✧ Provide rescue breathing in between trials.
- ✧ If trials fail and infant becomes unconscious, attempt to visualize foreign body and remove manually and repeat sequence as necessary.



i. First aid for the choking infant younger than 1 year of age

1- Hold infant prone with the head down.

2- Give 5 interscapular back blows, using heel of hand.

3- Turn the infant supine, with head dependent and perform 5 quick downward chest thrusts in same location as external chest compression .

ii. First aid for the choking child older than 1 year of age



A) In conscious patient ⇒abdominal thrust in sitting or standing:

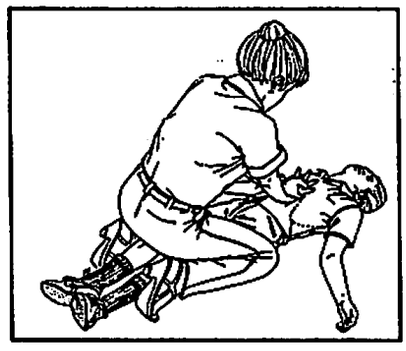
1- Encircle the child chest with arms from behind.

2- Place one fist against patient's abdomen in midline just below tip of xiphoid.

3- Grasp fist with other hand and exert 5 quick, upward thrusts.

4- Continue until foreign body is expelled or five thrusts are completed.

B) In unconscious patient ⇒abdominal thrust in lying down:



1- Place the patient supine.

2- Open patient airway using chin lift or jaw thrust.

3- Place heel of one hand on child's abdomen just below costal margins.

4- Place the other hand on top of the first hand.

4- Press both hands into abdomen with quick, upward thrusts in midline.

iii. Further interventions

1- Laryngoscopic removal with a Magill forceps.

2- If failed ; push foreign body more distally with intubation or bag and mask .

3- If failed, perform immediate cricothrotomy

Prevention

Avoid chocking materials in infants and young children e.g. small toys, nuts, popcorn

Dry Pleurisy

Definition: fibrinous inflammation of the pleura.

Causes

- Infections: Viral pneumonia, bacterial pneumonia , T.B.
- Thoracic wall or subphernic abscess
- Chest wall trauma
- Collagen diseases e.g rheumatoid arthritis, SLE.

Clinical picture

1- Manifestations of **the cause**
2- Chest pain: Stitching, ↑ with deep respiration, cough & sneezing
3- Patients may prefer to lie on same side.
4- Auscultation: Pleural rub: - scratchy sound.
- decrease by holding breathing.

Treatment: - Treat the cause.
- Analgesics.

Pleural Effusion

Definition: Serofibrinous inflammation of the pleura.

Types of effusion

Transudate	Exudate	Bloody	Cheylous
Ch.ch.: - Clear - proteins < 3gm/dl - ↓ cells - ↓ specific gravity - no organisms.	- turbid - > 3 gm/dl. - ↑ cells (PMNLs) - ↑ specific gravity - may reveal organisms - lactate dehydrogenase >200 iu /l	Bloody with RBCs on mic. examination.	- milky white - dissolved with ether - stained with sudan III - Spread on filter paper
Causes: - renal, cardiac & hepatic causes of generalized edema	- pneumonia. - T.B. - ruptured Lung abscess. - mediastinitis. - Non microbial: SLE, uremia, metastasis - T cell lymphoma.	- tumors - trauma - hemorrhagic blood diseases.	Thoracic duct obstruction or trauma.

Clinical picture

Symptoms

1- Manifestation of **the cause** (e.g fever, dyspnea,.....)
2- Respiratory distress
3- Chest pain: dull aching pain, patient prefers to lie on the affected side.

Chest examination

- Small effusion: picture of underlying causes e.g. pneumonia → bronchophony, bronchial breathing & crepitations.
- Massive effusion:
  - Inspection → Unilateral bulge.
  - Palpation → Decreased TVF & trachea shifted to opposite side.
  - Percussion → Stony dullness, rising to axilla.
  - Auscultation → Marked diminished breath sounds.
    → Aegophony (nasal tone of voice) may present.

Investigations

1- Chest X-ray in supine and upright positions show homogenous opacity:
   - Filling the costophernic angle
   - Rising to the axilla.
   - With shift of the mediastinum to the opposite side

2- Chest ultrasonography

3- Thoracocentesis:
   - For characters of the fluid (see before)
   - For culture & sensitivity.

Treatment

1- Treat the cause

2- Thoracocentesis with or without chest tube is indicated for:
   - Massive effusion with marked respiratory distress.
   - Effusion not resolved with medical treatment
   - Pleural fluid pH < 7.2
   - Pleural fluid glucose < 50 mg/dl

   * Site of aspiration → 5th space mid axillary line.

3- Treatment of chylous effusion:
   - Diet with low fat, high protein and calories.
   - Repeated aspiration.
   - Total parenteral nutrition.
   - Surgical ligation of thoracic duct.

Empyema
(purulent pleurisy)

Definition: Exudative pleural effusion with marked ↑↑ pus cells

Causes

1- Pneumomia (Staph, Pneumococci, H. influenza).

2- Rupture lung abscess.

3- Rupture abdominal abscess.

4- Contaminated chest trauma or surgery.

Clinical picture: same as pleural effusion with:
- High fever, toxic patient.
- High incidence of complications.

Complications

1- Local spread to:
- Lung → Bronchopleural fistula.
- Abdomen → peritonitis.
- Chest wall → empyema necessitatis.
- Pericardium → purulent pericarditis.

2- Distant spread: Meningitis, arthritis, osteomyelitis, septicemia.

3- In chronic cases: Excessive fibrosis may lead to lung collapse.

Investigations

1- Chest X-ray: as effusion but;
- Opacity is more dense.
- Ribs crowding & may be lung collapse in chronic cases

2- Thoracocentesis:
- For character of the fluid (exudate with ↑↑ pus cells).
- For culture & sensitivity.

3- Ultrasonography or CT chest for loculated empyema

4- Blood culture

Treatment

1- Thoracocentesis with closed drainage using intercostal tube with underwater seal.
- For about 1 week
- More than one tube may be needed to drain pockets of pus.

2- Antibiotics according to culture and sensitivity for 2- 4 weeks

N.B: Pseudochylous effusion: Chronic serous effusion with cellular degeneration:
Criteria: - High cholestrol level. - Low triglycerides.
- Doesn't clear with ether or alkali. - Doesn't spread on filter paper

Hydropneumothorax

Definition: Presence of both fluid & air in the pleural cavity.

Causes
- Thoracocentesis for pleural effusion → hydropeumothorax.
- Thoracocentesis for hemothorax → hemopneumothorax.
- Empyema with bronchopleural fistula → pyopneumothorax

Clinical picture

Chest examination
- Inspection → Unilateral bulge.
- Palpation → Decreased TVF & trachea shifted to opposite side.
- Percussion → Shifting dullness.
- Auscultation → Marked diminished breath sounds.
→ Succession splash.

Investigations

- As pleural effusion;
- Chest X-ray → air- fluid level

Treatment

1- Antibiotics according to culture and sensitivity.

2- Closed drainage with underwater seal.

⇒ If failed → surgical closure of the fistula.

Pneumothorax

Definition: Presence of air in the pleural cavity

Causes

- Rupture preumatoceles
- Rupture tuberculous cavity
- Rupture lung abscess.
- Rupture surface alveoli in air trapping
- Vigorous resuscitation
- Thoracocentesis
- Chest wall trauma

Clinical picture

Symptoms

- Asymptomatic (in small pneumothorax) → discovered accidentally
- Symptomatic: → respiratory distress (↑↑ with tension pneumothorax).
  → symptoms of the cause.

Chest examination

- Inspection → Unilateral bulge.
- Palpation → Decreased TVF & trachea shifted to opposite side.
- Percussion → Hyper resonance.
- Auscultation → Marked diminished breath sounds.
  → Coin test.

Investigations

1- Chest X-ray → jet black opacity with mediastinal shift to the opposite side

2- For the cause.

Treatment

1- Small pneumothorax: usually resolve within 1 week.

2- Symptomatic:

- Closed drainage with underwater seal.
- Tube is inserted in the 2nd space mid clavicular line.

3- Treat the underlying cause.

Tuberculosis

Definition: Chronic infectious disease caused by mycobacterium T.B bacilli (human & bovine types) which is alcohol & acid fast aerobic intracellular bacilli.

Modes of transmission

- Inhalation → pulmonary tuberculosis
- Ingestion(with milk) → intestinal T.B(& tonsillar tuberculosis)
- Wound contamination → cutaneous tuberculosis
- Hematological spread form primary T.B. focus

Risk factors

- Susceptible age : < 5 and >15 years.
- Race : more in Negroes
- Low socioeconomic standard.
- Immunodeficiency e.g. DM, HIV, malnutrition & immunosuppressive therapy

Pathogenesis

Primary exposure to T.B bacilli result in formation of primary complex at the site of entry of the bacilli (the commonest form in children).

1. Primary pulmonary complex:

Composed of: - Primary focus (Ghon's focus)
- Lymphangitis
- Hilar lymphadenitis

Comparison between the primary complex in the young and adult

Infants and young children	Adults
- Ghon's focus may be in any part esp. in the periphery	- Usually apical
- Lymph nodes more often involved	- Less involvement
- Parenchyma and nodal lesions heal by calcification.	- Heal by fibrosis
- Blood dissemination & miliary T.B occur more often	- Less often

2. Primary cervical complex (tonsillar T.B)

Composed of: - Primary focus in tonsils.
- Lymphangitis
- Cervical lymphadenitis.

3. Primary intestinal complex

Composed of: - Primary focus in pyere's patches.
- Lymphangitis
- Mesenteric lymphadenitis.

Each primary focus is formed of tubercles each tubercle is formed of :

- Central caseation
- Epitheloid cells
- Macrophages and lymphocytes
- Langerhans giant cells

Fate of primary pulmonary complex

With good immunity ⇓ **regression (in 90%)**

- Small focus → complete fibrosis
- Large focus → capsulation & calcification → In which T.B bacilli may remain viable for years (latent T.B. focus).

N.B. Reactivation of latent (dormant) focus may occur with:
- Pertussis
- Measles.
- Immunodeficiency e.g. prolonged steroids.

With poor immunity ⇓ **progression**

- **Primary Cavitation**
- **Direct spread** ⇓
  - T.B pneumonia
  - Tuberculous effusion
- **Bronchial spread (endobronchial T.B)** ⇓
  - Incomplete obstruction → emphysema
  - Complete obstruction → collapse
- **Heamatologic spread** ⇓
  - One organ T.B
  - Miliary T.B

Clinical picture

1- Pulmonary T.B

May be:

1- No or minimal symptoms: → may be mild fatigue & poor appetite.

2- Manifestations of toxemia (uncommon) → night fever & sweating.
→ loss of weight & appetite

3- Manifestations of hilar lymphadenopathy *may include*:
- Non productive brassy cough, face edema & cyanosis
- Dyspnea.
- Emphysema
- Lung collapse.
- Positive D'espine sign (Bronchial breathing below level of bronchial bifurcation)

4- Allergic manifestations: Erythema nodosum & phlyctens.

5- Manifestations of extension.
- Bronchopneumonia.
- Tuberculous effusion.
- Miliary tuberculosis

N.B cough with sputum is rare occur only in progressive 1ry pulmonary T.B with formation of T.B cavity.

2- Extra pulmonary tuberculosis

A. Miliary tuberculosis

Common in: infants, malnourished & immunodeficient.

Due to: Hemtogenous spread of T.B bacilli from any focus (usually pulmonary) → multiple organ involvement (lung, kidneys, liver, spleen, mininges).

Clinical picture: - High hectic spiking fever.
- Toxemia with bad general condition.
- Hepatosplenomegaly
- Generalized lymphadenopathy
- May be fine crepitations allover the chest

Fundus examination : choriod tubercles

Chest x ray: small miliary shadows (snow flake opacities).

Definitive diagnosis: By liver or bone marrow biopsy & histologic examination.

B. Tuberculous meningitis

Due to: Hematogenous spread either isolated or as a part of miliary T.B

Clinical picture: - In infancy and early childhood
- Insidious onset
- Pass in 3 stages (each 1-2 weeks)

Prodroma	Meningitis	Terminal stage
(non specific)	⇓	⇓
⇓	- Meningeal irritation.	- Hemiplegia or paraplegia
anorexia, vomiting	- Raised intra cranial tension	- Coma
irritability, fever	- Cranial nerve palsies	- Death

C. Intestinal tuberculosis

Occur secondary to:
- Ingested T.B bacilli in milk
- Swallowed sputum from T.B lesions in the lungs.

Clinical picture:
- Tabes mesentrica: - enlarged mesenteric lymph nodes.
- T.B enteritis : - chronic diarrhea → failure to thrive.
- chronic abdominal pain.

D. Tuberculous peritonitis

Occur 2^{ry} to: Spread from intestinal or genitourinary T.B lesions

Clinical picture: - Ascites
- May be adhesions.

Diagnosis of tuberculosis

1. History of :

- Contact with known or suspected case of active pulmonary tuberculosis
- Un resolving chest infection despite appropriate antibiotics in susceptible patients.

2. Tuberculin test:

✧ Detects delayed hypersensitivity reaction to tuberculoprotein

✧ Mantoux test: intradermal injection of 0.1 ml containing 5 tuberculin units of purified protein derivative (PPD).

✧ Interpretation: measure the induration after **48 -72** hours.

A. Positive test (indicate TB infection)

1. Induration ≥ 5 mm^2 in high risk patients;
   - Close contact with active tuberculosis patient
   - Child having clinical or chest x ray compatible with tuberculosis
   - Immunodeficiency
2. Induration ≥ 10 mm^2 in moderate risk patients;
   - Children < 4 years
   - Birth or recent immigration from endemic area
   - Exposure to people from endemic area
   - Medical conditions with increased risk e.g diabetes , renal diseases
3. Induration ≥ 15 mm^2 in any child above 4 years without any risk factors

B. False positive test ; usually less than 10 mm induration, consider:

- Recent BCG vaccination
- Non tuberculous mycobacteria

C. Negative test : induration less than 5 mm^2

* True negative test → no T.B infection

* False negative test → in

- Technical error
- Early in the disease
- Miliary T.B.
- Immunodeficiency(e.g immunosuppressive therapy , malnutrition)
- Transient suppression of tuberculin reactivity in viral infections e.g. measles, mumps or live virus immunization

3. Gastric aspirate :

✧ 3 samples in the early morning on 3 consecutive days before the child has arisen

✧ M. tuberculosis is isolated in 40 % of cases

4. Specific :

i- Pulmonary tuberculosis

1- Chest X-ray :may reveal

- Enlarged hilar lymph nodes.
- T.B bronchopneumonia → fluffy cotton appearance.
- Miliary T.B → small miliary shadows (snow flake opacities).
- Others → pleural effusion ,emphysema ,collapse.

2- Detect M. tuberculosis:

In : - Gastric aspirate in infants or sputum in older children

By: - Zehl Nelsen stain and light microscopy.

- Auramine rhodamine stain and flourescent microsopy.
- Culture using Lowenstein Jensen media or Bactec radiometric system
- Polymerase chain reaction (PCR)

3- Detect the pathology: in pleural biopsy or lymph nodes

4- Pleural fluid examination:

- Color : Yellow with blood tinge
- Chemical : Proteins 2- 4 gm/dl , glucose 20- 40 mg/dl.
- Cells : ↑ lymphocytes but it is very rare to discover T.B bacilli.

5- Blood: Elevated ESR.

ii- **Tuberculous meningitis** : CSF analysis (See neurology).

iii- **Intestinal tuberculosis** : Mesentric lymph node biopsy & ascitic fluid analysis.

Treatment

Prevention

* BCG vaccine(see before)
* Milk sanitation (avoid milk of infected cattle, boil milk for10- 15 minutes before use)
* Isolate and treat infective cases with open pulmonary TB.
* Avoid contact with cases.
* Chemoprophylaxis:
  - For children with unavoidable close contact to TB sources **or** latent TB infection ; (reactive tuberculin test , normal chest radiograph, normal physical examination)
  - INH 10 mg/kg/d is given until 3 months from last contact or last reactive test
  - Perform Mantoux test at end of this time; if positive (≥ 5 mm^2) continue INH for additional 6 months
  - If Mantoux test is negative ; INH can be discontinued
  - INH resistant BCG can be given during prophylaxis.
* Trace the possible adult source and treat adequately to prevent other secondary cases.

Curative

A. General lines

- Good nutrition & vitamins
- Fresh air
- Bed rest as needed.

B. Antituberclous drugs

Indications:

1. Active pulmonary lesions
2. All tuberculin positive children up to 4 years if un vaccinated
3. Recent convertors from tuberculin negative to tuberculin positive
4. Tuberculin positive children who have recently contacted an open TB case

First line drugs:

Drug	Action	Dose (mg/kg/d)	Side effects
Isoniazide (INH)	Bactericidal	10	- Hepatotoxic - Peripheral neuritis (add vit B_6)
Rifampicin	≈	15	- Hepatotoxic - Red staining of secretions
Pyrazinamide	≈	20- 40	- Hepatotoxic - Hyperuricaemia

Alternative drugs:

Used as additive drugs in: - Multiple drug resistant tuberculosis.
- Life threatening tuberculosis e.g. T.B. meningitis.

Drug	Dose (mg/kg/d)	Side effects
Streptomycin	20-40 (I.M)	Ototoxic & nephrotoxic
Ethionamide	15-20 (oral)	Hepatotoxic (similar to INH).
Ethambutol	15-20 (oral)	optic neuritis & color blindness. (so not recommended for young children).

N.B:. - Kanamycin & Amikacin are of value in streptomycin resistant T.B. but have more side effects.
- Para aminosalcylic acid (PAS) is gastritoxic → so it is obsolete

Regimens for treatment

1. Triple drugs regimen:
   Rifampicin and INH (for **6** months ; either daily or directly observed twice weekly) + Pyrazinamide (in the 1st **2** months)
2. Quadriple drugs regimen (4 drugs):
   Streptomycin **or** ethionamide **or** ethambutol is added to the previous regimen if INH resistance is strongly suspected or in disseminated disease in immunodeficeint.
3. In miliary T.B, meningitis & bone T.B ⇒ extend treatment period for **9-12** months.
4. In multiple drug resistance → extend treatment period for **12-18** months.

Steroids in T.B

Used in:

1- Miliary tuberculosis → to improve the general condition
2- Endobronchial tuberculosis with localized emphysema.
3- Enlarged hilar lymph nodes with airway obstruction.
4- Tuberculosis of serous cavities e.g Pleurisy , Pericarditis , Meningitis
5- Adrenal tuberculosis

Precautions:

1- Under umbrella of antituberculous drugs.
2- Dose 2 mg/kg/d for 4-6 weeks followed by gradual tapering.

Follow up by:

- Clinical improvement.
- Radiologic improvement.
- ESR.

Nephrology

Glomerulonephritis

Definition: Group of diseases with inflammation & proliferation of cells within the glomerulus initiated in most cases by immunologic mechanism.

Classification

i. Primary glomerulonephritis

1- Immune complex glomerulonephritis:
- Post infectious glomerulonephritis: May follow infection with Strept, Staph, Pneumococci, HBV, Echo, Coxachie.
- Membranoproliferative glomerulonephritis (MPGN).
- IgA Nephropathy (Berger's disease).

2- Anti glomerular basement membrane glomerulonephritis (Good–Pasteur syndrome).

3- Uncertain cause e.g. Focal segmental glomerulonephritis.

ii. Glomerulonephritis with systemic disorders:

1- Immune mediated: - Lupus nephritis.
- Henoch Shönlein purpura.

2- Heriditary e.g. Alport syndrome.

Acute Post Streptococcal Glomerulonephritis

Definition: Acute Nephritic syndrome which follow infection with nephritogenic strain of group A-β hemolytic streptococci (serotypes 4, 12 causing throat infection or serotypes 49 causing skin infection).

Pathogenesis

Streptococcal infection —latent- period→ Antibodies.

↓

Antigen + Antibody + Complement (C_3) immune complexes

↓

Deposited in glomerular basement membrane (subepithelial humps)

↓

Acute inflammation

Proliferation of mesangeal and endothelial cells.

↓

Glomerular capillaries obstruction.

↓

↓ Glomerular blood flow.

↓ Glomerular filteration rate.

↓

Oliguria

Fluid retention

↓

Hypervolemia

↓

Edema

Glomerular endothelial damage

↓

Escape of **RBCs** (and proteins) in urine

++ Juxta-glomerular apparatus (JGA)

↓

++ Renin- Angiotensin system

↓

Hypertension

Clinical picture

Peak age : 5-12 years.

Skin or throat infection 1-3 weeks ago is followed by

1- Hematuria : Painless, cola colored (smoky) urine rarely gross hematuria.
2- Oliguria : Urine output (UOP) < 1 ml/kg/hr or < 400 ml/m^2/day.
3- Hypertension : Transient , mild to severe.
4- Oedema : Mild, morning periorbital puffiness & pretibial oedema.
5- Non specific : Headache, vomiting, abdominal pain.

Complications

May be the presenting event

1. Heart Failure

- Due to hypertension or hypervolemia.
- Clinically: Tachycardia, tachypnea, tender liver up to acute pulmonary edema

2. Hypertensive encephalopathy

- Due to acute hypertension → punctate cerebral hemorrhage & edema
- Clinically: Severe headache & vomiting → convulsions → coma

3. Acute renal failure (ARF)

- Due to rapidly progressive(crescentic) glomerulonephritis
- Clinically: Marked oliguria or anuria, acidotic breathing,uremic encephalopathy.

Differential diagnosis: From other causes of Hematuria (see later)

Investigations

A. For diagnosis → Urine analysis :

- Color: Smoky **or** gross hematuria.
- Volume: Oliguria.
- Specific gravity: High
- Proteinuria: Usually less than 1gm/dl ; nephrotic range may be seen in 10-20%
- Microscopic examination: Dysmorphic RBCs & RBC_S casts (pathgnomonic to glomerular bleeding)

B. For effect

- Electrolytes → may be hyperkalemia & dilutional hyponatremia
- Renal function tests → may be impaired.
- Anemia → due to hemodilution

C. For etiology

1- Low C3 (hypocomplementemia).
2 - Evidence of recent streptococcal infection:-

* Throat or skin lesion swab culture
* Anti- streptolysin O (ASO) titre →> 1/200 todd unit; may be negative after skin infection.
* Anti Deoxyribonuclase B titre (Anti- DNase B).

3- Renal biopsy is indicated for :

- Absent evidence of streptococcal infection or low C3
- Nephrotic syndrome (nephritic nephrosis)
- Acute renal failure
- Persistence of gross hematuria , proteinuria , low C3 or impaired renal functions beyond 2 months of onset

Course

- Hypertension and proteinuria improve within 4- 6weeks of onset
- C3 normalize by 6 - 8 weeks of onset
- Microscopic hematuria may persist for 1-2 years

Treatment

1. Bed rest → As needed by the patient or with complications
2. Course of penicillin → For 10 days if positive culture is obtained.
3. Diet → Salt restriction
   → Fluid restriction: - In oligo-anuria to avoid hypervolemia.
   - Intake = urine out put + insensible loss (400ml/m^2/d)
   → Potassium & protein restriction→ only with renal failure.
4. Hypertension (Elevated blood pressure)

Mild to moderate hypertension	Severe hypertension
- Fluid restriction	- Furosemide (i.v).
- Furosemide	- Na nitroprusside (infusion)
- ACE inhibitor e.g Captopril	- Hydralazine
- Nifidipine or Amelodipine.	- Diazoxide (i.v. push).

5. Treat Complications (Failures) :
   ✧ Heart failure: Treatment depends on the underlying cause:
   - hypertensive heart failure→ treat hypertension
   - hypervolemic heart failure → diuretics ± dialysis.
   ✧ Acute renal failure: Conservative treatment with or without peritoneal dialysis (see later).
6. Discharge from hospital (Go home) if: - No gross hematuria
   - Normal renal functions.
   - No or controlled hypertension.

Prognosis

* Over 95% of post streptococcal glomerulonephritis recover completely
* Less than 5% go into rapidly progressive glomerulonephritis may end in chronic renal failure.
* Mortality is due to heart failure, hypertension and renal failure
* Recurrence is extremely rare

Hemolytic Uremic Syndrome (HUS)

Definition:- Group of diseases which include:-

1- Acute renal failure(ARF).
2- Micro angiopathic hemolytic Anemia. (MAHA).
3- Thrombocytopenia.

Causes

1- Acute bloody diarrhea caused by Shiga toxin producing E-coli O_{157}: H_7
   - In 80% of cases of HUS.
   - Transmitted from undercooked meat & unboiled milk
2- Other less common causes:
   - Bacteria → Shigella, Salmonella, Campylobacter, pnemococci.
   - Viruses → Echo, coxachie, influenza.
   - Drugs → Cyclosporin A.
   - Systemic lupus.

Pathogenesis

Toxins (bacterial & others) → + + Leucocytes → ↑ tumor necrosis factor & interleukin 2

↑ O_2 Free radicles. → endothelial damage

↑ procoagulants

→ Intra vascular thrombi

→ damaged circulating RBCs & platelets → Micro angiopathic hemolytic Anemia & thrombocytopenia.

→ glomerular obstruction. → Acute renal failure &hematuria

Clinical picture

✧ Common age: Usually < 5 years

✧ Bloody diarrhea or upper respiratory infection is followed 5-10 days later by :

1. Acute pallor & purpura
2. Acute renal failure; with:
   - Oliguria and edema
   - Hypertension
   - Acidotic breathing
3. Hematuria

✧ Extra renal manifestation:

- Central nervous system → seizures, infarctions, coma.
- Intestinal → perforation, intussusception.
- Liver →Hepatitis.
- Cardiac → Pericarditis.

Investigations

i- For ARF → high creatinine& urea
→ high potassium & metabolic acidosis (↓ pH, ↓ $PaCO_2$, ↓ HCO_3).

ii- For MAHA → low Hb %& reticulocytosis.
→ blood Film → fragmented RBCs (Helmet's cells)

iii-For bleeding → thrombocytopenia
→ coagulation profile → Normal.

Differential diagnosis

1- From other causes of intrinsic renal failure: e.g.

- Rapidly progressive glomerulonephritis.
- Neglected prerenal failure.
- Acute tublular necrosis.

2- From other causes of microangiopathic hemolytic anemia: e.g.

- Bilateral renal vein thrombosis (Marked renal enlargement – renal Doppler).
- Thrombotic throbocytopenic purpura.
- DIC.

Treatment

i- Prevention

1-Adequqate cooking of meat (Hamburger)

2-Isolation of cases to avoid cross infection with E.coli.

ii- Curative:

1- Packed RBCs if Hb< 6% (may be repeated as hemolysis take up to 2 weeks).

2- **Treat intrinsic ARF.**

iii- Long term follow up

N.B:
Antibiotics should be avoided in HUS associated with shiga toxin producing E-coli as it → kills bacteria → ↑↑toxin release → deterioration.

Prognosis

-HUS is the commonest cause of acute renal failure in Western countries

-With adequate treatment , 90% survive acute phase; 9% of them progress to end stage renal disease

Hematuria

Definition of hematuria

- Microscopic hematuria means presence of more than 5 red blood cells per high power field in sediment of 10ml fresh voided urine.
- Gross or frank hematuria is visible to the naked eyes.

Approach to diagnosis

I- is this red urine hematuria?

We should exclude other causes of red urine without RBCs by urine analysis (dipstick) which include:-

Heme positive:

i- Hemoglobinuria :-with acute hemolytic anemia.
- CBC show fragmented RBCs & reticulocytosis
- hemoglobin in urine

ii-Myoglobinuria:
- due to rhabdomyolysis (skeletal muscle injury) in viral myositis, crush, prolonged fits.
- high serum creatine kinase.

Heme negative:
-Foods : beet roots, black berries.
-Drugs: Rifamipicin, Desferal, Nitrofurantoin.
-Urate crystals (red diaper).

II- What are the causes of hematuria?

A. Glomerular Hematuria

1. Isolated Renal Disease

- Postinfectious GN (i.e., postStreptococcal GN)
- Focal Segmental glomerulosclerosis
- IgA nephropathy (Berger disease)
- Alport syndrome (hereditary nephritis)
- Anti–glomerular basement membrane disease
- Membranoproliferative GN

2. Multisystem Disease

- Systemic lupus erythematosus nephritis
- Henoch-Schönlein purpura nephritis
- Vasculitis Syndromes:Wegener granulomatosis ,Polyarteritis nodosa
- Goodpasture Syndrome
- Hemolytic-uremic Syndrome
- Sickle cell glomerulopathy

2- Extra glomerular:

1-Infection: -Bacterial
-Viral(adenovirus)
-Tuberculosis
-Schistosomiasis

2-Stones: -Urolithiasis/ Hypercalciuria

3-Anatomic: -Tumors (Wilms)
-Polycystic kidneys

4-Trauma.

5- Drug induced: -Cyclophosphamide → hemorrhagic cystitis.
-Aspirin & heparin → alter coagulation.
-Penicillin & sulpha → tubular damage

6-Vascular -Arteritis & infarction
-Renal vein thrombosis

7-Hematologic -Coagulopathy, purpura, sickle cell disease

Clinical approach of hematuria: Search for signs suggestive of each cause

Laboratory approach of hematuria

1- Localize hematuria:

	Glomerular	Extra glomerular
Color	Cola or tea colored	Bright red
Clots	Absent	May present
RBCs Shape	Dysmorphic (distorted)	Normal
RBCs casts	Present	Absent
proteinuria	> 100 mg / dL.	< 100 mg / dL.

2- For all cases:

1- Analysis of fresh urine sample for casts,bacteria,crystals, RBCs shape.
2- Abdominal ultrasound for stones, tumors, malformations
3- Blood picture with differential(*for value see later*)
4- Renal functions tests(Creatinine& BUN)
5- Serum C3 : Reduced in:
- Post infectious glomerulonephritis
- Systemic lupus nephritis
- Nephritis with chronic infection
- Membrano proliferative glomerulonephritis

6- 24 hours urine Calcium, uric acid & oxalate for crystalluria, stones

3- For Glomerular hemturia:

i- Reduced C_3 in: - Post infectious glomerulonephritis
- Systemic lupus nephritis
- Nephritis with chronic infection
- Membrano proliferative glomerulonephritis

ii- For post strept glomerulonephritis(see before)
iii- For lupus nephritis→ANA & anti double stranded DNA.

4- For extra glomerular hematuria:

1- Urine culture for urinary tract infections.
2-Cystogram & renal scan for hydronephrosis
3-Renal Doppler for renal vein thrombosis

5- Renal Biopsy

1- Unexplained persistent or recurrent gross hematuria
2- Lupus nephritis
3- Glomerulonephritis with: → nephritic nephrosis
→ absent low C_3
4- Unexplained acute renal failure

Proteinuria

Normal values: Most of filtered proteins are reabsorbed, So normal daily loss is < 4 mg/m^2/hr or < 150 mg/24hr.

Detection

1- Urine dip sticks
- Less sensitive, detects mainly albuminuria.
- Reported as: 1+ (30 mg/dl), 2+(100mg/dl), 3+(300 mg/dl), 4+(1000–2000mg/dl)

2- 24 hours urine protein
- Normal < 4 mg/m^2/hr.
- Abnormal 4 – 40mg/m^2/hr.
- Nephrotic range > 40 mg/m^2/hr or > 50 mg/kg

3- Urine protein / creatinine ratio
- Normal < 0.5
- Nephrotic range > 2

Causes of proteinuria

i- Transient proteinuria (never exceed 2+):
- Postural or orthostatic → proteinuria in upright posture only.
- Non postural: - Fever > 38.5 °C.
  - Vigorous exercise.
  - Seizures.

ii- Persistent proteinuria:

	Tubular	Glomerular
Due to	Decreased reabsorption of filtered proteins.	Increased glomorular basement membrane (GMB) permeability.
Level	Usually < 1gm/24 hours	Can exceed 1gm/24 hours
Type	Low molecular weight proteins	Low and high molecular weight proteins
Albuminuria	Absent.	Present.
Associations	Other proximal tubular defects e.g glucosuria, phosphaturia	Edema. May be hypertension, hematuria.
Causes	Fanconi syndromes (Cystinosis, Lignac,..... ...)	- Damage to GMB, e.g. glomerulonephritis. - Dysfunction of GBM e.g.: minimal change & congenital nephrosis.

Nephrotic Syndrome

Definition: Clinico-laboratory condition characterized by:-

1- Heavy proteinuria
2- Hypoalbuminemia
3- Generalized oedema.
4- Hyperlipidemia →↑ cholesterol & ↑ triglycerides.

Incidence: 15 times commoner in children than adults

Histological classification

1- Minimal change nephrotic syndrome (MCNS):
- Light microscopy & immunoflorescence → normal.
- Electron microscopy → lost foot processes of podocytes.
- Usually with selective proteinuria.
- Steroid responsive in > 95%.

2- Focal segmental glomerulosclerosis (FSGS):
- Light & electron microscopy → segmental sclerosis.
- Immunoflorescence → deposits of IgM & C_3.
- Steroid responsive in < 20%.

3- Mesangeal proliferative glomerulonephritis:
- Light & electron microscopy → increase mesangeal cells & matrix.
- Steroid responsive in < 50%.

4- Membrano proliferative glomerulonephritis.
5- Membranous

Causes of nephrotic syndrome

1- Idiopathic in 90% of cases

Histologic types:
1- Minimal change Nephrotic syndrome (85%)
2- Focal segmental glomerulosclerosis (10%)
3- Mesangeal proliferative (5%)

Etiology:
* Unknown
* In MCNS there is:
  - Genetic predisposition
  - Altered T-cell functions →↑ cytokines → altered GBM permeability

2- Secondary nephrotic syndrome

1- Any glomerulonephritis with heavy proteinuria e.g
- Systemic lupus nephritis
- Henoch Schonlein purpura.
- Infection → HBV, HCV, schistosomiasis, falciprum malaria.

2- Drugs e.g
- D penicillamine& heavy metals (e.g gold)
- Phenytion & procainamide

3- Tumors → e.g Hodgkin lymphoma and carcinoma(Para malignant manifestation)

3- Congenital nephrotic syndrome (See later)

Idiopathic nephrotic syndrome

Pathogenesis

1- Proteinuria

* Due to increased glomerular basement membrane(GBM) permeability (due to defect in size or altered negative charges of GBM barriers)

⇓

Proteinuria is either

- Selective = escape of low molecular weight proteins as albumin.
- Non selective = escape of both low & high molecular weight. proteins

⇓

2- Hypoproteinemia

Low total serum proteins → mainly hypoalbuminemia

3- Hyperlipidemia

mainly hypercholestrolemia.

Due to

- hypoproteinaemia → stimulate the liver → ↑ protein synthesis including lipoproteins which don't lost in urine
- ↓ lipoprotein Lipase → ↓ Lipid catabolism

4- Generalized oedema

Due to ↓ plasma osmotic pressure (↓ proteins & albumin)

↓

fluid shift to interstitial tissue (mainly in lax & gravity dependent)

↓

↓ intra vascular volume

- ↑ADH → H_2O retention
- ↓ renal blood flow → ↓ → ++ JGA → ↓ → ↑ aldosterone → ↓ → Na and H_2O retention

→ more oedema.

Clinical picture: (in MCNS → Peak age =2-8 years/ Boys: Girls 2:1).

The initial episode and relapses may follow viral upper respiratory tract infection.

1- Generalized edema:

- Start as morning periorbital puffiness then progress to involve lower limbs, genitalia and abdominal wall
- Oedema is very soft, pitting,
- Ascites and pleural effusion are very common.

2- Gastro intestinal mucosal oedema → anorexia, abdominal pain & diarrhea

3- Hematuria & hypertension may occur in non MCNS types.

Complications

1- Intra vascular thrombosis:

Due to: - Hypovolemia → sluggish circulation.
- ↑Platelet adhesiveness.
- ↓Anti thormbin III, protein S & protein C.

Sites: - Cerebral cortical veins.
- Renal vein thrombosis.
- Deep venous thrombosis.

2- Infections:

Due to - Loss of immunoglobulins.
- Loss of complement factor (properdin factor B).
- Oedema fluid favour infection
- Immuno suppressive treatment.

Common organisms: Commonly capsulated bacteria & viruses.

Pattern: - Pneumococci (peritonitis)
- E.coli (urinary tract infections).
- H.influenza (pneumonia)
- Staph aureus (cellulitis).
- Septicemica.

3- Acute renal failure (Nephrotic crisis):

Due to: - Severe hypovolemia → ↓↓ renal blood flow (pre renal failure).
- Renal vein thrombosis.

4- Relapse:

Definition: - Recurrence of significant proteinuria (≥ 3+)for 3 consecutive days during **or** immediate after steroid withdrawal.
- If > 4 relapses within 12 months → frequent relapsing nephrotic syndrome.

5- Complications in resistant & frequently relapsing nephrotic syndrome:

i- Protein depletion: muscle wasting, osteoporosis, short stature

ii- Chronic renal failure → in non- MCNS.

iii- Drugs complications:

Steroids
- Cataract
- Ulcers(peptic)
- Striae
- Hypertension
- Infections(immunosuppression)
- Necrosis of bone.
- Growth retardation.
- Osteoporosis.
- ↑ Intracranial tension.
- Diabetes Mellitus.
- Myopathy
- Adipose tissue hypertrophy (moon face, bufflo hump, trunkal obesity)
- Pancreatitis.

Cyclophosphamide
- Alopecia
- Bone marrow suppression
- Hemorrhagic Cystitis (prevented by I.V. Mesna)
- Decreased fertility

Cyclosporin A
- Hirsutism
- Nephrotoxic
- Hepatotoxic

Investigations

1- For diagnosis

A. Urine analysis

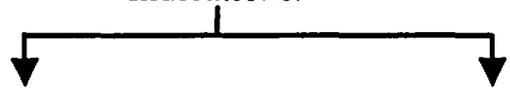
- Color: Yellowish, frothy.
- Volume: Normal, may be oliguria (may be polyuria with steroid ttt).
- Specific gravity: High
- Proteinura: Heavy; **> 40 mg/m^2/hr** or urine protein/ creatinine ratio **> 2.**
- Microscopic examination: - Waxy (lipoid) & hyaline casts.
  - Microscopic hematuria in about 20% of MCNS.

B. Biochemical

- Low serum albumin **< 2.5** gm/dl &low total proteins **< 4.5** gm/dl.
- Increased serum cholesterol **> 250** mg/dl.

2- For the cause → Renal biopsy

- Not indicated if MCNS is suggested.
- Indications.



Before treatment:

- Age < 1 **or** >12 years.
- Gross hematuria.
- Renal failure
- Low C3

After treatment:

- Steroid resistant nephrotic syndrome.
- Frequent relapser

Differential Diagnosis

1- Form other causes of generalized edema

	Renal	Cardiac	Hepatic	Nutritional	Angioneuritic
Age	Child	Any	Any	Infant	Any
- Start in (Tempo) - Ascites.	Periorbital (in the morning) +	L.L.(sacral in bed ridden) +	Ascites +	Dorsa of Hand & feet -	Tongue, Lips & cheeks. -
Associations	- Hematuria - Hypertension (absent in MCNS)	Heart failure. e.g - Dyspnea - Orthopnea	Liver failure e.g- Jaundice - Bleeding	- Poor dietetic history - Features of **KWO**	- Iching - Recurrence

2- From causes of secondary nephrotic syndrome:

Secondary nephrotic syndrome is more likely if associated with:

- Age > 8 years.
- Hypertension.
- Gross hematuria.
- Renal impairment.
- Extra renal symptoms e.g. arthritis, organomegaly.
- Low C_3.

3- Histologic type of nephrotic syndrome by renal biopsy

Treatment of Nephrotic Syndrome

i- Supportive

1- Hospitalize & monitor

- Daily weight
- 24 hr urine protein
- Urine out put
- Blood pressure.

2- Diet: - Salt restriction
- Fluid restriction **in** progressive weight gain.
- Increase proteins intake

3- Avoid infections

- Treat any latent infection e.g UTI.
- Avoid contact with infectious patients
- Perform tuberculin test before initiation of immunosuppressive treatment
- Pneumococcal & H. influenza vaccines for chronic cases and those on prolonged steroids or immunosuppressive treatment.

4- Avoid thrombosis

- Low dose aspirin.
- Avoid excess diuretics.

5- Salt free albumin

- Indications: Massive generalized oedema (anasarca) with respiratory difficulty
- Dose: 0.5 – 1 gm/kg salt free albumin infused over 4 hrs followed by frosemide (1 - 2 mg/kg I.V)

N.B. heavy use of diuretics alone in nephrotic syndrome carry risk of:
- Depletion of intravascular volume (hypovolemia)
- Pre-renal failure
- Thrombosis
- Hypokalemia.

ii- Curative

- Induction of remission by **Perdnisone** 60 mg/m^2/d (2 mg/kg/d) for 4 weeks in three divided doses

↓

Response

Remission of nephrotic syndrome

- Proteinuria < 4mg/m^2/hr (< 150 mg/d) &
- Serum albumin ≥ 3.5 gm/dl.

↓

Steroid responsive nephrotic syndrome

No response to prednisone For 6-8 weeks

↓

Steroid resistant nephrotic syndrome

1. Steroid responsive nephrotic syndrome:

After initial induction:

- Use alternate day prednisone 40 mg/m^2 as single morning dose for 4 weeks
- Followed by very gradual withdrawal over 2-3 months with monitoring for proteinuria:

Outcomes:

1. No relapses (30%) → Observe
2. Relapse > 3 months after steroid withdrawal (10%) → Restart treatment
3. Relapse while on alternate day steroid therapy or < 3 months after steroid withdrawal (Steroid dependent nephrotic syndrome ; 60%):

↓

- Daily steroid therapy and switch to alternate day 3- 4 days after remission then
- Prolonged alternate day steroid therapy ± levamizole

Persistent remission without growth impairment	More relapses with steroid side effects
↓	↓
Continue treatment for 12-18 mo	Cyclophosphamide 2 mg/kg/day for 12 weeks (often with alternate day prednisone)

No relapse	Relapse	Relapse with steroid side effects
	↓	↓
	Alternate day steroids for 12-18 months	Cyclosporin A for 1 year ± low dose alternate day steroids

N.B

* **Levamizole**: - Immuno modulator → consolidate remission in relapsers.
- Dose 2.5 mg/kg alternate days for 6-12 months.

* During treatment with cyclophosphamide , white cell counts must be monitored weekly and stop the drug if falls below 5000/mm3.

* Other options for maintaining remission in frequent relapsers: Tacrolimus (0.15 mg/kg/day divide every 12 hours) and Mycophenolate

2. Steroid resistant nephrotic syndrome: may benefit from

i- Mendoza protocol
- High dose pulse methyle prednisolone (30 mg/kg) slow I.V with the 1st six doses given every other day followed by tapering regimen over 18 months.
- Alternate day prednisone is used during tapering.
- Cyclophosphamide (I.V. monthly) can be added.

ii- Cyclosporin A 3-6 mg/kg/day

iii- Anti proteinuric agents: ACE inhibitors and angiotensin II blockers

Nephrotic syndrome in infants less than 1 year

Primary

1. Congenital nephrotic syndrome: (Fennish type)

* Autosomal recessive disorder
* Defect in nephrin or podocin proteins in glomerular basement membrane
* Presentation usually in the 1st 3 months.
* At birth: Large oedematous placenta.
* Prognosis: poor; ending in chronic renal failure.
* Treatment: - Albumin
  - ACE inhibitors e.g. enalapril.
  - NSAID e.g. ibuprofen.
  - Nephrectomy & transplantation.

2- Diffuse mesangeal sclerosis

3- Membranous nephropathy

4- Focal segmental sclerosis

5- Idiopathic

Secondary

1- Congenital infections (e.g.TORCH)

2- Drug induced

3- Systemic lupus erythematosus

4- Syndromes:

- Lowe s syndrome
- Denys Drash syndrome: Wilm's tumor, genitourinary anomalies , nephrotic sydrome.

Acute Renal Failure

(ARF)

Definition: Clinico-laboratory syndrome due to acute impairment of renal functions

Causes

Pre-renal (60%)	Renal (30%)	Post-renal (10%)
Due to: Marked reduction or renal blood flow	Renal parenchymal Damage.	Urine outflow obstruction
Causes: 1. Excess losses - Gastro-enteritis - Polyuria - Burns. - Hemorrhage. 2. Impaired cardiac output - Congestive heart failure - Shock 3. Hypo albuminenic states - Nephrotic syndrome - Liver failure	1. Tubular necrosis - Untreated pre-renal failure - Nephrotoxins e.g. aminoglycosides - Myoglobinuria. - Hemoglobinuria. - Crystal nephropathy. - Acute interstitial nephritis 2. Glomerular - Acute glomerulonephritis 3. Vascular - Renal vein thrombosis. - Hemolytic uremic syndrom	1. Obstructive uropathy: - Stones - Tumors - Urethral valve 2. Trauma.

Clinical picture

1- Manifestations of **the cause**

2- **Oliguric phase:**

i-. Early ARF: - Oliguria or anuria
- Edema
- Hypertension
- Acidotic breathing (rapid & deep)

ii- Advanced ARF ⇒ as above plus:

- ↑ Urea → uremic encephalopathy (confusion → convulsions → coma)
- Hyperkalemia → arrythmias.
- Hyponatremia → convulsions.
- Hypervolemia → heart failure up to acute pulmonary oedema
- Metabolic acidosis → stress ulcers.

3- **Polyuric phase**:- it may occur indicating early recovery → new tubular cells can't retain fluid & electrolytes → polyuria & electrolyte loss.

Diagnosis

1-Diagnosis of renal failure

1- Urine volume → oliguria (UOP < 1 ml/kg/hr or < 400 ml/m^2/day)
→ anuria (UOP < 30 ml/m^2/day)

2- Renal function tests → increased serum creatinine, urea & blood urea nitrogen.

3- Acid / base disturbance → metabolic acidosis(↓pH, ↓$PaCO_2$, ↓HCO_3).

4- Electrolytes → hyperkalemia.
→ dilutional hyponatremia.
→ hypocalcemia, hyperphosphatemia

2- Diagnosis of the cause

i. Post renal

1- Palpable bladder & kidneys.

2- Bladder catheterization

3- Abdominal ultrasound to exclude obstructive uropathy.

	ii. Pre-renal	iii. Intrinsic renal
Clinical	Intravascular volume depletion: - Hypotension - Tachycardia - Poor peripheral perfusion - May be dehydrated.	Intravascular volume overload: - Hypertension - Increased jugular venous pressure - May be edema
Laboratory - Urine osmolality - Urine specific gravity - Urine sodium - Blood urea nitrogen / creatinine ratio	 > 500 m.osml/L > 1020 < 20 meq/L > 20	 < 350 m.osml/L < 1010 > 40 meq/L < 20

Treatment of ARF

1. Hospitalization

And monitor → Blood pressure.
→ Urine out put
→ Intravascular volume → by central venous pressure (CVP)
→ Serum electrolytes & pH

2. **Correct Post-renal causes** → Remove obstruction (by catheterization ± surgical)

3. **Correct pre-renal causes** (improve renal blood flow):

- Fluid loss→ saline 20 ml/kg over 1/2 - 1 hr.
- Blood loss→ fresh blood transfusion
- Plasma loss → plasma transfusion
- Dopamine infusion 2-3 μ g/kg/min can increase renal blood flow (with good correction → patient will pass urine within 1-2 hours)

Treatment of intrinsic renal failure

1. Diet - Restriction of salt (Na), fruits (potassium) & proteins(to reduce urea)
- Fluids intake = insensible loss + ongoing losses

2. Diuretics :
- Value : Reduce volume overload & enhance potassium excretion
- Use : Furosemide 2-4 mg/kg/dose intravenous

3. Metabolic acidosis: Buffered by sodium bicarbonate 1-2 meq /kg slow intravenous

4. Electrolyte disturbance:

1- Hyperkalemia (potassium level ≥ 6 meq/L):-

a- Enhance GIT excretion by kayexalate (Na polyestrene resin) oral or enema.

b- Shift potassium intracellular by:
- Regular insulin ; 0.1 u/kg with glucose 50% solution , 1 ml /kg over 1 hour
- Salbutamol nebulizer
- Sodium bicarbonate 1-2 mEq/kg over 10 minutes i.v

c- Stabilize cardiac membranes by calcium gluconate 10%(1 ml/kg) slow I.V

d- Remove potassium by dialysis.

2- Hyponatremia (Na<130 meq/L): Usually dilutional ; respond to fluid restriction.

3- Hypocalcemia and hyperphosphatemia:-
- Tetany is rare as acidosis increases ionized calcium.
- Reduce dietary phosphate & give phosphate binders (calcium carbonate oral)

5. Treatment of complications:
- Anemia → Fresh packed RBCs transfusion.
- Hypertension → See glomerulonephritis.
- Infections → Use non-nephrotoxic antibiotics

6. Peritoneal dialysis:

Indications.

Clinical	Laboratory
1- Uremic encephalopathy 2- Anuria unresponsive to diuretics 3- Volume overload with heart failure or acute pulmonary edema 4- Intractable GIT bleeding.	1- Hyperkalemia (> 7 meq/L) uncontrolled medically 2- Intractable metabolic acidosis 3- Symptomatic hypocalcemia with severe hyperphosphatemia. 4- Blood urea nitrogen > 100 mg/dl

N.B. Normal values
- Blood urea = 20 – 40 mg/dl.
- Serum creatinine = 0.2 – 0.7 mg/dl.
- Blood urea nitrogen (BUN) $\approx \frac{\text{Blood urea}}{2}$

Chronic Renal Failure

Definition: - Irreversible decline of renal function over months or years → permanent reduction of glomerular filtration rate (GFR) < 75 ml /1.73 m^2/min

- In end stage renal disease, GFR is < 10 ml/ 1.73 m^2/min.

Causes

1- Congenital malformations e.g
   - Aplasia or hypoplasia.
   - Polycystic kidney.
   - Congenital nephrotic syndrome.
   - Obstructive uropathy.
2- Chronic glomerulonephritis.
3- Chronic pyelonephritis
4- Chronic interstitial nephritis
5- Vesico- ureteric reflux (VUR+UTI = reflux nephropathy).

Clinical picture

Non specific so, need high index of suspicion

Clinical feature	Mechanism
1- Growth retardation (Short stature)	- Resistance to growth hormone - Anemia - Anorexia (metabolic acidosis) - Renal osteodystrophy
2- Anemia	- ↓ Erythropiotine - Decrease intake of iron, B12, folic acid. - Bone marrow depression by uremic toxins - Defective iron utilization. - Frequent blood loss
3- Renal osteodystrophy (ROD)	- Hyperphosphatemia - Decreased 1,25 $(OH)_2D_3$ - Secondary hyperparathyriodism
4- Hypertension	- Increased renin & fluid retention
5- Bleeding tendency	- Platelet dysfunction
6- Infection	- Defective granulocyte function
7- Neurologic (fatigue , drowsiness, polyneuropathy)	- Uremic toxins
8- Pericarditis, cardiomyopathy	- Uremic toxins - Hypertension
9- Hyperlipidemia	- Decreased lipoprotein lipase activity

Diagnosis

1- Diagnosis of Renal Failure (see before)

2- Is it CRF ?

1- Renal ultrasound & DMSA scan show shrunken kidneys.

2- Estimate GFR by creatinine clearance & DTPA scan.

3- For complications:

1- CBC for anemia

2- Echocardiography for pericardial effusion & cardiomyopathy.

3- In ROD: - High phosphate - low calcium - high parathromone.

- Bone X-ray → subperiosteal erosions ± bone cysts.

Treatment

i- Conservative

1- Diet: - Restrict proteins.

- Salt & fluids → restricted if oliguric

→ increased if polyuric

2- treatment of hyperkalemia & metabolic acidosis ⇒ as in ARF

3- Treatment of complications:-

1- Hypertension
2- Infections
} ⇒ as in ARF

3- Anemia → Fresh packed RBCs transfusion.
→ Recombinant erythropioetine.

4- ROD → Phosphate binders (Ca carbonate)
→ Calcium (0.5 – 2 gm/d) oral
→ Vitamin D (One Alpha = 1 α (OH) D_3)
→ Partial parathyroidectomy

5- Growth failure → correct acidosis, anemia, ROD.
→ treat anorexia (e.g. tube feeding)
→ recombinant growth hormone (Controversial).

ii- Dialysis

Indications

As for ARF

Others
- Pericarditis
- Growth failure
- Resistant anaemia

Types

Hemodialysis (Preferable)

Continuous peritoneal dialysis

iii- Renal transplantation : Definitive treatment

Urinary Tract Infections

Urinary tract infections can present as

- Upper urinary tract infections → acute & chronic pyelonephritis.
- Lower urinary tract infections → acute & chronic cystitis & urethritis
- Asyptomatic bacteruria.
- Septicemia.

Causes

Predisposing factors.	Common organisms
- Females (short urethra) - Urinary tract abnormality e.g - Vesico ureteric reflux. - Obstructive uropathy. - Instrumentation. - Immunosuppression.	- G -ve → - Escherichia coli (80%) - Proteus (more in boys) - Pseudomonas - G +ve → staph, strept. fecalis

Clinical picture: (presentation differs according to age)

1- Asymptomatic bacteruria: - positive urine culture without manifestations

2- Newborn: - Sepsis (Jaundice,↓ feeding,.....)

3- Infant: - Fever.
- Screaming during micturation.
- Failure to thrive(vomiting→ weight loss)

3- Child: Localization

Upper urinary tract infections	Lower urinary tract infections
- Acute: Fever, rigors & loin pain	- Dysuria.
- Chronic: - Prolonged fever	- Frequency.
- May be hypertension	- 2^{ry} nocturnal enuresis.
	- May be hematuria.

Investigations

1- **Diagnosis of urinary tract infections**: by **Urine analysis**

Urine sample obtained by:

- Suparpubic aspiration (SPA) for infant < 1y & in sick pateints.
- Catheter sample.
- Urine bag for infant.
- Mid stream urine for child > 3years.

Examination:

- Pyuria: Pus cells ≥ 10/mm^3
- Gram stained films: For bacteruria
- Urine culture: **Diagnostic:**
  - In SPA → any growth is significant.
  - In catheter sample → ≥ 10^4 CFU/ml.
  - Clean voided urine → ≥ 10^5 CFU/ml.

2- Localize upper urinary tract infections by:
- Renal ultrasound.
- Renal DMSA scan.

3- For recurrent urinary tract infections:
- Renal ultrasound for obstruction.
- Voiding cysturethrography for vesico ureteric reflux.
- Renal functions tests.

Treatment

1- Adequate hydration.

2- Antibiotics:

Infant & severe infection	Well child
↓	↓
i.v. ampicillin & 3rd generation cephalosporin	Oral cotrimoxazole & ampicillin

Till results of culture and sensitivity

3- Follow up
- Urine culture after 1 week to ensure recovery.
- Urine culture after 3 months → detect recurrence

4- Prevention:- for recurrent urinary tract infections
1. Remove underlying risk factor e.g stones, constipation.
2. Adequate hydration.
3. Adequate bladder emptying.
4. UTI prophylaxis → low dose cotrimoxazole or nitrofurantion for 6 months.

Causes of sterile pyuria:
• Dehydration • urinary tract trauma • Renal T.B • Early glomerulonephritis

CHANGE IN COLOUR OF URINE

White milky urine	Green urine	Dark yellow urine	Red urine
1- Pus	1-Pseudomonas infection	1-↑ Billirubin	1- Hematuria
2- Phosphate crystals	2- Foods	2- Concentrated urine	2- Hemoglobinuria
3-Chylous			3- Myoglobinuria (muscle necrosis)
			4- Urate crystals
			5- Food: e.g - Beet root. - Berries. - Food dyes.
			6- Drugs: e.g - Rifampicin. - Desferal - Nitrofurantion

Systemic Lupus Erythematosis

Definition: Multisystem disease associated with auto-antibodies against self antigens resulting in inflammatory damage.

Risk factors: - Genetic predisposition.
- Hormonal role may exist.
- Females > males; usually > 5years.

Clinical Picture

I- Diagnostic criteria

1- Malar rash; fixed erythema over malar eminence.
2- Discoid rash.
3- Photosensitivity; unusual rash on exposure to sun light.
4- Oral ulcers; Painless
5- Arthritis.
6- Serositis: - Pleursy with or without effusion **or**
- Pericarditis with or without effusion.
7- Renal: - Proteinuria > 3+ **or**
- Cellular casts e.g. Red blood casts.
8- Neurologic: - Seizures **or** psychosis.
9- Hematologic: - Hemolytic anemia **or**
- Leucopnia **or**
- Thrombocytopenia **or**
- Lymphopenia.
10- immunologic disorders: - Anti double stranded DNA (ds DNA) antibody **or**
- Anti Smith antibody **or**
- Anti phospholipid antibodies.
11- Anti nuclear antibody (ANA).

For Diagnosing systemic lupus, 4 or more criteria from these 11 criteria serially or simultaneous.

II- Other Clinical finding

1- Malaise, weight loss, fever.
2- Hepatosplenomegaly.
3- Carditis (Libman sachs endocarditis).
4- Alopecia.

III- Other investigations (for effect)

1- Renal biopsy.
2- Very high ESR and low serum complement (↓C3, ↓C4).

Treatment

- Steroids oral **or** i.v
- Immunosuppressive drugs → cyclophosphamid & azathioprine.

Endocrinology

Hypopituitarism

Definition: Growth hormone deficiency occur either isolated **or** with other hormones of the anterior pituitary (panhypopituitarism)

Physiology of growth hormone

- Growth hormone is secreted form the anterior pituitary In bursts (i.e. pulsatile):
  - Stimulated by sleep, exercise and hypoglycemia.
  - inhibited by somatostatin.
- Growth hormone is under control of hypothalamic GH releasing hormone (GH. rH)
- Action: - Anabolic (especially on long bones)
  action is mediated by insulin growth factor 1 produced in liver
  - Increase protein synthesis
  - Anti insulin effect growth hormone → lipolysis & ↑ blood glucose.

Causes

i. Isolated growth hormone deficiency:

A. Genetic: due to

1- Mutation of growth hormone releasing hormone or growth hormone genes.

2- End organ resistance:

- Abnormal growth hormone receptors (Laron syndrome).
- Abnormal (inactive) growth hormone.
- Abnormal IGF-1.

B- Acquired:

1- Post cranial irradiation (e.g. for leukemia).

2- Idiopathic (The most common).

ii- Multiple pituitary hormones deficiency:

A- Genetic:

- Due to mutations of multiple pituitary hormones genes.
- Associations: May be optic nerve dysplasia (septo optic dysplasia).

B- Congenital:

- Pituitary aplasia or hypoplasia.
- Association: May be mid facial anomalies e.g cleft palate.

C- Acquired any lesion at hypothalamo- hypophyseal region:

1- Tumors e.g. craniopharyngioma.

2- Trauma.

3- Infiltration e.g. histoiocytosis.

Clinical picture

1- At birth:

- Normal size (growth hormone is not essential for fetal growth).
- Microphallus is diagnostic clue.
- May be neonatal emergency as apnea, cyanosis, hypoglycemia
- May be mid facial anomalies e.g. cleft lip & palate

2- Later on:

- Short stature: - proportionate
  - growth velocity < 5 cm/year.
  - appear by the end of the 2nd year
- Childish facies: - small face, nose & mandible
  - prominent forehead & depressed nasal bridge.
  - wide anterior fontanel & fine hair.
- Delayed teething
- Hypogonadism: genitalia are underdeveloped for age.
- Hypoglycemia (fasting).
- Normal intelligence.

3- May be features of associated hormonal deficiency e.g. hypothyroidism.

Investigations

1- To confirm growth hormone deficiency

Measure serum growth hormone after provocative agents; exercise, insulin, L-dopa, clonidine, or arginine:

- GH > 10 ng/ml ⇒ normal
- GH < 10 ng/ml ⇒ growth hormone deficiency

To confirm diagnosis provocative two tests should be done.

2- For associated deficiencies:

Measure other anterior pituitary hormones.

3- For the cause:

- Skull X-ray, CT & MRI for pituitary tumors, aplasia or hypoplasia.
- TRH stimulation test (differentiate between hypothalamic and pituitary causes)
- Laron syndrome: high growth hormone level and failure to respond to exogenous growth hormone.

4- For effect: Delayed bone age.

Treatment

1- Recombinant growth hormone:

- Dose: 0.18 - 0.3 mg/kg/week, divided into 6-7 daily subcutaneous injections.
- Used till growth rate < 1 inch per year or when bone age > 14 in females & > 16 in males.
- Side effects of growth hormone therapy:
  - Pseudotumor cerebri.
  - Slipped femoral epiphysis.
  - Risk of leukemia.

2- Recombinant IGF-1 for end organ unresponsiveness(e.g.Laron syndrome)

3- Treatment of other hormonal deficiency.

Thyroid Gland

Thyroid gland secrete

1- Thyroid hormones: Thyroxine (T4) & triiodothyronine (T3)(more potent than T4)

2- Calcitonin (which deposit calcium salts in bone).

Functions of thyroid hormones

1- Normal maturation of the growing brain in the 1st year of life.

2- Normal skeletal growth.

3- Oxidative metabolism & heat production in all cells

Thyroid hormones synthesis

1- Iodide transport (Trapping).

2- Iodide is oxidized to iodine by thyroid peroxidase enzyme (organification).

3- Iodination of tyrosine to form Mono & Di iodo tyrosine.

4- Coupling of:

- 2 Di iodotyrosine → T4.
- Monoiodotyrosine & Di iodotyrosine → T3

5- T3 & T4 are stored in thyroid gland as colloid (thyroglobulin).

6- Only 20% of circulating T3 is produced by thyroid while 80% is produced by peripheral conversion of T4 by deiodinase

Control of thyroid function:

1- Thyroid is regulated by pituitary thyroid stimulating hormone (TSH) in a feed back mechanism.

2- TSH synthesis & release is controlled by hypothalamic TSH releasing hormone (TRH).

Congenital hypothyroidism (cretinism)

Causes

A. Primary hypothyroidism:

1- Thyroid dysgenesis:
- The commonest cause (90%).
- Aplasia, hypoplasia or ectopic gland (may be lingual, sublingual or subhyoid).

2- Defective thyroid hormone synthesis (Dyshormonogenesis):
- The second common.
- All are autosomal recessive disorders.
- Associated with giotre.

☆Types: - Iodide transport defect.
- Organification defect: Due to lack of thyroid peroxidase enzyme.
- Thyroglobulin synthesis defect.
- Iodotyrosine deiodination defect.

3- Transient hypothyroidism:

✧ Transplacental passage of maternal:
- TSH receptor blocking antibodies.
- Drugs e.g.: - Anthyroid drugs. - Excessive iodine.

✧ Neonatal iodine containing antiseptics.

4- Maternal iodine deficiency: Endemic goiter.

5- End organ unresponsiveness to: - TSH.
- T3 & T4 (Pseudohypothyroidism).

B. Secondary hypothyroidism:

Due to TSH deficiency either: - Isolated or.
- With multiple pituitary deficiencies.

C. Tertiary hypothyroidism:

Due to TSH releasing hormone deficiency.

Incidence: 1:4000, female : male = 2:1.

Clinical picture

A. In neonatal period: there is may be

1- Prolonged physiologic jaundice
2- Lethargy; cry little, sleep much.
3- Poor feeding; Lack intrest, chocking spells during feeding.
4- Wide posterior fontanel
5- Noisy breathing due to large tongue.
6- Distended abdomen , constipation with umbilical hernia.
7- Heavy at birth
8- Subnormal temperature

But baby may be asymptomatic (why?), so neonatal screening is mandatory.

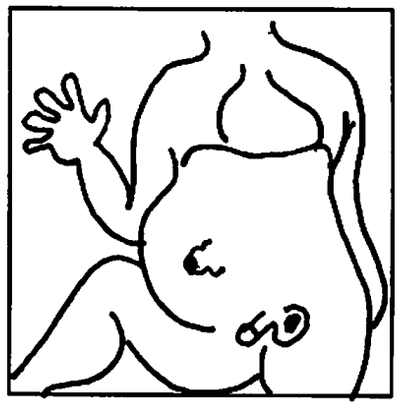
B. Full picture (by age 3-6 months):

* Delayed growth ⇒ proportionate short stature
* Delayed mental milestones
* Delayed motor milestones
* Physical features may include:



Head
- Hair is coarse, brittle with low anterior hair line
- Delayed closure of anterior fontanel
- Eyes are puffy, narrow palpebral fissure
- Broad nose & depressed bridge
- Delayed teething
- Thick large protruding tongue
- Hoarse cry

Neck
- Short neck with supraclavicular pad of fat
- Thyroid is enlarged in:
  - Endemic goiter.
  - Dyshormonogenesis
  - Pseudohypothyroidism



Cardiac
- Bradycardia
- Pericardial effusion.
- Cardiomegaly

Abdomen
- Protruding with umbilical hernia
- Constipation

Genitalia
- Delayed sexual maturation
- Rarely precocious puberty

Limbs
- Short broad hands
- Generalized hypotonia
- Occasional reversible generalized pseudohypertrophy most prominent in calf (Kocher Debre Semelaigne Syndrome)

Skin
- Cold
- Dry (↑ myxoedematous tissue)
- Pale (resistant anemia)
- May be yellow(↑ carotene)

Investigations

1- Confirm diagnosis of hypothyroidism

- Low serum T_4;(normal level = 4-9 μ g/dl)
  - In hypothyroidism there's compensatory increase in peripheral conversion of T_4 to T_3 ; so measuring of T_3 may be misleading
- SerumTSH ; (normal level <10 μ unit/ml post neonatal):
  - High in primary hypothyroidism(> 100 μ unit/ml)
  - Low in secondary & tertiary hypothyroidism.

  In pseudohypothyroidism all T4, T3& TSH are high

2- **For effect**

i- X-ray findings

a- Delayed bone age :

- At birth → absent distal femoral epiphysis (by knee x-ray)
- Later → delayed appearance of ossific centers (by wrist x-ray)

b- Epiphyseal dysgenesis: multiple foci of ossification in heads of femur & humerus.

c- Beaking of anterior part of T_{12} & L_1 vertebrae.

d- Skull X-ray → intrasutural (Wormian) bones , large fontanels, delayed teething.

d- Chest x ray → may show cardiomegaly

ii- Cardiac

- ECG show bradycardia and low voltage.
- Echo may show cardiac enlargement and effusion.

iii- Others

- High serum cholesterol
- Macrocytic anemia

3- **For the cause**

a- Thyroid scintigraphy (using radioactive ^{123}I):

- Absent uptake in aplasia or iodide trapping defect
- Increased uptake in dyshormonogenesis.
- Can localize ectopic thyroid.

b- TRH stimulation test: (performed only with ↓ TSH)

differentiate between hypothalamic & pituitary defects ⇒ i.v. bolus of TRH:

- if T_4 increases → hypothalamic defect (Tertiary hypothyroidism).
- if T_4 does not increase → pituitary defect (secondary hypothyroidism).

c- Skull X-ray, CT & MRI for pituitary tumors.

Treatment

⊕ Replacement therapy with sodium L-thyroxin (Eltroxin 50 mcg tablet) for life.

⊕ Dose: - **10** mcg/kg/d in neonate
- **6** mcg/kg/d in infant
- **4** mcg/kg/d in child

⊕ Dose is adjusted according to clinical response:

* Overdose → diarrhea, fever, tachycardia, increased appetite
* Low dose → constipation, hypothermia., bradycardia, decreased appetite

⊕ Follow up: - Clinical → monitor activity, milestones & growth.
- Laboratory → monitor T_4 and TSH (should kept in normal range).
- Radiologic → monitor bone age

Prognosis

- Diagnosis & treatment before 3 months → good mentality.
- Diagnosis & treatment at 3-6 months → variable response.
- Diagnosis & treatment after 6 months → permanent MR.
- As diagnosis of hypothyroidism is difficult in the first 3 months screening for thyroid function for all neonates is done in the first week of the life.

Acquired Hypothyroidism

Definition: Juvenile hypothyroidism with manifestations appearing after the 1st year. (After a period of normal thyroid function).

Causes

1- Thyroiditis
- Autoimmune thyroiditis(Hashimoto disease ,lymphocytic thyroditis): The commonest cause, either isolated or part of autoimmune polyglandular disorders
- Suppurative.
- Viral e.g. mumps.

2- Infiltration → in hemochromatosis, tumors, cystinosis.
3- Injury to thyroid → trauma, surgery, irradiation.
4- Iodine containing drugs e.g. cough mixtures.

Clinical picture

- Lethargy and poor academic progress.
- Short stature
- Skin: cold, pale, excess myxoedematous tissue
- Cold intolerance
- Constipation
- Delayed puberty (may be precocious).

Investigations

As before but:

a- Search for auto antibodies for Hashimoto thyroiditis e.g.
- Thyroid anti peroxidase antibody
- Anti thyroglobulin antibody.
- TSH receptor blocking antibodies

b- Check for associated auto immune disorders e.g. auto immune hepatitis, diabetes

Treatment: As in congenital hypothyroidism in addition to treating underlying cause.

- Goitre is enlargement of the thyroid
- Causes of congenital Goitre:
  1- Pendred syndrome.
  2- Endemic goiter.
  3- Dyshormonogenesis (but goiter may be delayed for months).
  4- Transplacental antithyroid drugs.
  5- Maternal Grave's disease.

N.B. Causes of deafness & hypothyroidism:
1- Pendred syndrome → organification defect , goitrous hypothyroidism & positive perchlorate discharge test (perchlorate discharge 40-90% of radioiodine, in contrast to 10% in normal subjects)
2- Endemic goiter
3- Neglected hypothyroidism
4- Congenital rubella syndrome.

Short Stature

Definition: height below 3rd percentile for age and sex (3 standard deviation below mean)

Classification

Proportionate	Disproportionate
- Upper segment/lower segment is normal for age - Height equal span	- Upper segment/lower segment is abnormal for age. - Height not equal span

I- Proportionate Short Stature

A- Normal types of short stature (about 90% of cases)

1- familial (genetic) short stature	2- constitutional growth delay
- Small birth length (normal for the family)	- Normal birth length up to 6 month then decrease for 2-3 years to become below 3rd centile.
- Normal bone age	- Delayed bone age
- Normal age of onset of puberty	- Delayed puberty
- Short adult height like their parents (around 3rd – 5th centile)	- Normal adult height as growth continue beyond the time the average child has stopped growing.

B- Pathologic types:

❶ Chronic undernutrition → marasmus & nutritional dwarfism

❷ Chronic systemic disease
- Malabsorption syndrome e. g celiac disease , inflammatory bowel disease
- Chronic hemolytic anemia e.g thalassemia
- Chronic renal failure , renal tubular acidosis, urinary tract infections.
- Chronic chest diseases e.g. cystic fibrosis, asthma , upper airway obstruction
- Chronic heart diseases : congenital , rheumatic , cardiomyopathy, endocarditis

❸ Endocrinal causes:
- Hypothyroidism.
- Hypopituitarism.
- Hypercortisolism (Cushing syndrome) and adrenal insufficiency
- Precocious puberty
- Diabetes mellitus.
- Diabetes insipidus.

❺ Psychosocial dwarfism: Due to disturbed maternal-infant relationship (maternal neglect or emotional deprivation).

❹ Syndromes with short stature e.g.:
- Turner
- Down
- Prader Willi

❻ Intra uterine growth retardation: 10 –15% will be short.

II- Disproportionate Short Stature

A. With short limbs e.g.

- Achondroplasia
- Rickets
- Osteogenesis imperfecta

B. With short trunk e.g.

- Skeletal dysplasia
- Fanconi anemia

Approach to Diagnosis

I- History

* Perinatal for:- Exposures ; infections , maternal drugs
  - Birth weight and length (differentiate prenatal and postnatal causes)
  - Problems e. g microphallus & hypoglycemia in hypopituitarism.
* Past history suggestive of: - Chronic systemic disease.
  - Endocrinal disorder
* Dietitic history for undernutrition or eating disorders.
* Family history for: - Parent height
  - Other short siblings
  - Onset of puberty in parents & siblings.
  - Infant / mother relationship

II- Examination

a. Clinical tests

* Check parent height → to rule out genetic causes.
* Evidence of maternal neglect e.g. dirty closing , bad infant / mother relationship
* Assess pubertal development by Tanner classification
* Determine type of short stature → proportionate or disproportionate
* Plot patient weight & height on growth charts:

Weight loss more than height loss in	Increased weight for height in
- Chronic systemic disease - Chronic undernutrition	- Hypothyroidism - Cushing - Hypopituitarism

b. Clinical examination

1- Evaluate nutritional state: check for muscle wasting , subcutaneous fat loss and signs of vitamin deficiencies.

2- Complete systemic examination: including cardiac, chest, abdomen, neurologic

3- Check for features suggesting endocrinal disorders e.g: hypothyroidism .

4- Check for dysmorphic features e.g Down , Turner

III- Investigations

1. Assess bone age by left wrist X-ray:
   - Normal in familial short stature
   - Delayed in most other causes
2. Search for systemic diseases by:
   - Urine analysis → for glucosuria, UTI, osmolality
   - Stool analysis → for malabsorption
   - CBC → for anemia
   - ESR → increased in infection & inflammation.
   - Urea, creatinine → for renal failure
   - Chest X-ray → for suspected chest disease
   - Echocardiography → for suspected cardiac defect
   - Serum electrolytes, pH ,calcium, phosphate for renal tubular and metabolic bone disease.
3. Hormonal assay:
   - Free T4 & TSH for hypothyroidism
   - Provocative growth hormone level & IGF-1 for hypopituitirsm
   - Night time blood or salivary cortisole level for Cushing
   - Blood glucose for diabetes.
   - Serum &urine osmolality for diabetes insipidus
   - CT skull for suspected pituitary tumor.
4. Chromosomal analysis (e.g. Karyotyping) for suspected cases

Treatment

1- Treat the cause e.g - EL-troxin for hypothyroid
- Recombinant growth hormone for hypopituitarism.

2- Growth hormone can be used in short stature with: - Chronic renal failure
- Turner
- Thalassemia

3- Adequate balanced diet

4- Psychologic support

Puberty

Definition: It is a period of growth lasting 5 years, consisting of 3 stages and includes physical, sexual & psychological changes.

Onset Girls: 8-13 years, Boys: 9-14 years.

Girls	Boys
- Breast development	- Testicular growth
- Pubic hair	- Pubic hair
- External genitalia maturation	- Penis and scrotal growth
- Feminine habitus	- Increased muscle bulk
- Axillary hair	- Body hair(beard, axillary)
- Oil secretion and acne	- Oil secretion and acne
- Menstruation	- First seminal discharge.

Diabetes Mellitus

Definition: chronic metabolic disease with:
- Deficiency of insulin **or** its action.
- Subsequent defect in metabolism of carbohydrates, protein & lipids.

Actions of insulin
- ↓ Blood glucose by → ↑ glucose uptake by cells.
  → ↓ Gluconeogensis.
  → ↓ Glycongenolysis.
- ↑ Lipogenesis.
- Anabolic effect.

Definitions

Diabetes mellitus is either insulin dependent (IDDM) or Non insulin dependent diabetes mellitus (NIDDM; maturity onset diabetes mellitus).

	Fasting plasma glucose	2hours post prandial
• Diabetes mellitus	> 126	> 200
• Impaired glucose tolerance	110-125	140 - 200

Values in mg/dl

Insulin dependent diabetes mellitus

Etiology: unknown, may be related to:

i- Genetic predisposition: associated with HLA -DR_3, DR_4, B_8 & B_{15}

ii- Auto immune response(Humoral & cell mediated response against islet cells):
Evidence:Presence of autoantibodies: Islet cell cytoplasm antibody (ICA),Insulin auto antibody (IAA),Glutamic acid decarboxylase antibody (GAD 65 antibody).

iii- Environmental factors:
Viral infection e.g.: mumps, coxachie B, measles, EBV

Pathogenesis

Insulin deficiency result in disturbance of carbohydrate, fat & protein metabolism.

1- Fat metabolism: ↓ Lipogenesis → ↑ free fatty acids (FFA) →↑ Ketone bodies.

2- Carbohydrate metabolism:
- Hyperglycaemia due to - ↓ glucose uptake & utilization by the cells
  - ↑ gluconeogenesis & glycogenolysis
- Hyperglycaemia leads to osmotic diuresis → polyuria & polydipsia

3- Protein metabolism: ↑ proteolysis → ↓ body wteight.

Clinical picture

Common presentations ⇓
- Polyuria, polydipsia, polyphagia & weight loss.
- Diabetic keto-acidosis (DKA).
- Secondary nocturnal enuresis

Insidious ⇓
- Lethargy & abdominal pain.
- Recurrent infections.

Diagnosis

- Fasting blood glucose > 126 mg/dl
- Glucosuria with or without ketonuria.
- Glucose tolerance test.

Complications

Coma ⇓
- DKA
- Hyperosmolar coma.

Complications of treatment ⇓
- Hypoglycaemia & hypoglycaemic coma.
- Insulin resistance
- Hypersensitivity to insulin

Chronic complications ⇓
- Growth retardation.
- Impaired immunity
- Microangiopathy ⇓
  - Neuropathy
  - Retinopathy
  - Nephropathy

Diabetic Keto Acidosis (DKA)

Definition: metabolic disorders due to acute insulin insufficiency.

Pathogenesis

Exposure of diabetic patient to stresses (e.g. infection, trauma, psychic).
⇓
Acute insulin insufficiency

- Hyperglycemia → Osmotic diuresis → Polyuria ⇓ Dehydration
- ↑↑ FFA → ↑↑ ketone bodies. → Ketonemia
  - Aceto acetic acid & B (OH) bytric acid ⇓ Metabolic acidosis → ketonuria
  - acetone → acetone odor of breath

Acute abdominal pain & vomiting → Dehydration

Rapid & deep breathing (kussmaul breathing)

Dehydration along with metabolic acidosis ⇒ coma.

Clinical stages of DKA

Early	Then	Later
♦ Polyuria ♦ Abdominal pain & vomiting	♦ Dehydration ♦ Acidotic breath	♦ Impaired Consciousness

Investigations

1- Diagnostic

Diabetic	Keto	Acidosis
♦ Blood glucose > 300 mg/dl ♦ Glucosuria	♦ Ketonaemia Serum ketones > 3 m.mol/l ♦ Ketonuria	♦ Metabolic acidosis - pH < 7.25 - HCO_3 < 15 meq/L - ↓ $PaCo_2$

2- Others

- Serum electrolytes (Sodium and potassium)
- Sepsis workup if suspected(WBCs count, blood culture, urine culture)
- ECG for hypo or hyperkalemia.

Differential diagnosis

❶ from other cause of acute abdominal pain

❷ from other causes of metabolic acidosis:

- Renal failure
- Organic acidemias.
- Lactic acidosis with sepsis & shock
- Ingestions → Salcylates
  → Ethylene glycol
- Acute diarrhea
- Renal tubular acidosis

❸ From other causes of coma in diabetic child:

A. Hyperosmolar non ketotic coma (rare):

- Blood glucose > 800 mg /dl
- Serum osmolality > 350 m.osmol/L
- Severe dehydration
- No or slight ketones
- Acidosis is mainly due to lactic acidosis

B. Hypoglycemic coma:

- Known diabetic with insulin overdose or exercise or delayed meals
- Reactive sympathetic stimulation(↑catecholamines): Pallor , hunger pains, tachycardia, sweating ,jitterness, tremor, irritability
- Glucopenia of CNS : Lethargy, limpness , may be seizures.
- Blood glucose < 50 mg/dl (< 2.6 m mol /l)
- Rapid response to I.V. glucose

Management

A. Acidotic phase (in ICU)

Insert 2 i.v lines ; one for I.V fluids & the other for I.V insulin(*given simultaneously*)

1. Fluid therapy

a. Shock therapy : - Saline or lactated ringer
- 20 ml/kg over 1 hour.

b. In the 2nd hour and until resolution of DKA: **(Milwaukee protocol)**

* Deficit is given with maintenance and given over next 24 hour

* Amount = $\frac{\text{85 ml/kg + Maintenance-Bolus}}{\text{23 hours}}$

- Deficit :85 ml/kg
- Maintenance (24hr) = 100ml/kg(for the 1st 10 kg) + 50ml/kg (for the 2nd 10) + 25 ml/kg (for all remaining kg)

* Type of fluid:
  - 0.45% NaCl plus 20 mEq/L K phosphate and 20 mEq/L K acetate
  - When blood glucose reaches 250 mg/dl add glucose 5% to saline as 14 mmol/L.
* Precautions:
  - Slow correction to avoid brain edema.
  - Acidosis almost always corrected by fluids &insulin infusion so, Sodium bicarbonate is not usually indicated. It is given only in severe intractable acidosis unresponsive to other therapy (pH < 7.1)

2. Insulin therapy

* Use regular (crystalline) insulin as slow infusion **0.1** unit/kg/hour without bolus dose
* Decrease insulin infusion rate when the patient become conscious and blood glucose drop below 300 mg/dl to avoid hypoglycemia
* Shift to subcutaneous insulin (0.2- 0.4 u/kg every 6-8 hr) when:
  - pH > 7.30
  - HCO_3 > 16 meq/L
  - Sodium is stable between 135-145 mEq/L.
  - No vomiting.

3. Flow sheet: For electrolytes , blood glucose , pH ,and fluid balance every 1-4 hours.

4. Treat precipitating factors e.g. Antibiotics for infections.

Hazards during treatment:

* Hypokalemia. * Hypoglycemia. * Brain edema

B. Post acidotic phase

Regular Insulin	Diet
Dose: 0.2-0.4 u/kg/ 6-8 hrs; SC Given 0.5 -1 hr before meals	- Sips of water , skimmed milk, Dietetic juice. Two days later give average diet (limit fat & carbohydrate)

C. Life long management

1. Insulin

Dose:

- Prepubertal **0.7** unit/kg/day
- Midpubertal **1.0** unit/kg/day
- End of puberty **1.2** unit/kg/day

Types:

- Short acting: - Regular insulin(Crystalline insulin, Humulin R)
  - Insulin Aspart (Novolog) /insulin Lispro (Humalog)
- Intermediate insulin(NPH, insulin Monotard , Humulin N)
- Long acting insulin(Glargine ; Lantus)

Regimens:

1. Two injections regimen:
   - 2/3 the total daily dose before breakfast
   - 1/3 the dose before evening meal
   * Each dose contain 1/3 rapid analog & 2/3 NPH(old method)
2. Three injection regimen:
   - NPH and rapid acting analog bolus at breakfast
   - Rapid acting analog bolus at supper
   - NPH at bed time
3. Multiple dose injections (recent ,very effective but expensive):
   - Use Glargine as basal insulin and premeals boluses of short acting analogs as Insulin Aspart (A) or Insulin Lispro (L)
   - Galrgine dose should be 25-30% of total insulin dose in toddlers and 40-50% in older children
   - The remaining part of insulin dose is divided evenly as 3 premeal boluses of insulin Aspart or Lispro
4. Continuous subcutaneous insulin infusion using automated insulin pump (recent)
5. Once daily long acting insulin at bed time plus pre meals inhaled insulin (recent)

Adjustment:

Increase **or** decrease insulin dose by 10% to keep:

- Fasting blood glucose = 60-80 mg/dl.
- Post prandial blood glucose below 180 - 220 mg/dl.

NB Ketonemia without dehydration & with normal pH will require 1 or 2 injections of insulin intramuscular or subcutaneous 0.1- 0.2U/kg 1 hour apart to halt ketogenesis.

2. Instructions

* Diet → 3 main meals with 2 snacks.
* In infections increase rapid acting insulin by 10%
* Decrease insulin before exercise

3. Monitor

a. Daily blood glucose at least 4 times;

- Before break fast
- Before lunch
- Before supper
- At bed time.

Initially test blood glucose also between 12AM & 3AM.to exclude nocturnal hypoglycemia

b. Glycosylated hemoglobin (Hb A_{1C}).

* Fraction of hemoglobin to which glucose has been attached.
* Measured as a percent of total hemoglobin.
* Value: Reflect average blood glucose over previous 2-3 months:
  - Normal, non diabetic → < 6%
  - Good control → 6 – 7.9
  - Fair control → 8 – 9.9
  - Poor control → > 10

(Nelson 2008)

Honey moon period

* Due to residual β-cell function → release insulin so About 75% of new diabetics complain recurrent hypoglycaemia which may recur for weeks to months.
* Advice: never stop insulin but reduce the dose to avoid hypoglycaemia.

Somogi phenomenon

* Due to large insulin dose > 2 u/kg/d → Late nocturnal hypoglycemia occur → ↑↑ anti insulin hormones → early morning hyperglycemia.
* Advice: Reduce the evening intermediate insulin by 10%

Dawn phenomenon

* Due to overnight growth hormone secretion → antagonise insulin action → early morning hyperglycamia.
* Advice: increase the evening intermediate insulin by 10%

Polyuria

Definition: Passage of excessive urine output > 2 litres/m^2

Causes

Endocrinal	Renal	Psychogenic
* Diabetes mellitus * Diabetes inspidus	* Hypokalaemia (<2.5 meq/l). * Renal tubular acidosis * Barttar syndrome * Hypercalcemia (> 13 mg/dl). * Chronic renal failure.	* Compulsory water ingestion

Diabetes Insipidus

Definition

Inability to produce concentrated urine due to either

1. Decrease ADH production ⇒ Neurogenic diabetes insipidus.
2. Lack of response of renal tubules to ADH ⇒ nephrogenic diabetes insipidus.

Clinical picture

i- Polyuria = Urine output : 4-10 Liter/day.

- Polydipsia (Irritable infants)
- 2ry nocturnal enuresis.
- If water inaccessible → Dehydration
  → Electroyte disturbance.
  → Fever (no sweating).
  → Shock in severe cases.

ii- Growth retardation

iii- May be features of the cause e.g ↑ ICT in craniopharyngioma

Investigations

1. Urine:
   - Specific gravity: 1002-1005 (diluted)
   - Osmolality : low (50-200 m.osmol/L)
   - No pathological constituents
2. Plasma osmolality : High (> 295 m.osmol /L)
3. Water deprivation test.
4. Vasopression stimulation test

Treatment

- ♦ Neurogenic → Desmopressin intranasal twice daily
- ♦ Nephrogenic → Adequate hydration.
  → Correct hypokalemia by:
  - Oral potassium.
  - Potassium sparing diuretics.
  → Indomethacine.

Neurology

Meningitis

Definition: inflammation of the membranes covering the brain & spinal cord.

Types: - Bacterial
- Aspetic e.g. viral, fungal
- Tuberculous

Bacterial (septic) meningitis

Causes

	G –ve bacteria	G +ve bacteria	
Cocci	• Nisseria meningitides type A, B, C, D, Y, W 135	• Pneumococci • Staphylococci	} ++ in infants & children
		• Streptococci	} ++ in neonates
Bacilli	• E.coli	• Listeria monocytogenes	
	• Hemophilus influenza.		

N.B. Peak of H. influenza infection between 6-12 month → incidence declined by vaccination

Transmission: - Droplet infection mostly
- Blood borne ⇒ in neonatal sepsis

Clinical picture

1. **Non specific**
   - High fever (may be hypothermia in neonates).
   - Poor feeding
   - Rose spots may appear on the trunk & extremities in meningeococcal septicemia.
2. **Features of increased intracranial tension**
   * Before fontanel closure → tense, bulging anterior fontanel
   * After closure of fontanels:
     - Severe bursting headache (irritability)
     - Blurr of vision
     - Projectile vomiting (in the morning, not preceded by nausea)
     - Cushing response (hypertension & bradycardia)
3. **Features of meningeal irritation**: (less sensitive in infants)
   * Neck rigidity (stiffness) → limited neck flexion
   * Opisthotonus → arched back
   * Kernig's sign → inability to extend the leg after the thigh is flexed to a right angle with the axis of the trunk.
   * Brudzinski leg sign: Passive flexion of one hip → flexion of the other hip and knee
   * Brudzinski neck sign: Passive flexion of the neck → flexion of the hip & knee.

4. Neurologic signs

* Stupor & drowsiness.
* Convulsions → usually generalized
* Coma

Clinical types

1- Meningitic form → the classic presentation as before.

2- Fulminant meningitis.

- Abrupt fever.
- Severe headache and convulsions.
- Rapidly progress to coma.
- Fatal within 48 hrs.

3- Septicemic form (usually complicating meningeococcal form)

- Very bad general condition
- Shock
- Purpura & ecchymosis
- Meningitis develop within 1-2 days (**or** not at all)

Complications

1- Syndrome of inappropriate secretion of antidiuritic hormone (SIADH) → so, maintenance fluids must be at 2/3 normal to avoid brain edema.

2- Neurologic complications:

- Increased intracranal pressure. → may leads to cerebral or cerebellar herniation
- Subdural effusion
- Cranial nerve lesions (commonly oculomotor, 6th & 8th nerves).
- Hydrocephalus.

3- Peripheral circulatory complications

i- Waterhouse Friedrichson syndrome

- Septicemia
- Shock
- Extensive purpura
- Adrenal hemorrhage (acute adrenal failure).

ii- DIC: Gangrenous patches & extremities

4- Dissemination of infection: endocarditis, arthritis , osteomyelitis

Investigations

1- CBC → leucocytosis.

2- Blood culture → may detect the causative bacteria.

3- Lumbar puncture & CSF examinations:

- Diagnostic for infection
- Determine appropriate antibiotics by culture & sensitivity.
- Evaluate treatment : CSF become sterile within 24- 48 hours of appropriate antibiotics
- Avoided in: marked increase intracranial pressure , shock and with bleeding disorder.

Condition	Appearance	Pressure (mmH_2o)	Protein (mg/dl)	Glucose (mg/dl)	Leukocytes / ml	Organism
Normal CSF	Clear	50 - 80	5 – 20	40-80	0-5 (monocytes)	Nil
Bacterial meningitis	Turbid	↑↑	↑↑ (> 100)	↓↓	↑↑ (100-60.000) Mainly PMNLs	* +ve Gram stain * +ve culture
TB meningitis	Web On stand	↑↑	↑↑ (> 100)	↓↓	↑ (10-500) Early PMNLs then lymphocytes	* Acid fast bacilli by zehl nelsen stain.
Viral meningitis	Clear	Normal or slightly ↑	Mild ↑ (< 100)	Normal or ↓↓	↑ (10-500) Early PMNLs later mononuclear cells predominate	* Viruses may be isolated

Differential diagnosis

1- From other causes of meningitis

2- Meningism :

- Non infectious meningeal irritation due to extracranial lesions
- Causes : Upper lobe pneumonia, otitis media, shigellosis
- CSF is normal

3- Brain abscess

4- Encephalitis

Management

A. Treatment

1- Antibiotic therapy

* Parenteral antibiotics according to culture and sensitivity for **2- 4** weeks
* While waiting for culture results ;the following combination is recommended:
  Ampicillin 200 mg/kg/d + 3rd generation cephalosporins 100- 200 mg/kg/d

* In suspected organisms:

Meningococci	- Penicillin G 400.000 unit/kg/d.
H.influenza	- Ceftriaxone100mg/kg/day
Pneumococci	- Vancomycin 60 mg/kg /day + 3rd generation cephalosporin (cefotaxime 200mg/kg/day or ceftriaxone) - Chloramphenicol 100mg/kg/day
Pseudomonas	- Ceftazidime
Listeria	- Ampicillin

(Nelson 2008)

2- Supportive therapy

✧ Measures to ↓ ICT:

- Hyperventilation to keep paco2 at 25 mmHg
- Mannitol 0.5 –1gm/kg iv
- Furosemide 1mg/kg iv

✧ Corticosteriods

Indications:

a- H. influenza meningitis:

- Value: Reduce inflammatory response caused by cell lysis
- Use dexamethazone 0.15 mg/kg/dose every 6 hours for 2 days

b- Septic shock to improve general condition.

c- Adrenal failure

✧ Treatment of convulsions:

- Immediate relief by diazepam or lorazepam
- Then phenytoin loading and maintenance

✧ Treatment of complications

B. Prevention:

- Isolation of the case
- Vaccination against H.influenza, meningococci, pneumococci.
- Chemoprophylaxis for contacts: e.g. rifampicin 10-20 mg/k/day ⇒ for 2-4 days.

Prognosis Depends on:

1- Age: the younger the age, the worse the prognosis.

2- Course: fulminant meningitis has worse prognosis.

3- Cause: - E.coli & staph →↑ fatality & ↑ long term sequalae.
- H.influenza & pneumococci → moderate prognosis.
- Meningococci → < 5% fatality & no residual disability.

Aseptic meningitis

Meningitis with no micro organisms detected in CSF by gram stain or bacterial culture.

Causes:

- Mostly viral → Herpes simplex virus
  → Enteroviruses (Echo & coxachie)
  → Mumps
  → Ebstein barr virus
- Protozoa → Malaria
  → Toxoplasma
- Non infectious → CNS leukemia
  → Intrathecal injection
  → Post vaccination.

Diagnosis: - CSF analysis
- Viral isolation

Treatment: - Supportive ± antiviral.

Seizures

Definition: Paroxysmal , time limited , involuntary change of motor activity and /or or behavior due to abnormal electric activity of the brain (**Nelson 2008**)

Convulsions

Definition: Excessive abnormal muscle contractions , usually bilateral , that may be sustained or interrupted (motor seizures)

Causes

A- Acute convulsions

1- Febrile convulsions.

2- First epileptic fit.

3- CNS causes:

- Infection → meningitis, encephalitis, brain abscess.
- Irritation → brain edema
- Tumors of the brain
- Toxic → tetanus *or* drug (e.g aminophylline)
- Hemorrhage → trauma, hemorrhagic blood diseases.
- Hypoxia → hypoxic ischaemic encephalopathy.
- Hypertensive, uremic, or hepatic encephalopathy.

4- Metabolic causes:

- Hypo (glycemia, calcemia, magnesemia)
- hypo **or** hypernatremia.
- pyridoxine (B_6) deficiency

B- Recurrent convulsions

1- Epilepsy

2- Tetany

3- Degenerative brain diseases

4- Chronic metabolic causes

- Hepatic encephalopathy
- Uremic encephalopathy.

Febrile convulsions

Definition: Convulsions in age vulnerable children due to:
- Rapid rise of body temperature.
- Due to extracranial causes(mostly viral)

Incidence:
- Affect 4% of children.
- Family history in about 20 % of cases (genetic base do exist)
- Recurrent in 30-50% of cases specially in those with family history

Diagnostic criteria

1- Age: 9 months - 5 years (rare before **or** after this age)

2- Temperature: Usually > 39°C, fits occur within 8-12hrs from onset of fever.

3- No evidence of CNS infection (e.g. meningitis, abscess)

4- Evidence of extracranial infection (e.g. tonsillitis, otitis media, roseola)

5- Type of convulsions:

Typical (simple)	Complex
- Generalized tonic-clonic. - Last < 15 min. - One fit only in the same illness. - The commonest form	- Focal - Last > 15 min - Recurring during the same illness - Uncommon.

6- Investigations

* Usually not needed in children with simple febrile convulsion.
* For complex form:
  - Lumber puncture and CSF analysis (specially if consciousness is clouded after a short post ictal phase)
  - Neuro imaging (CT, MRI)
  - Others : blood glucose , serum electrolyte , toxicology screen and EEG

Differential diagnosis

From other causes of convulsions with fever :

1- Meningitis.

2- Viral meningeo encephalitis (commonly herpes simplex)

3- Brain abscess.

4- Epileptic fit precipitated by associated fever.

Treatment

1- Fever control by paracetamol and tepid sponges or cold bath.

2- Diazepam (I.V. **or** rectal 0.5 mg/kg) if the fit lasts more than **5** minutes.

3- Treat the underlying cause → antibiotics.

4- Parent advice about fever control

5- At the onset of each febrile illness oral diazepam 0.3 mg/kg q8 hours is given for for 2-3 days to reduce risk of recurrence

6- Prophylactic anti-convulsants therapy (**Na valproate**) was used for cases that carry risk to develop epilepsy (e.g Complex form or with positive family history of epilepsy) .However , it is controversial now and no more recommended.

Epilepsy

Definition: Two or more unprovoked seizures that occur at interval greater than 24 hours (i.e recurrent seizures)

Causes

1. Idiopathic (primary) in 80% of cases
   - Genetic basis exist for many epileptic syndromes
2. Organic (secondary) in 20% of cases
   - Congenital cerebral malformation.
   - Degenerative brain diseases.
   - Post-traumatic.
   - Post-hemorrhagic.
   - Post-infection.
   - Post-toxic.
   - Post-anoxic.

Classification

A. Focal (partial) seizures

* Only one part of the body is involved i.e. focal.
* Types:

a- Simple partial seizures (SPS)	b- Complex partial seizures (CPS)
- No aura	- Preceded by aura (e.g. headache)
-May be motor, sensory or autonomic	- Only motor fits
- No automatism	- Automatism may occur → automatic behaviors as chewing, suckling, lip smacking or aggressive actions as rubbing & pulling of clothing.
- Consciousness is intact.	- Consciousness is impaired.

c- Partial seizures with secondary generalization.

B. Generalized seizures

The whole body is affected.

1- Absence seizures (petit mal)

Incidence: More in girls, uncommon below 5 years.

Description:

- Sudden cessation of all motor activities or speech with a blank facial expression and flickering of eye lids
- Precipitated by hyperventilation for 3-4 min or photic stimulation.
- Last < 30 seconds; after seizure patient resume preseizure activity.
- Frequently recurrent; may occur countless daily
- No aura , loss of consciousness nor postictal phase
- EEG → typical 3/second spike and generalized wave discharge.

2- **Generalized tonic clonic seizures** (Grand mal).

* The commonest form; pass in 3 phases.

Aura (pre ictal phase)	Attack (ictal phase)	Post ictal phase
A warning signs before the attack may exist suggesting a focal origin of the epileptiform discharge: e.g. localized muscle spasm or paraesthesia.	- Sudden loss of consciousness - Tonic phase: tonic contraction of whole body → rigid posture, apnea, cyanosis, rolling of eyes & drolling of saliva. - Clonic phase: rhythmic contraction. & relaxation of all muscles groups → tongue biting & loss of sphincter control.	- Semiconscious for 30 min-2hr. - Headache - Sleep.

3- **Myoclonic epilepsies**

- Sudden shock like repetitive contractions of group of muscles → with loss of body tone.
- Intact consciousness.
- EEG → 4-6 /sec. irregular polyspike waves.

4- **Infantile spasms**

- Starts in the 1st year of life ; peaking between 4- 8 months
- Brief symmetric tonic contractions of the neck ,extremities & trunk
- Which may be flexor, extensor or mixed
- Repetitive; usually in the morning
- A cry may precede or follow the spasm ; so may be confused with colic
- May be associated with developmental delay (West syndrome)
- EEG → commonly show hypsarrythmias (irregular, high amplitude waves)

5- **Atonic seizures**: sudden loss of body tone.

Investigation

1- EEG (Electro Encephalogram).
2- Metabolic screen: Serum Na, Ca, Mg, glucose
3- CSF examination in suspected CNS infections.
4- CT brain in - Focal lesions
- Increased intra cranial pressure
- Resistance to treatment

5- Serum anticonvulsant level for:
- At the onset of anti convulsant therapy to confirm therapeutic range
- Polytherapy
- Status epilepticus
- Drug toxicity

Differential diagnosis: from conditions mimic epilepsy

1- Syncopal attacks: - Fainting with loss of consciousness due to brief brain ischemia.
- Due to vagal stimulation (or arrythmia).

2- Breath holding attacks: - Occur between 3 mo - 6y.
- The child cries → hold his breath → turn cyanotic → becomes limp → rapid recovery.

3- Hystrical fits

Treatment of epilepsy

a. Advise the parent → to watch the child during swimming, passing traffic, ...
→ never to stop the antiepleptic drug suddenly.

b. Anti-epileptic drugs

* Rules - Only **one** drug is used with small dose → if no response → gradually increase the dose.
- In resistant cases a 2nd drug can be used alone or in combination.
- Duration of therapy is at least 2 years after last attack

	Na valproate	Carbamazepine	Phenytoin	Phenobarbitone
Use	Broad spectrum	- Generalized tonic colonic - Partial	Same	Same
Dose	20-40 mg/kg/d	10-20 mg/kg/d	3-5 mg/kg/d	Same
Side effect	drowsiness	+ GIT upset + anemia & leucopenia	hepatotoxic ataxia & rickets	drowsiness rickets

* Absence: Ethosuximide, Clonazepam(Rivotril), Nitrazepam (Mogadon), or Valproate
* Infantile spasm: ACTH or prednisone, or Vigabatrin (Sabril 30 mg /kg once daily)
* Adjunctive to poorly controlled seizures (add on drugs):
- Lamotrigine (Lamictal) - Topiramate(Topimax) - Gabapentin (Neurontin)
* Adjunctive to complex partial seizures : Tiagabine (Gabitril)

c. Ketogenic diet: - For infants < 2year with resistant myoclonic epilepsy.
- Most calories given form fat.(never used with valproate)

Status Epilepticus

Definition: Seizures continuous for more than 20-30 minutes or repetitive serial convulsions without return of consciousness.

Etiology

1. Prolonged febrile seizures (the commonest cause)
2. Sudden withdrawal of anticonvulsants in epileptic patients.
3. CNS anomalies or infections (e.g. encephalitis) or tumors.
4. Metabolic disorders e.g hypoglycemia, hypocalcemia and intoxications.
5. Inborn errors of metabolism.

Clinical types

1. Generalized (common): - Convulsive (tonic, clonic, myoclonic).
- Non convulsive (absence, atonic).
2. Partial (simple or complex).

Management

a. Initial treatment: ABCs

a) Airway: - Maintain airway.
- Section of secretions.

b) Breathing: - O_2 inhalation , assisted ventilation

c) Circulation: - I.V. fluids.

d) Samples of :

i- CSF to rule out CNS infections:

ii- Blood for: - CBC & arterial blood gases.
- Electrolytes (calcium, magnesium, Na).
- Glucose, urea, creatinine.
- Anticonvulsant level.
- Metabolic & toxicology screen.

e) Give glucose 10% 5ml/Kg for hypoglycemia.

b. Anticonvulsant drugs

1. Control convulsions by:

IV line available	- Diazepam or Midazolam 0.3 mg/Kg slow I.V. - If convulsions persist , repeat the dose (no more 3doses) - Alternative : Lorazepam 0.1 mg/kg slow iv
IV line un available	- Diazepam gel (Diastat) rectal or - Sublingual lorazepam or - Rectal diazepam or lorazepam diluted in 3 ml saline

↓

- Give immediately phenytion loading 15-30 mg/kg in 10 mg increments under ECG monitor (Phosphenytion ; Cerebyx is alternative).
- Some centers use phenobarbitone instead of phenytion

↓ ↓

If seizures un controlled	If seizures controlled
* Intubate and assist respiration * Drug options: - Midazolam infusion 20-400 µg/kg/hr - Propfol 2-10 mg/kg/hr - Barbiturate coma for 48 hours - Paraldehyde in glucose 5 % 150 – 200mg/kg slow iv - General anesthesia	Use maintenance dose of phenytion 3-5mg/kg in two equal doses started 12 hours later (or phenobarbitone)

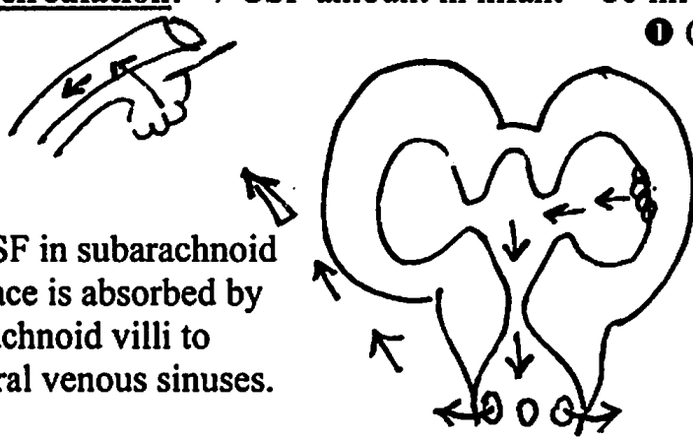
2. After control:

1. Maintenance of phenytoin & phenobarbitone 3-5 mg/Kg/day, devided/12hrs.
2. Search for & correct underlying cause e.g:
   - Antibiotics for infection.
   - Electrolyte disturbances.

Hydrocephalus

Definition: Enlargement of cerebral ventricles due to excessive accumulation of CSF. (with or without increase CSF pressure)

CSF circulation: → CSF amount in infant = 50 ml (150 in adult)



❶ CSF is formed by active secretion by choroids plexus in the lateral ventricles then → pass via foramen of Monro to the 3rd ventricle → then via aqueduct of Sylvius to the 4th ventricle → then via foramena of lnuscka & Magendi to the subarachnoid space

❷ CSF in subarachnoid space is absorbed by arachnoid villi to dural venous sinuses.

Causes of hydrocephalus

Obstruction of CSF flow within the ventricular system	Dysfunction in absorption **or** secretion of CSF
⇓	⇓
Obstructive **or** non communicating type	Non obstructive **or** communicating type

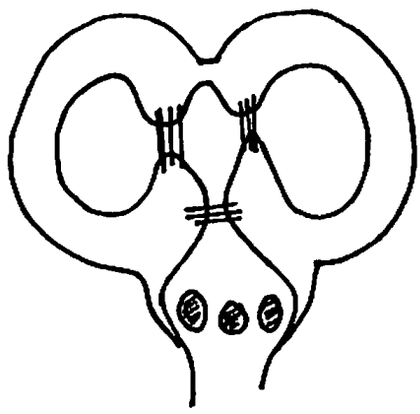
I- Causes of obstructive hydrocephalus

1- Obstruction of aqueduct of sylvius:

* Congenital atresia: - may be sex linked recessive.
  - may be associated with spina bifida occulta
* Obstruction from outside by: - brain tumors.
  - malformation of vein of Galen.
* Obstruction from inside: - Post hemorrhagic (specially in premature).
  - Post meningitic (T.B., pneumocci, mumps)

2- Congenital atresia of:

* Foramen of Monro.
* Foramina of Luscka & Magendi : cystic dilatation of 4th ventricle usually with agenesis of cerebellar vermis (**Dandy Walker malformation**).



3- Arnold Chiari malformation:
Congenital downward displacement of cerebellum, pons & medulla.

4- Congenital infection especially toxoplasmosis

5- Brain tumors

II- Non obstructive hydrocephalus

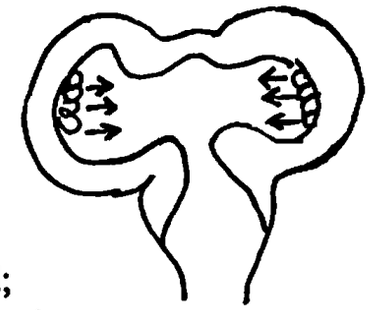


Defective CSF absorption

* Subarachnoid space adhesions
  - Post hemorrhagic
  - Post meningitic
* Leukemic infilteration.
* Dural sinus thrombosis
* Achondroplasia due to narrow jugular foramina →sigmoid sinus compression

Excessive CSF secretion

(Rare) due to:
- Choroid plexus papilloma
- Choriod plexus congestion as in meningitis.



Clinical picture

In infant:

1- Head signs are marked as cranial sutures are still opened;



- Large head with progressive increase in size (increasing head circumference on serial measurement).
- Fontanels are widely opened & bulging.
- Sutures are widely separated.
- Dilated scalp veins.
- Eyes deviated downwards → sunset appearance
- Skull percussion → cracked pot sound (Macewen sign).
- Craniotabes in all bones.
- Back of the skull:- Promeninet occiput in → Dandy Walker.
  - Foreshortened occiput in → Arnold Chiari.

2- Neurologic sings:

Mild, as rapid ↑ in skull size protect against marked increase intra cranial tension.
- Mild vomiting
- Squint
- Delayed motor milestones
- Pyramidal tract lesion signs are common specially in lower limbs.
- In advanced cases mental retardation & optic atrophy may occur.

3- General examination :
- Back of spine for tuft of hair, lipoma or angioma in spina bifida.
- Menjngeomyelocele in Arnold Chiari malformation.
- Cerebellar ataxia in Dandy walker malformation.
- Fundus examination for chorioretinitis in toxoplasmosis.

In older child:

Marked neurologic manifestations as the sutures are not easily separated with subsequent marked increase intracranial tension..
- -Bursting headache ,severe in the morning
- -Blur or vision
- -Projectile vomiting (unrelated to meals, not preceded by nausea)
- -Bradycardia & hypertension (Cushing response)

Diagnosis

1. Clinical picture
2. Cranial X-ray
   - Before closure of sutures - Wide fontanels, wide separation of sutures.
     - Craniofacial disproportion with large cranium.
   - After closure of sutures increase intra cranial tension (beaten silver appearance, wide sella)
3. Trans fontanel cranial ultrasound
4. CT & MRI → diagnostic; can detect ventricular dilatation.
   → detect degree of cortical atrophy.
   → may detect the cause.
5. Simultaneous lumbar & ventricular manometry:
   - Normally, both are equal
   - Ventricular pressure > spinal pressure in obstructive hydrocephalus
6. CSF examination: xanthochromia & cytoalbuminous dissociation in obstructive type

N.B: Transillumination is +ve in
- Hydrancephaly → relative increase CSF due to cortical brain atrophy.
- Severe hydrocephalus (marked ventricular dilatation).

Treatment

i- Medical: Decrease CSF by
- Carbonic anhydrase inhibitors; acetazolamide (Diamox tablets).
- Frosemide

Draw backs: - Transient effect. - Electrolyte & pH disturbances.

ii- Surgical - Choroid plexectomy or diathermy for choroid papilloma
- Extra cranial shunt operation.

Types	Complications
- Ventriculoperitoneal - Ventriculo artial (right). - Ventriculopleural.	- Shunt nephritis (immune complex mediated) - Obstruction - Infection commonly with staph epidermids. - Relative shortening as the child grow

N.B.: Shunt operation is of no value in:
Marked cortical atrophy (< 1 cm) – mental retardation– motor disability & blindness

Differential diagnosis

From causes of **macrocephaly** (H.C> 2 standard deviation above mean)

i- Cranial causes
- Conistitutional
- Achondroplasia
- Familial
- Anemia (chronic hemolytic)
- Rickets

ii- Intracranial causes
- Hydrocephalus
- Hydrancephaly
- Space occupying lesion e.g. tumor
- Subdural heamatoma or effusion
- Megalencephaly which may be due to:
  Cretinism
  Storage diseases (e.g. mucopolysacharidosis).
  Familial

Microcephaly

Definition: head circumference below the 3rd percentile for age, sex, or more than 2 standard deviation below mean for age, sex.

Causes

1- True microcephaly due to small sized brain.
2- Craniosynostosis due to early fusion of sutures.

I- True microcephaly

Criteria

- Skull sutures & fontanelles → normal.
- No increase intra cranial tension.
- Skull X ray show small vault.
- CT scan show brain atrophy.

Etiology

a. Genetic

- Familial → AR, (severe atrophy of frontal lobes → camel head)
- Chromosomal → trisomy 21,18,13

b. Non genetic

* Prenatal:
  - TORCH infection.
  - Fetal irradiation.
  - Maternal diabetes or phenyle ketonuria.
  - Maternal drugs e.g. phenytoin, &alcohol.
* Natal: Hypoxic ischemic encephalopathy.
* Post natal: Early meningitis& Encephalitis

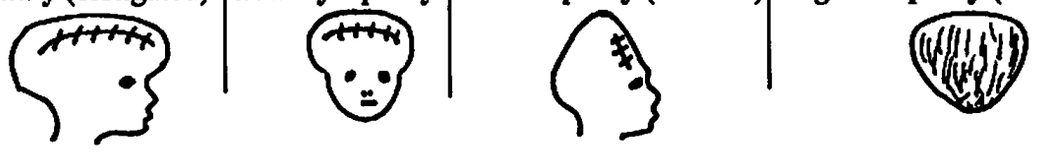
II- Craniosynostosis

Definition: early fusion of skull sutures;

1- Palpable ridge is felt at the affected suture.
2- If multiple sutures are affected:
- Microcephaly → brain atrophy.
- Increase intra cranial tension → hydrocephalus& beaten sliver appearance in skull X ray.

3- Skull examination → abnormal skull shape which may be:

Scaphocephaly (elongated) | **Brachycephaly** | **Acrocephaly** (Conical) | **trigonocephaly** (triangular)



Treatment

Surgical separation of skull sutures is indicated in:
- Cases with hydrocephalus.
- Cases with progressively increase intra cranial tension.
- Cosmotic reasons.

Cerebral Palsy
(Little Disease)

Definition

- Group of non curable motor syndromes resulting from disorders of early brain development.
- The term static encephalopathy is inaccurate as features of cerebral palsy often change with time.

Associations:

1- mental retardation (50%).
2- epilepsy (30%)
3- impaired hearing
4- impaired vision
5- supra nuclear bulber palsy may lead to:
   - feeding disorder (poor suckling & swallowing).
   - squint (30%)
   - speech disorders.
6- Persistence of primitive reflexes.

Causes

Pre natal (80%)	Natal (10%)	Post natal (10%)
- TORCH infection	- Birth asphyxia (HIE)	- Intraventricular hemorrhage.
- Cerebral dysgenesis	- Birth trauma.	- Meningitis, encephalitis.
- Fetal irradiation		- Metabolic e.g. phenyle ketonuria
- Placental dysfunction		- Hypoglycemia.
- Maternal infections during pregnancy		- Hyperbilirubinaemia.
		- Hydrocephalus.

Presentation:

1- Delayed mental milestones.
2- Delayed motor milestones.
3- Feeding difficulties.
4- Abnormal gait.

Topographic classification: (distribution of motor defect)

1- Monoplegia → Only one limb is affected
2- Hemiplegia → Upper and lower limbs on one side are affected
3- Diplegia → All limbs are affected, the lower more affected than the upper limbs
4- Paraplagia → Only both lower limbs are affected
5- Quadriplegia → All the four limbs are affected

Clinical Types

1- Spastic cerebral palsy

Criteria:

1- The commonest type (75%).
2- Pyramidal tract lesion signs:
   - Hypertonia.
   - Hyperreflexia
   - Positive Babinski sign.
   - May be clonus.

Types:

1- Spastic hemiplegia:
- Hand preference occur at early age.
- Walking is delayed, gait is circumdactive.

2- Spastic diplegia:
- Crawling is commando like rather than four limbed crawling.
- When suspended from axilla the lower limbs take scissoring posture.

3- Spastic quadriplegia:
- The most severe type.
- High incidence of associations e.g. (mental retardation, seizures,... .....).

4- Spastic monoplegia.

5- Spastic paraplegia.

2- Ataxic cerebral palsy

Criteria: of cerebellar ataxia(trunkal ataxia, nystagmus, stacatto speech,intention tremors, incoordination of voluntary movements,hypotonia)

3- Extrapyramidal (dyskinetic, asthetoid) cerebral palsy

Common causes: Kernicterus & birth asphyxia

Criteria:
- Hypotonia, replaced with time with hypertonia & rigidity.
- Abnormal movements chorio asthetosis.
- Supra nuclear palsy → feeding & speech disorders.
- May be deafness.

3- Atonic cerebral palsy
- Hypotonia → floppy infant
- Preserved deep tendon reflexes

5- Mixed cerebral palsy

Investigations

1- CT & MRI → detect degree of brain atrophy.
→ may detect the cause e.g. brain malformations.
→ rule out brain tumors & degenerative brain disease.

2- TORCH screen.

3- Metabolic screen.

4- For associations ⇒ audiometry, fundus ex. & EEG for cases with epilepsy.

Treatment
- Psychosocial support
- Care of feeding & defecation
- Physiotherapy
- Anti spastic drugs e.g. Dantrolene sodium, baclofen , Botox A injection
- Assist vision and hearing
- Assist walking: Walkers, standing frames, motorized wheel chair
- Treat epilepsy
- Rehabilitation according to the degree of mental retardation

Mental Retardation

Definition: Handicapping disorder with age of onset below 18 years characterized subnormal I.Q. (< 70%).

$$\text{I.Q. (Intelligence Quotient)} = \frac{\text{Mental age}}{\text{Chronological age}} \times 100$$

Diagnostic criteria

1- Subnormal intelligence quotient "IQ" (less than or equal to 70%)

2- Limitations exist in two or more of the adaptive skills e.g. communications, social skills, self care, safety, functional academics, work

3- Manifest before age of 18 years(if after 18 years, it is called dementia.)

Etiology

1.Non-organic causes (Physiological group)

- In about 80-90% of cases.
- Usually mild
- No demonstrable brain abnormality.

2.Organic (Pathological group)

* Chromosomal anomalies; e.g. Trisomy 21,18,13, klinefelter syndrome
* Genetic disorders e.g. Fragile-X syndrome , prader willi syndrome
* Cerebral palsy(See Before)
* Developmental brain abnormalities e.g. hydrocephalus
* Inborn errors of metabolism
* Familial retardation (environmental , genetic)
* Congenital infections
* Congenital hypothyroidism

Presentations

Age	Area of concern
Newborn	- Dysmrophic syndrome , microcephaly - Major organ system dysfunction (e.g. feeding and breathing)
Early infancy	- Concern about vision and hearing impairment - Failure to interact with environment
Late infancy	- Gross motor delay
Toddlers(2-3 yr)	- Language delay /difficulties
Preschool age	- Language delay /difficulties - Behaviour difficulties - Delayed fine motor
School age	- Behaviour difficulties - Academic under achievement

(Nelson 2008)

Prevention

- Proper prenatal- natal and post natal care.
- Vaccination against rubella for females (not during pregnancy).
- Neonatal screening to identify preventable causes of MR (e.g. phenylketonuria).
- Treatment of neonatal jaundice, hypoglycemia, hypothyroidism ....

Evaluation:

1. History for → Peri natal events
   → Developmental mile stones
   → Detailed pedigree
2. Examination for → Dysmorphism
   → Neurologic
   → Development
3. Vision and Hearing testing
4. Karyotyping
5. Fragile X screen
6. Neuro imaging
7. T4 ,TSH
8. Serum lead → If risk factors exist
9. Metabolic testing → e.g. plasma amino acids , urine organic acids , lactate

Treatment

Only rehabilitation of the child depending on the degree of mental retardation:

- ✧ Mild MR (IQ **50-70**) → educable (may need special classes)
- ✧ Moderate MR (IQ **35-50**) → trainable (they are trained to care for themselves)
- ✧ Severe MR (IQ **20-35**) → ± trainable.
- ✧ Profound MR (IQ **0-20**) → non trainable (so, they need full time nursing care).

Acute post infectious polyneuropathy
(Guillian Barre syndrome)

Etiology

- Auto immune demyelinating polyneuropathy; usually follow viral infection.
- Mainly affects motor nerves, but sometimes also sensory & autonomic nerves.
- It is affecting all ages → common at 3 – 12 yr.

Clinical picture

☆ **Motor** → acute ascending flaccid paralysis:

Criteria:

- Bilateral & symmetric usually
- Associated hyptonia & hyporeflexia even in uninvolved muscles.

Progress:

- Lower Limb → trunk → upper limb.
- Bulbar palsy → dysphonia, dysphagia & lost bulbar reflexes.
- Respiratory muscles → respiratory failure.

☆ Sensory → mild; tender calf.

☆ Autonomic → labile blood pressure & heart rate

Diagnosis

1- CSF → Cyto albuminous dissociation (↑↑↑ proteins & white cells <10/mm^3).

2- ↓ Nerve conduction velocity.

Fate : Regress in 90% in descending march over weeks to months.

Treatment

I. Supportive: Hospitalization and

- Cardiac monitoring
- Respiratory support
- Nasogastric feeding
- Care of bladder (catheterization & neostigmine).
- Physiotherapy

II. Specific

- IVIG : 0.4gm/kg/day for 5 days.
- Alternatives: - Plasmapharesis is equally effective as IVIG.
  - Combined IVIG and interferon is effective in some patients
  - Steroids are not effective **(Nelson 2008)**

Differential diagnosis: Causes of acute flaccid paralysis e.g.

1. Transverse myelitis
2. Poliomyelitis
3. Rabies virus
4. Varicella-zoster virus
5. Guillain-Barre syndrome
6. Tick-bite paralysis
7. Diphtheria
8. Botulism
9. Myasthenia gravis
10. Myositis
11. Hypokalemic periodic paralysis

Coma

Definition:Coma is a state of unconsciousness in which the patient can not be aroused even with painful stimuli.

Mechanism

1- Bilateral diffuse cortical lesion impairing all cortical functions.

2- Focal brain stem lesion affecting the reticular activating system.

Causes

A) Structural lesions:

Tumors, hematoma, infarction, abscess, hydrocephalus.

B) Non structural lesions:

Seizures: - Postictal - Non convulsive status epilepticus	**Vascular:-** - Confusional migraine - hypertensive encephalopathy - Vasculitis
Drug/poisons: - Barbiturates - Opiates - Carbon monoxide - Salicylates - Heavy metal	**Metabolic:** - Hypoglycemia - Hyperglycmia - Renal failure - Hepatic coma - Thiamine deficiency - Reye's syndrome - porphyria.
Infections: - Meningitis - Encephalitis - Septic shock - Hemolytic uremic syndrome	**Endocrine:** - Pituitary apoplexy - Hypo/hyperthyroidism - Hypoadrenalism

Management

1. A,B and C assessment
2. Start I.V. line and take blood sample for:
   - CBC.
   - Blood culture & toxic screen
   - Glucose& electrolytes
   - BUN& blood gases
   - Liver function tests, ammonia& lactate.
3. Urine specimen for routine analysis, CT scan, lumbar puncture are requested according to the clinical situation.
4. Control blood pressure, convulsion, and temperature control.
5. Antibiotics combinations for meningitis and acyclovir if herpes simplex encephalitis is suspected.

Pediatric basic life support (BLS)

- Step by step maneuvers that done by a rescuer to save life of an apparently collapsed victim

1. Safety: of the rescuer and then the victim

2. Stimulate

- Verbal and tactile stimulation.
- Never shake child.

☆If the child responds:

- No need for the Cardio pulmonary resuscitation (CPR).
- Reassess the case.

☆If does not respond: proceed in CPR

3. Shout

☆Shout for "help" while remaining with the child.

☆ Initiate BLS maneuvers immediately.

☆Alert the emergency Medical Services EMS providing the following information:

1- Location of the emergency and telephone number used.

2- Type of accident, severity, and urgency of situation.

3- Number and age of victims.

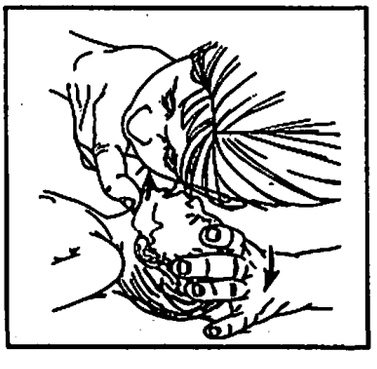
4- End the phone call only after the controller.

4. Airway

A) Opening the airway:

- secure the airway in the unconscious by one of the following methods:

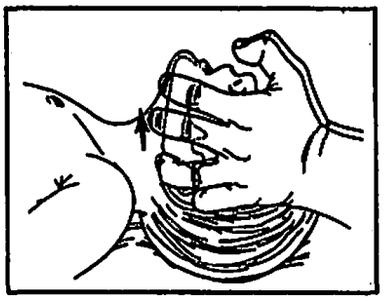
1- Head-tilt-chin lift:



✧ Suitable for all cases except when cervical trauma is suspected.

- Tilt the head back with one hand on the forehead .
- Place the head in neutral position in infants and slightly extended in older child
- Lift the chin upwards with finger tips of the other hand.

2- Jaw thrust maneuver:



✧ For suspected cervical injury.

- The hands placed on either side of the child head.
- raise both angles of the child's lower jaw
- Rescuer's elbow should rest on the surface on which the victim is lying.

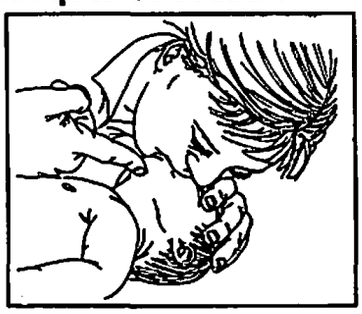
B) Checking the air way:

- Look into the mouth.
- Bind finger sweeps must never be performed
- If there is visible foreign bodies that can be removed by one finger sweep the rescuer can try if not, leave it.

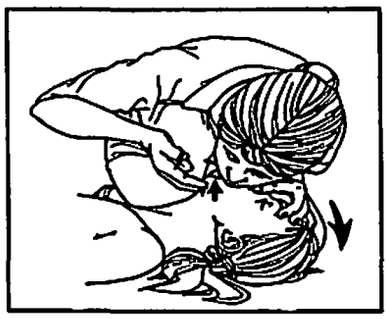
5. Breathing

- Check breathing: look, listen and feel (time allowed 10seconds).
- If the child is breathing spontaneously and effectively: reassess.
  - If no spontaneous effective breathing: rescue breathing.
  - Rescue breaths: up to five initial rescue breaths should be attempted, each breath should be slow, 1-1.5 seconds and taking breath inbetween .

Techniques of breath:



1. For infants⇒ Mouth-to-mouth and nose



2. For children⇒ Mouth-to-mouth, (nostrils should be closed).

✧ If chest movement not seen check position of airway.

✧ If despite repositioning of airway, foreign body obstruction is suspected.

✧ Once initial rescue breath has been delivered proceed to circulation.

6. Circulation

- The standard method for assessing circulation is feeling effective central pulse.
  - In infants: brachial pulse or femoral pulse.
  - In children: carotid artery.
- Observe sings of circulation "signs of life" as cough, moving or normal breath as not to spend time in feeling pulse.
- If pulse is found or there are signs of life: reassess breathing
- If no effective spontaneous breathing, rescue breaths should be continued at a rate of 20 breaths/min.
- If signs of circulation are absent e.g.:
  - No pulse
  - No signs of life.
  - Pulse is very slow < 60/min, with signs of poor perfusion Or you are totally unsure

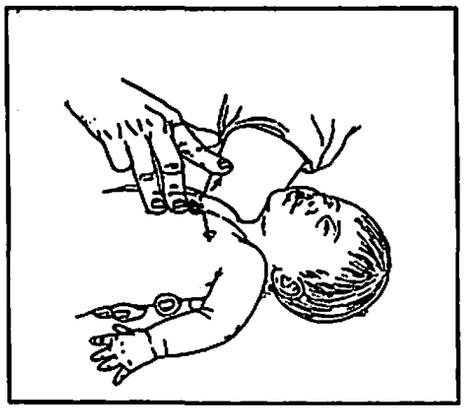
  Decision⇒ start external chest compressions.

Principles of external chest compression (ECC):

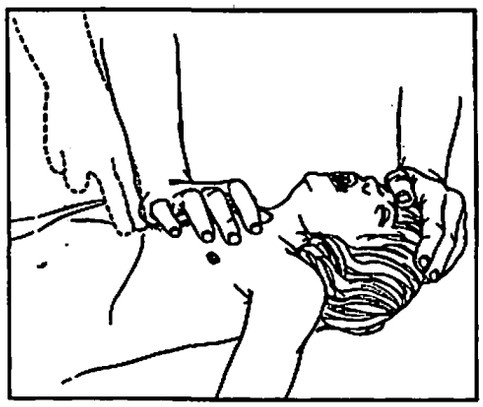
✧ Serial rhythmic compressions of the anterior chest wall that causes blood to flow to the vital organs.

✧ Place the child supine on a hard flat surface while keeping airway opened.

✧ Depress the chest tip approximately 1/3 to 1/2 the antero posterior diameter.



1. **In infants:**
   - Site of compression is one finger breadth below the inter-nipple line
   - Use two fingers technique or two thumbs-encircling hands technique.



2. **In children:**
   - Site of compression is one finger breadth above xiphoid process.
   - One hand technique is recommended for child<8 years
   - In older child (>8years) use two hands technique.

Compression ventilation ratio:

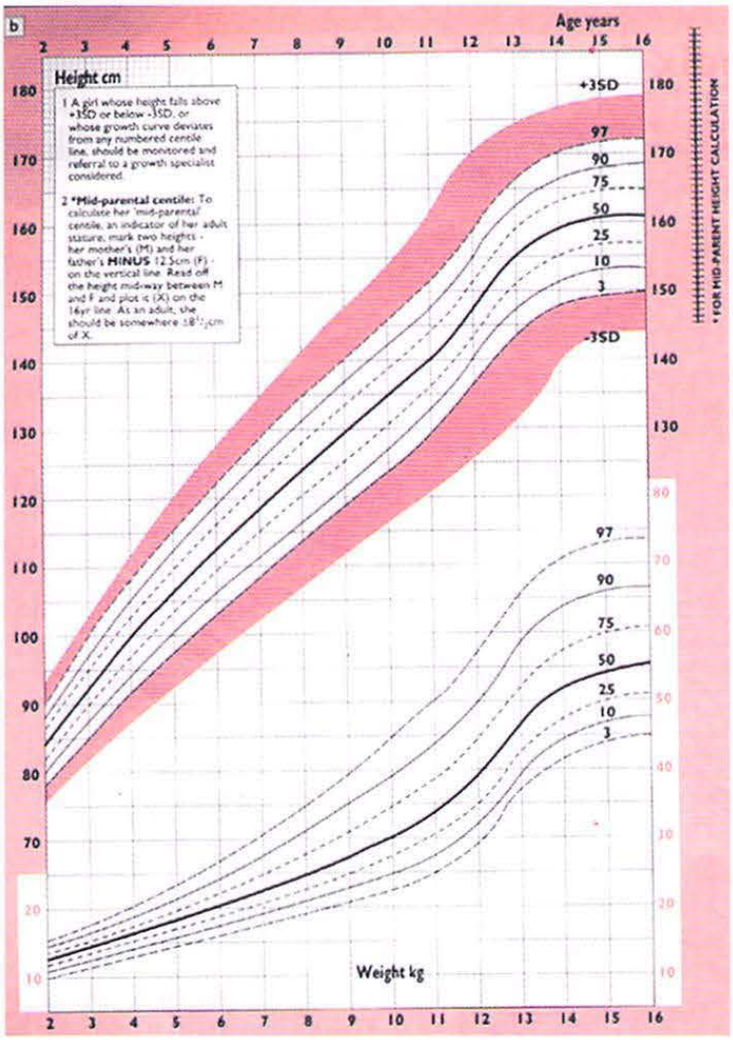
- In new born ratio of 3/1
- In infants and children ratio of 5/1
- In children > 8 years and adults ratio of 15/2

Reassess

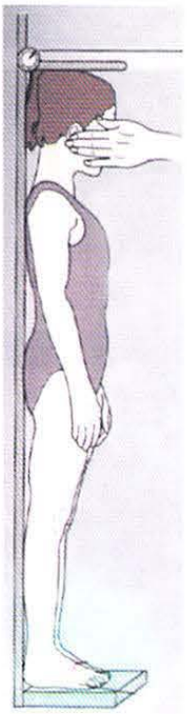
- After one minute CPR delivering, the rescuer should briefly stop to assess the ABC.

Commercial Press - Kalyoub - Egypt

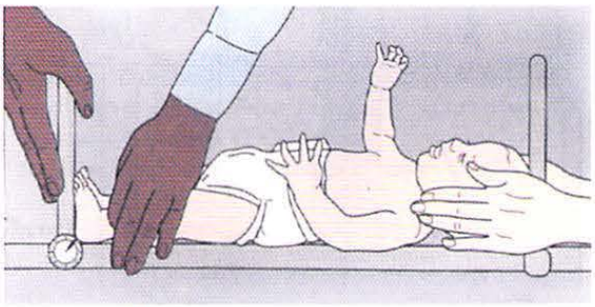
Growth



Growth chart for females form 2 to 16 years for weight & height.



Measuring of height.



Measuring of length.

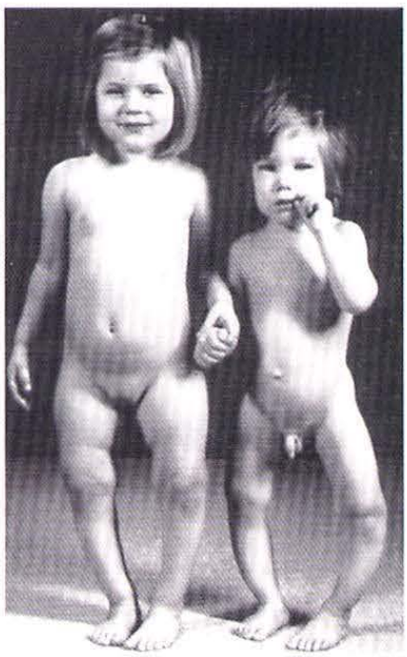
Nutrition



Cleft lip & palate.



Napkin dermatitis.



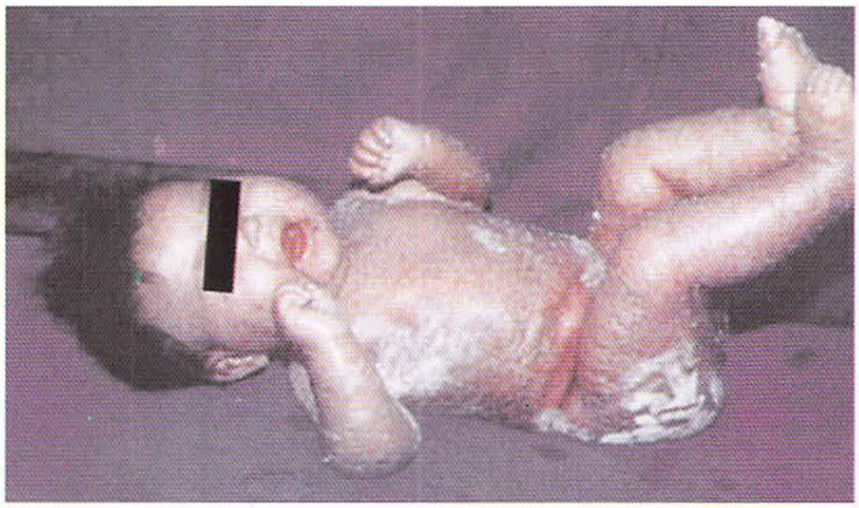
Familial hypophosphatemic rickets (note bowing of legs)



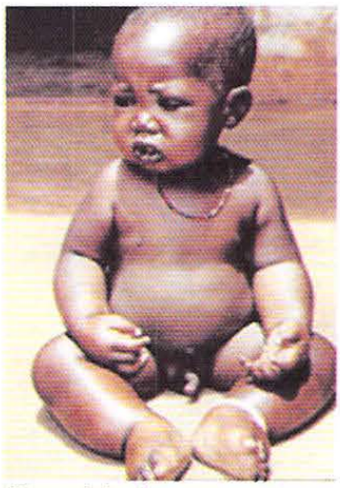
Marasmus (3 rd degree).



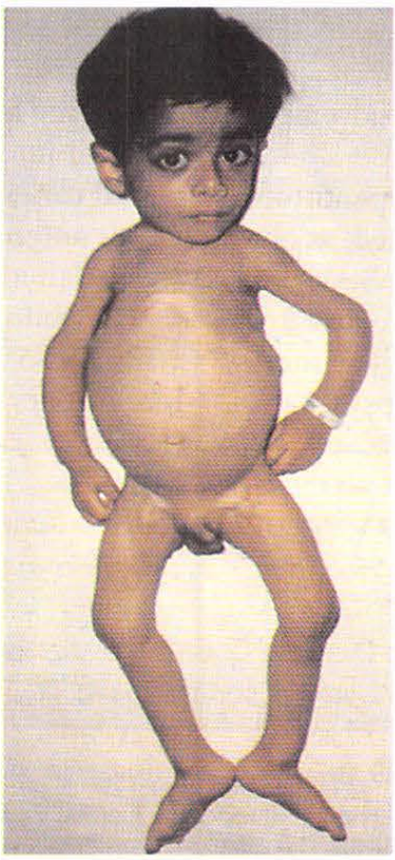
Marasmus with skin lesions.



Kwashiorkor



Kwashiorkor



Rickets.



Metaphyseal dysplasia (condition resemble rickets).

Down syndrome



Mongole Face



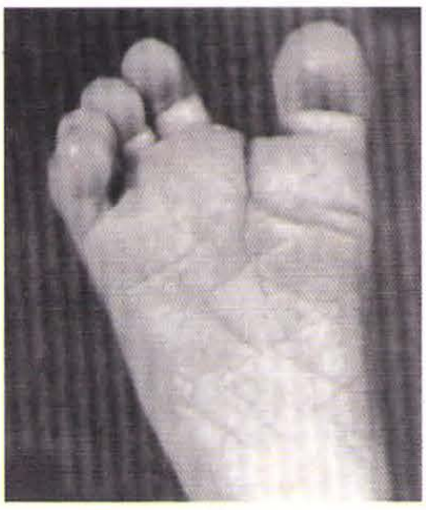
Bruschfield spots.



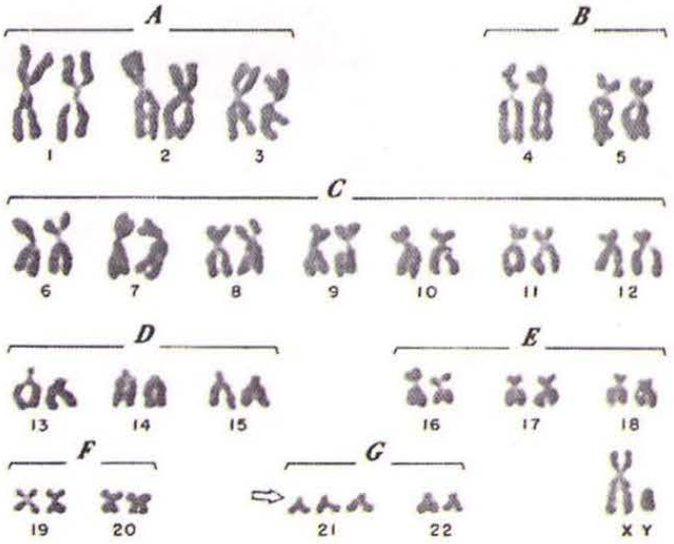
Simian crease.



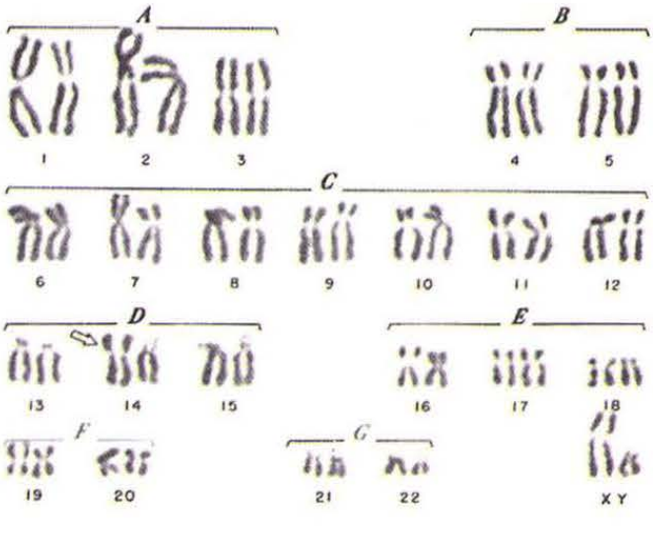
Marked hypotonia (Acrobat sign)



Wide space between first & second toes & ape crease.



Karyotype of non disjunction down 47(+21).



Karyotype of translocation Down ; 46 (t21,14)

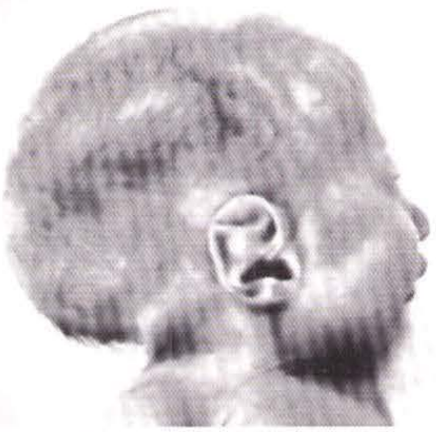
Edward syndrome (trisomy 18)



Fisting of hands.



Rocker bottom heel.



Prominent occiput.

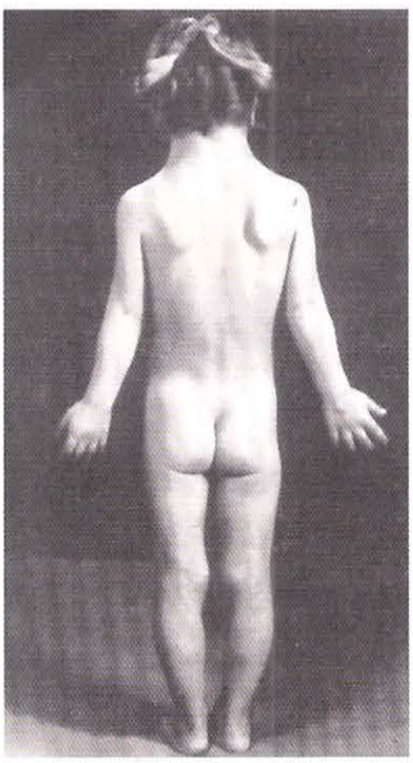
Turner syndrome.

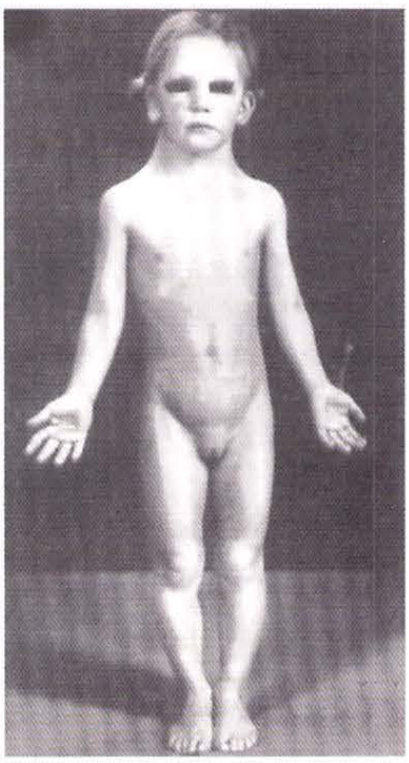


Low posterior hair line.



Webbing of the neck.





Short stature , wide carraying angle , wide spaced nipples.



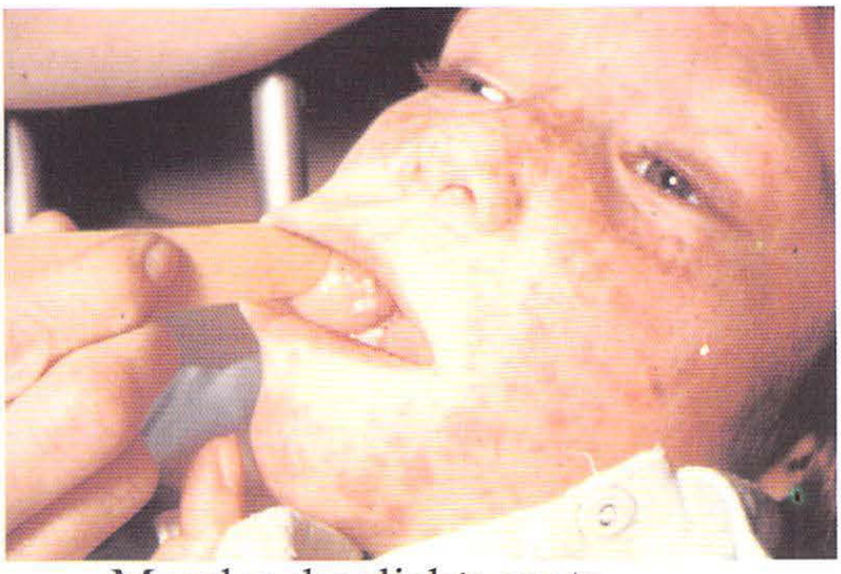
German measles.



Measles rash.



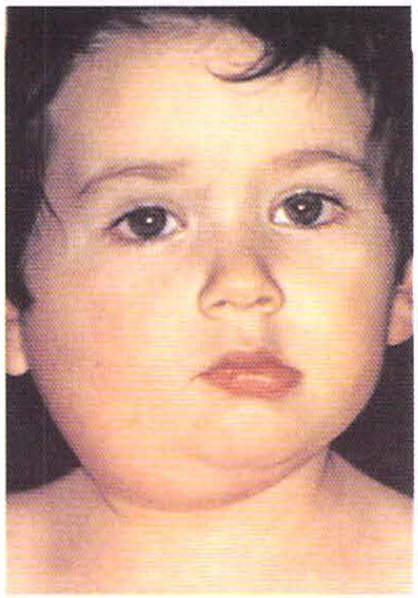
Measles rash ; early stge.



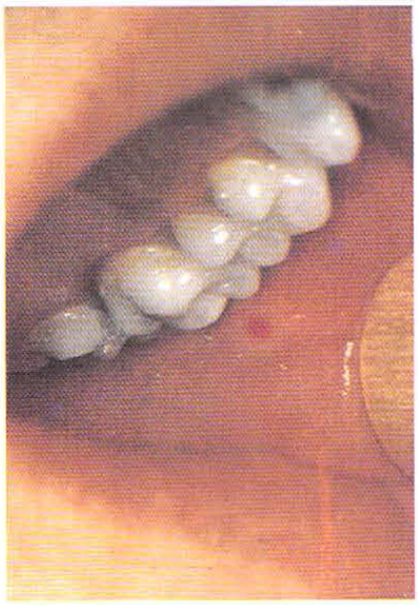
Measles ;koplick's spots.



Erythema Infectiosum
(slapped cheeks)



Mumpes (Unilateral)



Mumpes ; hyperemia of stenson duct.

Scarlet fever



White strawberry tongue.



Red strawberry tongue.



Pastia 's lines



Circumoral pallor.



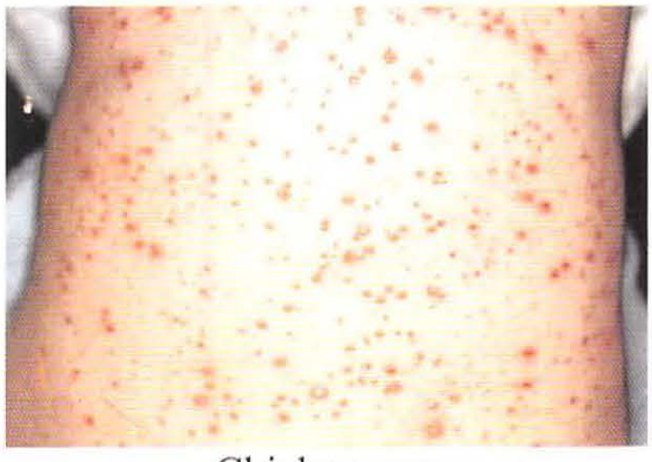
tonsillitis with pus exudate.



Pertussis (subconjunctival hemorrhage).



Diphteria (Bull neck).



Chicken pox



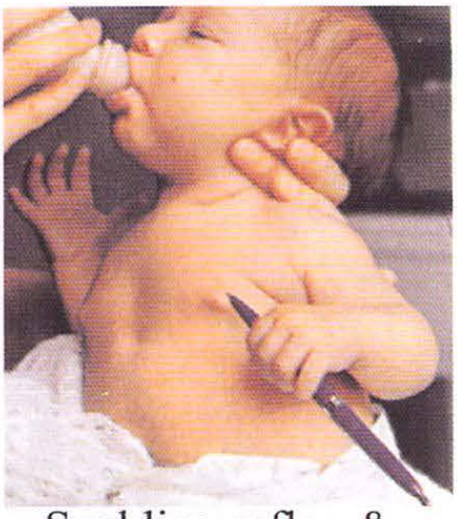
Chicken pox



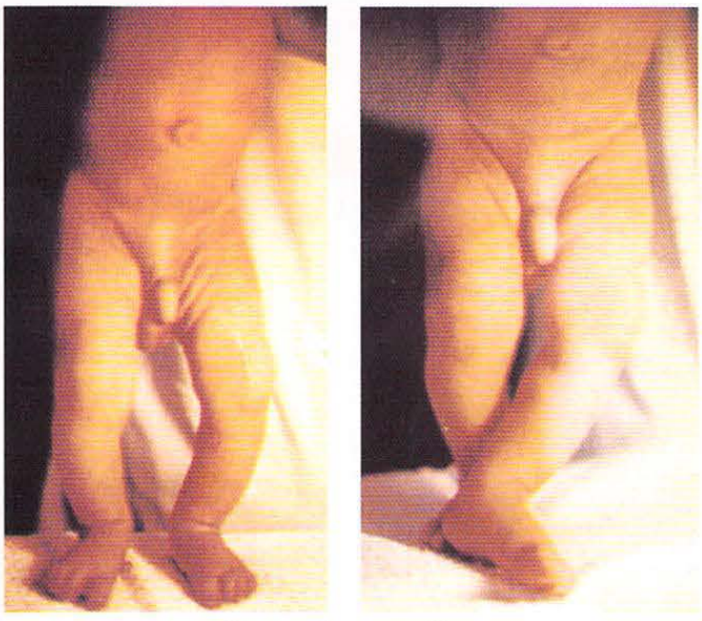
Cardiopulmonary resuscitation.



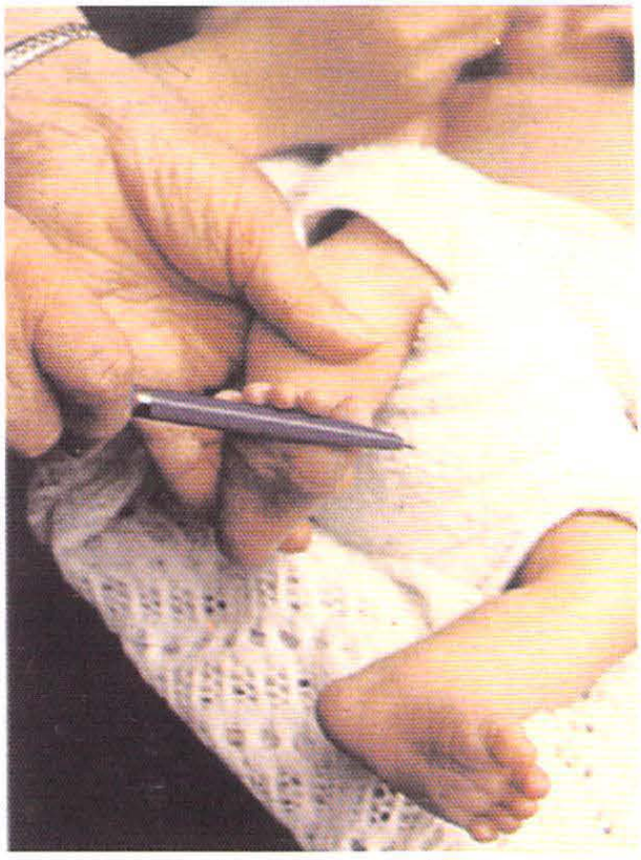
Moro reflex



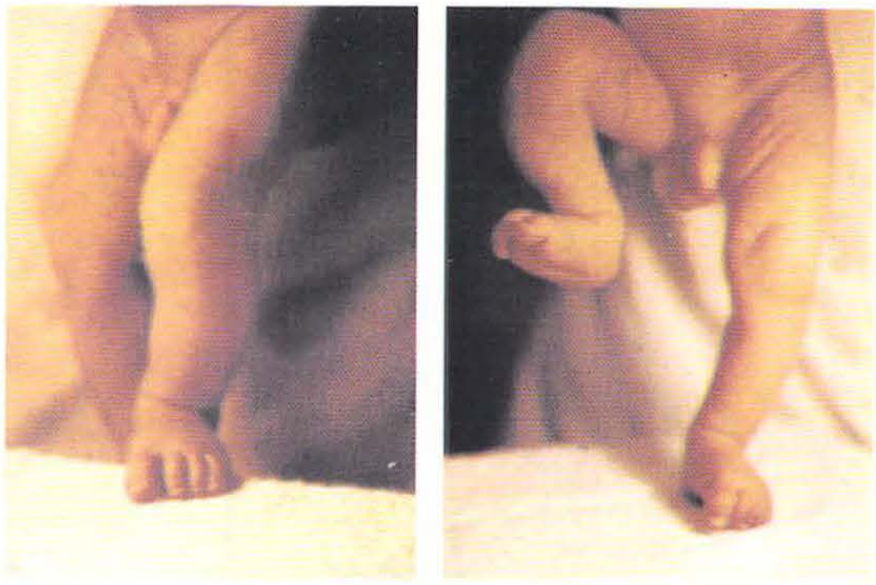
Suckling reflex &
palmar grasp reflex.



Stepping reflex.



Solar grasp reflex.



Placing reflex.



Caput succidenium.



Cephalhematoma (unilateral).



Cephalhematoma (bilateral).



Left facial & right klumpk 's palsy.



Erb 's palsy.



right facial palsy.



Phototherapy.



Normal Newborn.



premature.



Postmature.



Late sepsis with HSM & DIC.



Macrosomic baby.

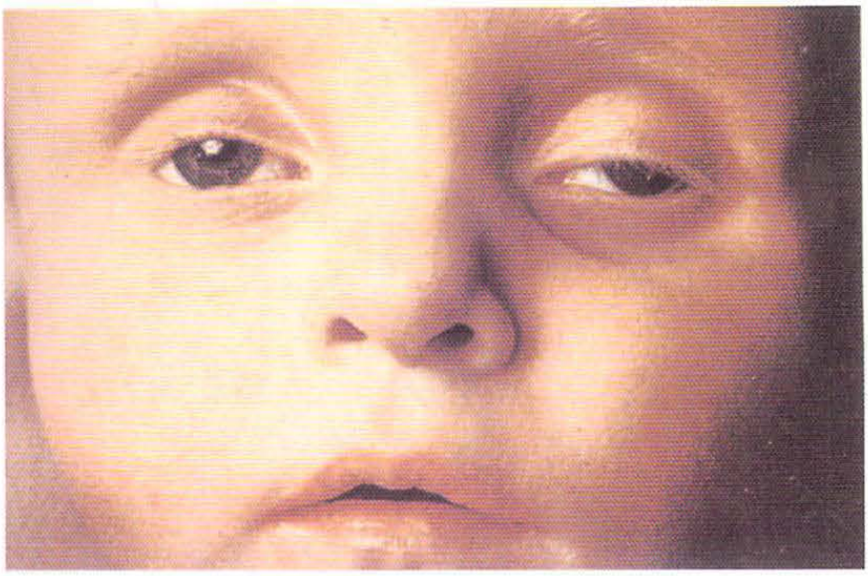


Mongolian spots.



Imperforate anus.

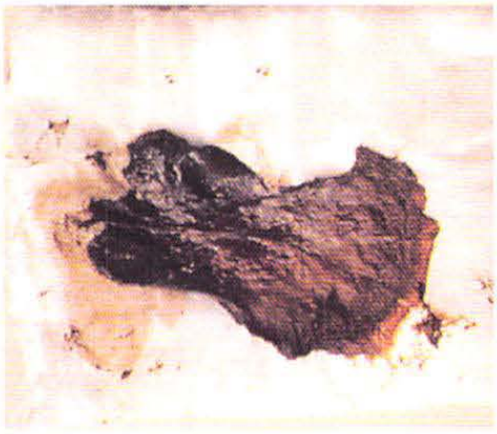
Diarrheal disorders



Dehydation ; sunken eyes.



Breast fed stool.



Starvation stool
(scanth , greenish).



Artificial fed stool.



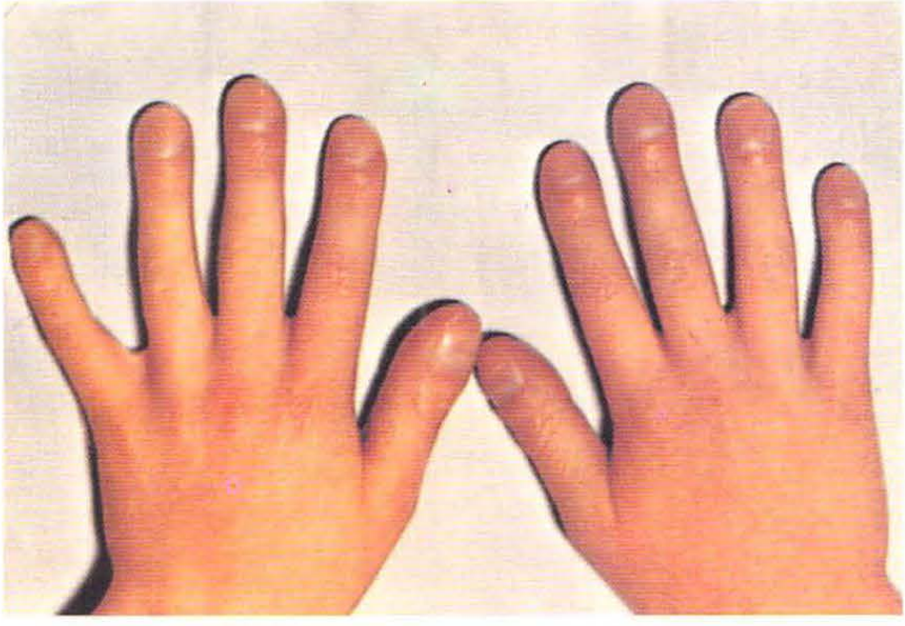
Oral rehydration.



Central cyanosis.



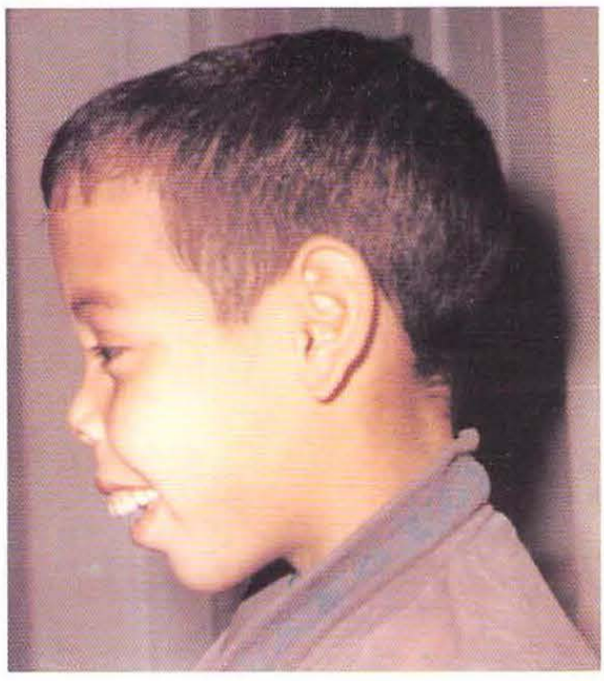
Erythema marginatum.



Clubbing (drum stick).



Splinter hemorrhage.

thlassemia.




purpura.




Henoch schonlein purpura.

Gastro enterology



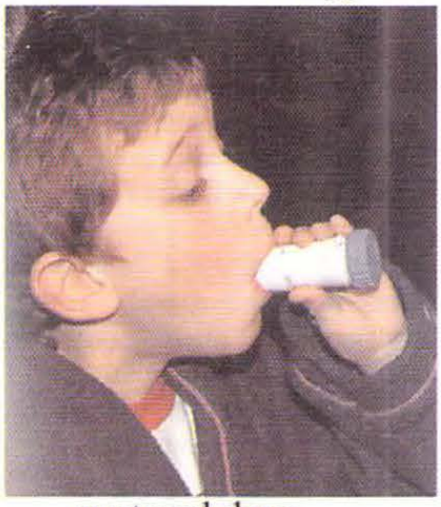
Tense ascites.



Congenital pyloric stenosis (visible peristalsis)

Chest

inhalation therapy in asthma.



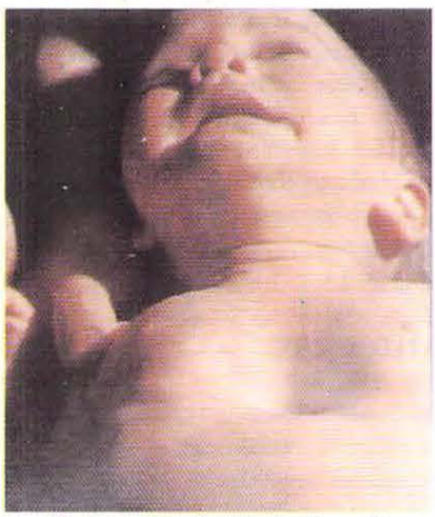
metered dose inhaler(MDI)



MDI with aerochamber.



Nebulizer



Substernal retraction in upper respiratory obstruction.



Closed drainage With underwater seal.

Nephrology



systemic lupus erythematosis
(malar rash).

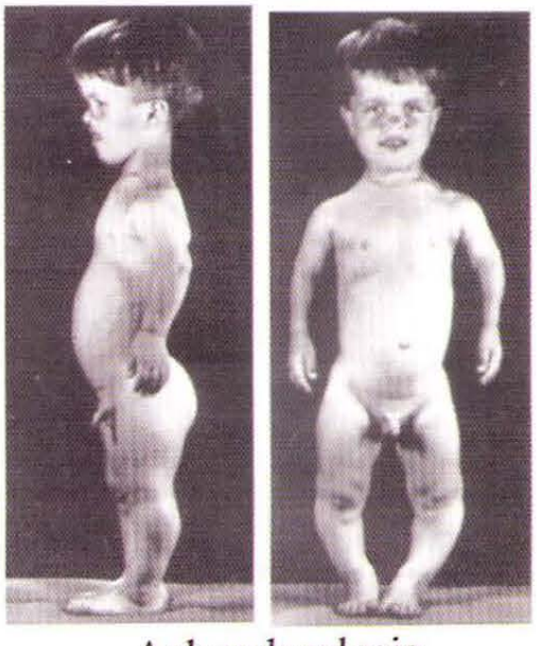


Cushingeod features.



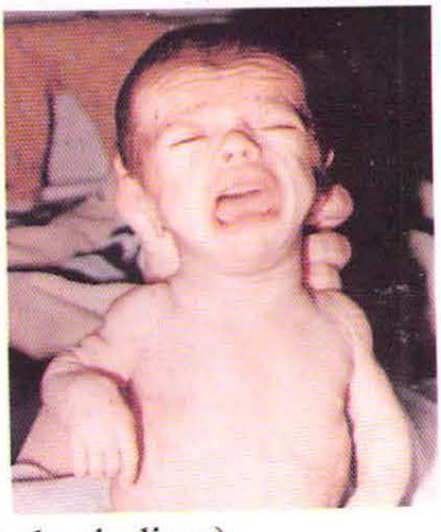
Ascites & Scrotal oedema
(nephrotic syndrome).

Endocrine



Achondroplasia.





Cretinsm (Congenital hypothyriodism)





meningitis (septicaemic form) before & after treatment.



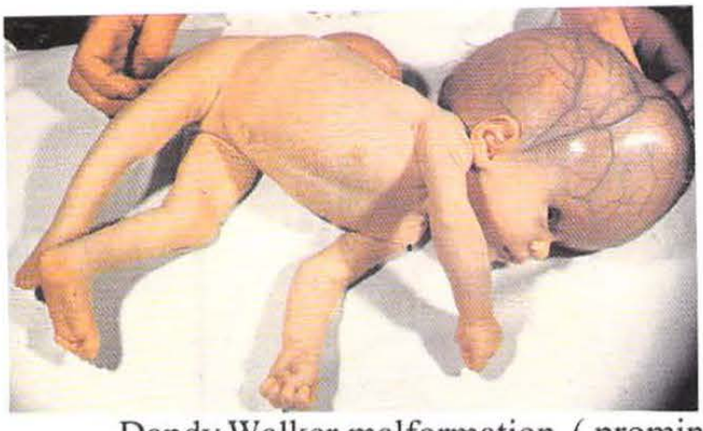
Oxycephaly.



hydrocephalus



hydrocephalus
(sunset appearance).





Dandy Walker malformation (prominent occiput & meinengeomyelocele).

Tetanus
(tonic convulsions) ▸

