NUTRITION AND MACRONUTRIENT DISORDERS

Energy: 1 gm of Carbohydrate gives 4 kcal.
1 gm of protein gives 4 kcal
1 gm of fat gives 9 kcal

By WHO: Energy requirement at 0-6 months → 118 kcal/1g/day
7-12 months → 108 kcal/1g/day
• Infants (up to 1 yr): Requires, on an average 103 kcal/kg/day energy.
At 1 yr → 1000 kcal 3 yrs → 1300
2 yrs → 1200 10 yrs → 2000

Proteins: Types - Non-essential amino acids (AA).
- Essential amino acids
• Essential amino acids are (**MeTT VIL PHLY)**: Methionine, threonine, Tryptophan, Valine, Isoleucine, leucine, Phenylalanine and Iysine.
• Histidine and Arginine are essential AA during infancy (as rate of synthesis of these AA is inadequate).

Requirement of protein: Adults 1 gm/kg.
1-3 months → 2.3 gm/kg 1-2 yrs →1.8 gm/kg
3-6 months → 1.85 gm/kg 2-4 yrs → 1.6 gm/kg
6-9 months → 1.65 gm/kg 4-6 yrs →1.5 gm/kg
9-12 months → 1.5 gm/kg 6-12 yrs → 1.4 gm/kg
***** Egg protein is considered a reference protein.

Protein efficacy ratio = $\frac{\text{wt gain or increase (in grams)}}{\text{Grams of protein consumed}}$

Digestibility coefficient = $\frac{\text{Nitrogen absorbed}}{\text{Nitrogen intake}} \times 100$

Biological value of protein = $\frac{\text{Nitrogen retained}}{\text{Nitrogen absorbed}} \times 100$

Net protein utilization = $\frac{\text{Nitrogen retained by body}}{\text{Nitrogen intake}} \times 100$
= digestibility coefficient × biological value

Amino acid score: $\frac{\text{No of mg of one AA per grams of protein}}{\text{Number of mg of same amino acid per grams of egg protein}} \times 100$

Lipids: Saturated FA are from animal source except coconut oil.
• Unsaturated FA (USFA) are mainly of vegetable source.

Essential fatty acids: There are two families of Poly USFA.
1. Omega 6 FA: Linoleic acid and arachidonic acid.
2. Omega 3 FA: Linolenic acid, Eicosopentonic acid (EPA) and Docosahexaehonic acid (DHA).
***** A minimum 3% of energy should be derived for linoleic acid 0.3% from linolenic acid.

Minerals: **Macro minerals**– Those with requirement > 100mg/day e.g.–Na, K, Cl, Ca, PO4, Mg, Se etc.

Breast Feeding

• Should be initiated as soon possible with in ½ hr in normal delivery; and 2 hrs in caesarian section.
• Average quantity of milk production is 500-800 ml/day.
• Exclusive breast feeding is for initial 6 months.

Comparison between different milk

	Human milk	Buffalo	Cow
Fat (g)	3.4	6.5	4.1
Protein (g)	1.1	4.3	4.2
Lactose (g)	7.4	5.1	4.4
Calcium (mg)	28	210	120
Iron (mg)	–	0.2	0.2
Vitamin (mg)	3	1	2
Energy (kcal)	65	117	67

Constituents of breast milk

Proteins: *Low as compared to cow's milk*.

• The proportion of whey proteins (lactalbulmin and lactoglobulin) is higher than that of caseinogen (60% to 40%).

• Whey proteins form fine curds which are easily digested.

Fats: Higher content of polyunsaturated fatty acids (PUFA), which promotes brain growth and may protect the individual from atherosclerosis in later life.

• Breast mild is also contains omega 2 and omega 6 (very long chain) fatty acids which are important for the formation of prostaglandins and cholesterol.

Minerals: low mineral and sodium contest. Breast feeding also protects from hypocalcaemia and tetany (due to its ideal 2:1 calcium phosphorus ratio and better calcium absorption).

• Iron present in the breast milk is low but very well absorbed.

Protection against infection:

• Breast milk is clean and uncontaminated. It has high concentration of secretary IgA, IgM, lysozyme, anti-staphylococcal factors and specific inhibitory substances against viral infections.

• High bifidus factor protect from infection by E coli.

• PABA provides protection against malaria.

• Breast feed infants has lesser diarrhea and respirator infections.

• Lactoferrin protects baby from enterobacteria.

Contraindications:

• Galactosemia and phenylketonuria.

• Congenital lactose intolerance.

• Mother on anticancer drugs, anti-thyroid drugs or sulphonylurias
Antipsychotic drugs (lithium), radioactive Iodine.

Virus that can be transmitted via breast milk: HIV, CMV-more trouble some in preterm, HBV, HSV, Rubella.

Weaning: It means taking the infant away from the breast and nourishment by other means.

Age	Foods	Frequency	Amount
6 months:	Soft porridge (khichdi, dalia); Well mashed potato	2times/day;	2-3 TSF
7-8 months:	Mashed food;	3 times /day;	2/3 of 250 ml cup
9-11 months:	Finely chopped; Or mashed food in between meals	3 meals + 1 snack;	3/4 of 250 ml cup
12-24 months:	Family foods; (Chopped or mashed) in between meals	3 meal + 2 snacks;	A full 250ml cup

Protein Energy malnutrition

Malnutrition includes Protein energy malnutrition and Obesity.

Wasting: Wt for ht < 2 S.D or < 3rd percentile i.e. < 80% of expected. It indicates acute onset malnutrition.

Stunting: Ht for age < 2 S.D or < 3rd percentile i.e. < 90% of expected It indicates chronic onset malnutrition.
Wasting and Stunted: If both Wt for ht **and** Ht for age < 2 S.D.
Assessment of nutritional status is by anthropometry, which includes: Weight, Height, MAC (mid arm circumference) etc.
Expected means the median (50th percentile) value of the reference standard.

Classification of protein energy malnutrition
IAP classification: Based on wt for age. Normal weight for age is > 80% of expected for age and sex.
Grade I PEM = 71-80% of expected for age and sex.
Grade II PEM = 61-70% of expected for age and sex.
Grade III PEM = 51-60% of expected for age and sex.
Grade IV PEM = < 50% of expected for age and sex.
Alphabet K is postfixed in presence of edema. For e.g. a male child weighting 8 kg at 2 years of age with pedal edema (50th percentile for 2 years is 12.3 kg) is classified as PEM Grade II (K).
***** IAP classification is simple, but it does not take in account the child's height.

WellCome Trust classification: Based on weight for age and presence or absence of edema
Kwashiorkor = Weight for age 60-80% of expected AND edema.
Undernutrition = Weight for age 60-80% of expected AND No edema.
Marasmic kwashiorkor = Weight of age < 60% of expected AND edema.
Marasmus = Weight of age < 60% of expected AND No edema.

WHO classification for undernutrition: Takes account of
1. Symmetrical edema 2. Weight for ht (wasting)
3. Height for age (stunting)

	Moderate undernutrition	**Severe undernutrition**
1. **Symmetrical Edema**:	No	Yes (edematous malnutrition)
2. **Wt for ht**:	70-79% of expected (< 80%) S.D score is –2 to –3 S.D (Wasting)	< 70% of expected S.D score is < –3 S.D (Severe wasting)
3. **Ht for age**:	85-89% of expected (< 90%) S.D score is –2 to –3 S.D (Stunting)	< 85% of expected S.D score is < –3 S.D (Severe stunting)

Age independent Anthropometric indices:

		Normal (severely malnourished)
Dugdale's	$\frac{\text{Wt (kg)}}{(\text{Ht in cm})^{1.6}} \times 100$	0.88–0.97 (< 0.79)
Rao's	$\frac{\text{Wt (kg)}}{(\text{Ht in cm})^{2}} \times 100$	0.15-0.16 (< 0.14)
Kanawati	$\frac{\text{Mid arm circumference (cm)}}{\text{Head Circumference (cm)}}$	0.32–0.33 ($\leq$ 0.25)
MAC (1-5 yrs)	Mid arm circumference	> 13.5 cm (< 12.5 cm)

***** Nutritional marasmus and kwashiorkor are two extreme forms of malnutrition.
***** Nutritional marasmus ↔ Mild to moderated undernutrition ↔ Kwashiorkor.

Mild to moderate undernutrition: Wt will be less. If nutrition deficit continue ht will also stunted. HC is not reduced significantly.
• Chest Circumference may not be > HC.

• Normally at birth HC > chest circumference. Chest circumference = HC by 9 months of age, after this chest circumference > HC.

Sequence of Loss of fat: Starts from buttocks → thighs (wrinkling of skin) → abdomen → scapula and then buccal pad for face (saturated fat is last to be depleted).

Marasmus: It is *characterized* by: **1**.Gross wasting of muscles and s/c tissue.
2. Stunting **3**. No edema
• Body wt < 60% of expected for age. Alert but is often irritable.
• Loose folds of skin at Glutei, inner side of thighs.
• Skin is dry, scaly, inelastic, and prone to be infected.
• Decreased MAC, prominent bony points. Hairs are hypopigmented.
• Abdomen is distended (wasted and hypotonia).

Kwashiorkor: It is *characterized by*: **1.** Marked growth retardation
2. Psychomotor changes (lethargic, apathetic) **3**. Edema
• Deficit is height is less than that in marasmus.
• Muscle wasting is masked by well preserved s/c tissue and edema.
Edema: Is due to following factors:
• Hypoalbuminemia.
• Retention of fluid and water due to increased capillary permeability as a result of infection; potassium deficiency (being contributing factor).
• Free radical induced damage of cell membranes.

Difference between marasmus and kwashiorkor

	Marasmus	**Kwashiorkor**
Appearance:	Old man appearance	Mooning of face, Dependent edema
Age group:	Infants	1-5 yrs
Prevalence:	Common	Rare
Weight:	< 60% of expected	60-80%
Growth retardation:	++	+
Edema:	Nil	++
Apathy:	Nil/mild	++
Mood:	Alert	Apathetic
Appetite:	Good	Very poor
Hair changes:	Nil/mild	+ (flag sign)
Skin changes:	Nil/mild	++ (Flaky paint dermatosis, ecchymosis, petechiae, follicular keratosis)
Fatty liver:	Absent/mild	++
Infections:	+	++
Life threatening Emergencies:	+	++
Serum protein and Albumin:	low to normal	Very low
Anabolism:	+	Very low
Response to Rx:	Good	Poor
Hormones		
Growth hormone:	Normal/High	Very High
Glucocorticoids:	Very High	High
Insulin and IGF:	Normal	Low
Glucagon:	Normal /Variable	Normal /Variable
Thyroxin:	Normal /Variable	Normal /Variable

*** Flag sign** is appearance of alternate bands of hypopigmented and normally pigmented hair.
*** Flaky paint dermatosis** is appearance of old paint flaking off the surface of the wood. It is due to hyperpigmented patches of skin desquamation to expose raw hypopigmented skin.

Etiology of PEM:
1. **Classical theory of protein deficiency:**
• In marasmus principal lacking factor in diet is energy.
• In kawashiorkor principal lacking factor in diet is protein. Edema is caused by hypoalbuminemia secondary to lack of protein diet.

2. **Gopalan theory of dysadaptation**: Outcome of protein energy deficiency is determined not by diet but child's response to deficient nutrients.
• Adaptation to chronic nutritional deficiency via cortisol leads to **marasmus.**
• **Kwashiorkor** is an acute condition where in body fails to adapt to the nutritional stress.

3. Golden theory of free radicals: Kwashiorkor results from an imbalance between the production of free radicals and their safe disposal → ↑↑ free radical peroxides and carbonyl formation.
• Free radicals → cell membrane damage → ↑permeability → edema

Changes in Body composition
1. Total body water is increased to 70-80% (normal is 60%).
2. BMR is decreased.
3. Synthesis of all protein is decreased.
4. GFR decreased.
5. Insulin decreased.
6. GH and cortisol increased.
7. Impaired chemotaxis, ↓Cell Mediated Immunity.
8. Normal phagocytosis, circulating immunoglobulin levels are normal or increased.

Management:
Treatment of complications: SHIELDED. That is treatment of-
S: Sugar deficiency (Hypoglycemia)
H: Hypothermia
I: Infections and septic shock
EL: Electrolyte imbalance
DE: Dehydration
D: Deficiencies of iron, vitamins and other micronutrients
(A) Hypoglycemia: When Blood Sugar < 54 mg%, give 1/v fluid 5 ml/kg of 10% dextrose stat and then dextrose fluid.
(B) Hypothermia: In < 1 yr, marasmic, and infections.
(C) Infections:
1. Gm -ve organisms: klebsiella, salmonella and opportunistic infections.

2. Work up for infections-at skin, UTI, chest, malaria etc.

3. Treatment includes broad spectrum antibiotics (3rd generation cephalosporin and aminoglycoside).

Septic shock: In 1st 2 hrs treat as for severe dehydration. If improvement occurs then treats as severe dehydration.
• If no improvement occurs then treat as septic shock.
(D) Potassium: Give 4 meq/kg/day (add after child has passed urine).
Sodium: Sodium should be restricted to prevent sodium over load, which can lead to CCF.
• CCF is due to over hydration, severe anemia, and high Na intake.

(E) ORS in malnutrition: **Resomal** (Rehydration solution for severely malnourished child). Can be made by mixing standard ORS 1 packet in 2 L of water and add 50 gm sugar and 40 ml Mineral mix solution.

Comparison between Std (standard) ORS and Resomal.

	Std ORS (mmol/L)	Resomal (mmol/L)
Glucose	111	125
Na	90	45
K	20	40
Cl	80	70
Citrate	10	7
Mg	-	3
Zinc	-	0.3
Copper	-	0.045
Osmolarity:	311	300

(F) Anemia: Hb < 4gm% or Hematocrit < 12%.
Give Blood transfusion slowly.
(G) Vitamin A deficiency: In < 6 month → give 50, 000 I.U.
6 month-1 yr → 1 lakh IV
> 1 yr → 2 lakh IU
***** If Xeropathalmia: Rpt above dose on Day 2 and Day 14.
***** For children > 1 yr but wt < 8 kg = ½ dose should be given.
***** Vitamin K: Single dose 2.5 mg.
***** Mg sulphate: 0.2 ml/kg of 50% solution.
***** Folic acid: 5 mg and then 1mg daily.

Dietary therapy: Remember by **BEST**
(B): Beginning of feeding (0-7 days)
(E): Energy dense feeding (After 7 days)
(S): Stimulation of emotional and sensorial development
(T): Transfer to home based diet (Before Discharge)
(B): It should be milk based, small amount, and frequent.

Energy: Start with 80kcal/kg/day (***** Weight is present wt).
• Over a week increase to 150-220 kcal/kg/day.
Fluid: 100-125 ml/kg/day.

Protein: Start with 0.7gm/kg/day. Over a week increase to 2-3 gm/kg/day and maximum to 4-5 gm/kg/day.10% of total calories should be from protein of higher biological value.

Nutrients: Give Zn, F.A, Copper, Se, Mg except Fe.
(E): Calories-150-220 kcal; Protein-4-5 gm/kg/day.
Minerals + vita + iron

Primary failure: When • failure to regain appetite by D4.
• Failure to start losing of edema by D4.
• Failure of disappearance of edema by D10.
• Failure to gain weight at least 5 gm/kg/day by D10 of theory.

Secondary failure: If weight gain not > 5gm/kg/day for 3 consecutive days at any time during rehabilitation phase.

Nutrition recovery syndrome: Apparent worsening with increase in liver size during nutritional rehabilitation.

Clinical Features:
- Hypertrichosis
- Gynaecomastia
- Parotid swelling
- Abdominal distension
- Ascitis
- Splenomegaly
- Eosinophilia
- tremors

Etiology: It is due to hormonal secretion or protein excess.

Obesity/over weight

Definitions:
1. Excess accumulation of fat in the s/c tissue and other parts of body.
2. BMI > 22 → overweight
   BMI > 25 → obesity
   ***** BMI = Wt (kg)/ HT $(m)^2$
- Body mass index (BMI) > 85^{th} percentile for the age and sex is overweight.
- BMI > 95^{th} percentile for the age and sex is obesity.

3. Skin fold thickness > 85^{th} percentile for age and sex is obesity.
4. Wt/Ht: Upto 120% of expected is over weight.
   > 120% of excepted is obesity.

Etiology: Exogenous factors (90%); Endogenous factors (10%).

Exogenous factors:
- Dietary factors
- Habits: sedentary life style, more T.V watching etc
- Decreased energy expenditure
- Genetic factors: Parental obesity. '**Ob gene**' codes for protein called leptin, which affects the appetite set point.

MC4R gene: Melanocortin receptor gene is being studied.
Treatment: Decrease Caloric intake, Increase Physical activity and Behavioral modification.

Endogenous factors: (A) Genetic factors

1. **Prader-willi syndrome**: Hypotonia, Hyperphagia, Areflexia.

2. **Pickwickian syndrome**: Due to deposition of fat in interstitial tissue of lung and abnormal ventilation response to CO_2.
- Deletion on chromosome 15. Short statured.
- It is Hypogonadotropic hypogonadism.

3. **Lawrence moon-Biedl Barget syndrome**: It has
- Retinitis pigmentosa
- Renal anomalies
- Hypogradism
- Mental retardation
- Obesity
- Polydactyly

4. **Beekwith-Widemann syndrome**: Foetal overgrowth syndrome

5. **Carpenter syndrome** (craniosynostosis): It has
- Acrocephaly
- Syndactyly
- Mental Retardation

(B) Hormonal causes:

- **Hypothyroidism**
- **Hypogonadism**: Hypogonadotropic hypogonadism. It causes abnormal deposition. Lack of anabolic steroid causes → decrease muscle growth.

• **Growth hormone deficiency**: Mild obesity

• **Pseudohypoparathrodism**: This present as mental retardation, short stature, Moon shape facies, Stocky body, Bone abnormalities, Seizures (hypocalcemic).
• **Hypercortisolism** or **Cushing's syndrome**: Centripetal obesity, Hypertension, Violaceous striae on abdomen, decreased glucose tolerance, Poor growth.

• **Hyperandrogenic ovary syndrome** (PCOD): Weight gain, Hirsutism, early virilism, Menstural irregularities.
(C) Hypothalamic obesity:

• **Froehlich syndrome**: Obesity, Short stature, Hyperphagia, Sexual infantilism and sometimes blindness.
• Traumatic, inflammatogic or neoplastic lesions of hypothalamus and pituitary regions.

Risk factors for obesity:

• Insulin resistance (DM) • HT • Cancer

• Gall bladder disease • Atherosclerosis

Treatment: Dietary modification.

Drugs: Binding agents: Ultrathin, non digestible fibre.
Bulking agents: Methylcellulose and ispaghula husk.
Pancreatic lipase inhibitor: Orlistat etc.
Surgery: Gastroplasty, Liposuction.

MICRONUTRIENTS IN HEALTH AND DISEASE VITAMINS

Vitamin A: Retinol, Retinal, Retinoic acid (most active form).
• Antioxidant property
• Richest source is Cod liver oil. Others Shark liver oil, Liver
• Vitamin A deficiency is called xeropthalmia.
• Vitamin A and β carotene are said to reduce incidence of cancers of Breast, Lung, Oral, Esophagus, and Bladder.

WHO classification of Xerophthalmia
Primary signs: X_1A: Conjunctival xerosis
X_1B: Bitot's spot
X_2: Corneal xerosis
X_3A: Corneal ulceration (< 1/3 of cornea)
X_3B: Corneal ulceration (> 1/3 of cornea)

Secondary signs: XN: Night blindness
XF: Fundal changes
XS: Corneal scarring
RDA: Infants: 300-400 µg; Children: 400-600 µg
Adolescent: 750 µg
Phrynoderma: Skin becomes scaly and load like. Now believed to be due to essential Fatty Acid deficiency.

Hyper vitaminosis A: This leads to *rupture of lysosomal membrane*.
Acute intoxication: signs and symptoms include
• Headache, vomiting, dizziness.
• Signs of increased ICP: Bulging Anterior Fontanel and/or Papilledema. Pseudotumour cerebri.
Chronic intoxication: Anorexia, dry skin, weight loss, Hepatosplenomegaly, Anemia, sparse hair etc.
In pregnancy if given (Retinoid) in 1st 6 weeks: It causes congenital craniofacial malformation in fetuses.

Folic Acid

• Folic acid is required for synthesis of purine, pyrimidine, and nucleoproteins and for methylation reactions that play important role in cell division and development.
• It prevent occurrence of recurrence of neural tube defect (NTD).

Deficiency causes: Ulcers, glossitis and impaired immunity.
• Impaired DNA synthesis and most commonly affects rapidly dividing cells e.g. intestine and bone marrow leading to Diarrhea and megaloblastic anemia (earliest manifestations).
• Increased thrombotic events (by reducing Homocysteine level).

Diagnosis: Red cell folate is considered to be more reliable index for assessing Folic acid deficiency and better indicator of body folate stores.
Requirement: RDA is 100 µg.
• All woman of child bearing age should consume 400 µg or 0.4 mg of folic acid to prevent NTD (To be taken *in peri-conception* period; *1 month before conception to 3 months* of gestation)
• **If previous affected** (NTD) **child**: 4 mg of Folic acid daily to be taken in peri-conception period.
***** 75% neural tube defects are preventable.

Vitamin C

• Antioxidant agent. It is essential for formation of collagen and intercellular matrix in teeth, bones and capillaries.

• Also involved in tyrosine metabolism, adrenal cortical functioning and electron transport.
Sources: Citrus fruits and vegetables.
RDA: 50 mg in preterm, 30 mg in term, 40 mg in older children.
Scurvy: Deficiency of vitamin C is Scurvy.

Clinical features: Present at 6-18 months.
• Breast feed infants are protected (except when mother is deficient in vitamin C).
• Child is listless, anorexic, and fretful. Wound healing in delayed.
• Gum bleeds, periosteum hemorrhage, conjunctival bleed.
• Bones are tender. Child keeps limbs in a frog like position (**pseudoparalysis**).
• Costochondral junctions become prominent → sharp and Angular (**scorbutic rosary** → separation of epiphysis of ribs and backward displacement of sternum).
• **Ricketic Rosary** → Dome shaped and semicircular. It is seen in rickets.
X-ray: Mainly seen at the lower end of femur and upper ends of humerus and tibia.
• It shows Ground glass appearance with **pencil thin cortex**.
• Metaphyses shows zone of well-calcified cartilage (**white line of frenkel**).
• Epiphyseal centers of ossification are surrounded by a white ring (**Wimburger sign**).
• Zone of rarefaction or destruction appears proximal and parallel to the white line.
• There is Sub-periosteal hemorrhage → periosteal elevation.
***** Ascorbic acid content of WBC offers a sensitive estimate of its status in the body (20-40mg/100 mg is normal).

***** ***White line of frenkel*** may also be seen in:
• Healing rickets • Severe PEM • Plumbism (lead poisoning)
• Acute leukemia • Congenital syphilis

***** ***Other causes of pseudoparalysis*:**
• Septic arthritis • Osteomyelitis • Congenital syphilis

Vitamin D and rickets

Dietary sources (D_2 or D_3)
(Skin) Sunlight (UV radiation) ↓ (Vit D3)
Physiology: 7-dehydrocholesterol ——→ Cholecalciferol

• Vit D_3 ——→ 25 (OH) D_3 (25- hydroxy-cholecalciferol)
In liver ↓
↓←——PTH←——↓Serum calcium
1, 25 $(OH)_2$ D3 (In kidney)

***** PTH = Parathyroid hormone
• 1, 25 $(OH)_2$ D3 is Metabolic active form of vit D. it stimulates:
1. Absorption of calcium, phosphate in GUT.
2. Promotes bone dissolution and mineralization.
(Therefore ↑serum calcium and alkaline phosphate activity).

Source: Fish, Liver, oil, egg yolk, butter.
RDA: Infants- 200 1.U ; Children- 400 1.U
Biochemical changes:
Decreased vitamin D3 →↓ absorption of Ca+ from GUT
↓
Increased PTH
↓
On Bone →Release of calcium
On kidney →↓ calcium excretion, ↓ PO_4 absorption (tubular)

↓

Normalization of Serum calcium and ↓Serum phosphate.

• After some time, compensatory ↑ in PTH cannot sustain normal calcium and so leading to ↓ Calcium and ↓ PO4, which interference with calcification of the osteoid tissue. Hence leads to manifestations of rickets.

***** Aminoaciduria in commonly associated with rickets.

Skeletal changes: **Normally** cartilage cells grow in parallel column from the thin epiphyseal plate towards metaphysis. These undergo proliferation and degeneration by osteoclastic activity → Calcium is deposited in the zone of degenerating cartilage, called zone of preparatory calcification.

In rickets: In this process of proliferation, degeneration and calcifications is incomplete.

• Cartilage cells are not degenerated and reabsorbed.

• Proliferation occurs irregularly.

• Calcification of osteoid tissue is also irregular and incomplete.

Clinical Features: Usually manifest in later half of the Ist year or in the second year.

Head: *Craniotabes.* It is earliest manifestation. Cranium felt like a ping pong ball, if compressed and release from sides.

• AF is large and open. Closure is delayed

• Frontal and parietal bossing.

• Eruption of primary teeth is delayed.

Trunk: **Rachitic rosary**: Costochondral junction becomes prominent.

• Pigeon chest: Sternum projects forwards.

• Harrison's groove: Horizontal depression, corresponding to insertion of diaphragm.

• Kyphosis, scoliosis or lordosis may occur.

Limbs: Widening of long bones (*broadening of waist*).

• Bowing of legs, knock knee, coxa vera.

Abdomen: Pot belly (protuberant) because of marked hypotonia.

• Visceroptosis.

***** In infancy: B/L lamellar cataracts.

X-ray: At lower end of radius and ulna:

• Fraying: Irregular epiphyseal plate.

• Cupping: Cup shaped depression at growing end.

• Widening/flaring of the metaphysis on either side.

• Diaphysis/Shaft of bone: Rarified and soft.

***** On administration of vitamin D, first radiological sign of healing is appearance of a white line of calcification.

Biochemical changes:

• S. Calcium is normal or low (normal is 9.5-11mg %)

• S. Phosphorus is low (< 4 mg %)

• S. alkaline phosphate high (> 500 mg %)

• PTH is raised (important finding).

Management: 1. Vitamin D3: 6 lakhs units stat 1/m. **or** orally over 10 days.

• Do X-rays after 4 weeks (to look for healing line of Rickets i.e. zones of preparatory calcification). If healing occurs no further treatment required.

• If no healing seen. Repeat dose and again look for healing after 4 weeks. If no healing then it is vitamin D resistant Rickets (After 2 doses of 6 lakhs units).

2. Deformities are corrected by orthopedic measures: Osteotomy, but after control of rickets.

3. Diet rich in Calcium and vit D3.

4. Steatorrhea/ malabsorption of fat: when present should be treated.

X-linked Vitamin D resistant rickets

• Most Common non-nutritional form of rickets.
• X-linked dominant disorder.
***** Defect is in proximal tubular reabsorption of phosphate and conversion of 25-(OH)D_3 to 1,25$(OH)_2D_3$. Therefore urinary phosphate excretion is increased.

Clinical Features: Lower limbs are involved.
• Short stature • Waddling gait
• Bow legs, caxa vara • Genu valgum
Investigation: Serum calcium normal or low. • *PTH Normal*
• Phosphorus decreased • Alkaline phosphate increased
***** Aminoaciduria, glycosuria and bicarbonaturia is absent.
Treatment: Oral phosphate (0.5gm-4gm/day in 4-6 divided doses) along with vitamin D (dihydrotachysterol)-0.02 mg/kg/day.

Vitamin D dependent Rickets (VDDR)

• Also called pseudo vitamin D deficiency.
Type I (VDDR- I): Autosomal recessive disorder.
• Manifest at around 3-6 months
• Defect is in enzyme 25 (OH) D_3 1α hydroxylase.
• Low levels of 1, 25 $(OH)_2$ D_3 even in presence of hypocalcemia, hypophosptatemia and increased PTH.

Treatment: Massive dose of Vit D_2 (2 lakh to 1 million U).

Type II (VDDR-II): Defect lies in reduction of binding of 1, 25 $(OH)_2$ D3 to its nuclear receptor and defective nuclear translocation.

Causes of rickets:
1. If ↓PO4 with aminoaciduria: Vit D deficiency or Malabsorption.
***** If glycosuria is present: Fanconi's disease, Hepatic disease, Anti epileptic drugs.
2. If ↓ Phosphate level without aminoaciduria: Proximal RTA
(Urine PH will be acidic)
3. If Normal Phosphate level: Vitamin D dependent rickets, Metaphyseal dysostosis.
4. If ↑ Phosphate levels: Renal osteodystrophy (in Chronic renal failure), Hypophosphatasia.

Zinc

• Necessary for RNA, DNA and ribosome stabilization.
• Critical for functioning of biomembranes.
• Synthesis and degradation of carbohydrates, lipids, proteins and nucleic acids.
• Part of several enzyme systems of body carbonic anhydrase etc.
Source: Red meat, Cheese, whole wheat, nuts, legumes.
***** Phytates and Iron (metals) inhibits zinc absorption.
Requirement: Preadolescent: 10 mg/day; in diarrhea 20 mg/day
Adolescent Male: 15 mg; Female: 12 mg
Deficiency causes:
• Growth retardation • Hypogonadism
• Anorexia, Alpoecia, acral dermatitis, Acrodermatitis entropathica
• Behavioural changes
• Increased susceptibility to infections (secondary to defective CMI)
• Zn deficiency in women causes: Premature delivery, IUGR, Neural tube defects.

Hemorrhagic disease of Newborn (HDN)/ Infancy

• A moderate decrease in factors II, VII, IX and X normally occurs in all newborn infants by 48-72 hrs after birth, with a gradual return to birth levels by 7-10 days of age.

• This transient deficiency of Vitamin K dependent factors is probably due to lack of free Vitamin K in the mother and absence of the bacterial intestinal flora in newborn.
• Breast milk is a poor source of Vitamin K. HDN appeared *more frequently in breast fed* than in formula fed infants.

Types of HDN:

	Early onset	**Classic Disease**	**Late onset**
Age:	0-24hrs	2-7 days	1-6 months
Site of Hemorrhage	Cephalohematoma, Subgaleal, Intracranial,GIT, umbilicus,intra-abdominal	GIT,Ear-Nose-throat (Mucosal),Intracranial,Circumcision, Cutaneous,injection sites	Intracranial,GIT, Cutaneous,Ear-Nose-throat (Mucosal),injection sites
Etiology/ Risk	Maternal drugs (Phenobarbital, Phenytoin, Warfarin, INH, Rifampin) that interfere with vitamin K. Inherited coagulopathy.	VitaminK deficiency, Breast feeding.	Cholestasis-Malabsoption of Vit K (Biliary atresia, cystic fibrosis, hepatitis) • Warfarin ingestion • Abetalipoprotein deficiency •Idiopathic in Asian breast feed infants
Prevention:	Possible Vit K at birth or to mother (20 mg) before birth. Avoid high risk medication	Parental Vit. K at birth. Oral vitamin K regimen requires repeated dosing over time.	Parental and high dose Vit K during periods of mal-absorption/cholestasis.
Incidence:	Very rare	2% if Vit K not given	Dependent on primary disease

***** PIVKA (Protein induced in Vitamin K absence). This is sensitive marker for vitamin K Status.

Treatment: Vitamin K.
• Fresh frozen plasma for serious bleeding.
***** PT/PTTK is prolonged. After Vit K administration → become normal.

NEWBORN INFANTS

• Average weight at birth is 2.8 kg.

• Normal birth weight is 2.500 to 3.999 kg.

• Low birth weight < 2.5 kg. Very low birth weight (VLBW) < 1.5.

• Extremely low birth weight (ELBW) < 1 kg.

• AGA is appropriate for gestational age.

• Small for gestational age (SGA): Birth weight < 10^{th} percentile.

• Large for gestational age (LGA): Birth wt > 90^{th} percentile.

• Preterm: Born before 37 weeks of gestation.

• Term: Any neonate born between 37 and 42 weeks of pregnancy.

• Post term: Born at gestation age of 42 weeks or more.

• HR is120-160 / min.

• Normally newborn pass urine with in 48hrs and pass meconium with in 24 hrs.

• Normal baby loses during Ist week. Regain weight by D10 and then continues to gain weight at 25-30 gm/day for next 3 months.

• Low Birth Weight: loses 10-15% of weight during 1^{st} week. Regain birth weight by 10-14 days.

• Term neonates: Wt loss (ECF) is 7-8% (5-10%) during 5-7 days of life. Regain birth weight by 7-10 days.

• Preterm neonates: Wt loss (ECF) is 10-15% during 7-10 days of life. Regain birth weight by 10-14 days.

Neonatal resuscitation

Normal fetal to neonatal transition –

The changes that occur soon after birth are –

1. Fluid in the alveoli of the lungs is absorbed and replaced by air
2. Low resistance placental circulation is replaced by high resistance systemic circulation.
3. The pulmonary blood vessels relax and pulmonary vascular resistance falls. Increase in O_2 concentration causes closure of ductus arteriosus.

Initial breaths require high inspiratory pressure (30-40 cm of water) to expand the lungs and remove the fluid from alveoli. Subsequently lower inspiratory pressures (15-20 cm of water) are adequate to maintain gaseous exchange.

Response of the baby in abnormal transition

- Cyanosis
- Bradycardia
- Systemic hypotension
- Depression of respiratory drive due to poor oxygenation of the brain

- Poor muscle tone due to low oxygen supply to brain and muscles

Physiology of asphyxia

- Oxygen deprivation

Rapid breathing f/b

- Ceasing of respiratory efforts
- Falling of heart rate
- Neuromuscular tone decrease

Primary Apnoea

Responds to tactile stimulation & oxygen

If oxygen deprivation continues then

- Gasping respiration & HR falls
- **Blood pressure falls**
- Infant becomes flaccid

Secondary Apnoea

Responds to positive pressure ventilation

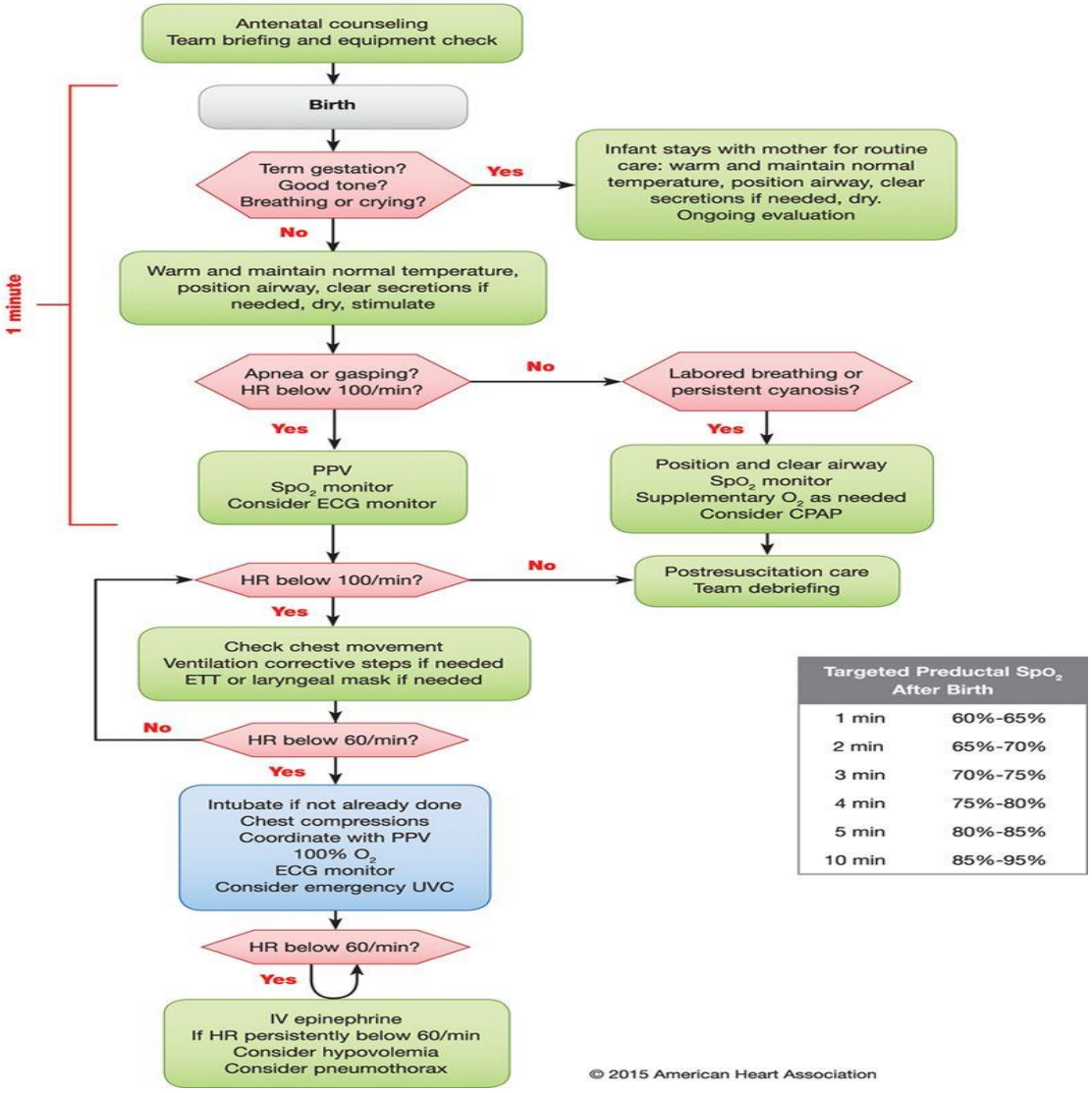
TO SUMMARIZE In utero or perinatal compromise

- Heart rate falls at the time of primary apnea
- HR & Blood pressure falls after the onset of secondary apnea

Neonatal Resuscitation

SUMMARY OF NRP: 2015

Neonatal Resuscitation Algorithm—2015 Update



Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

• **The American Academy of Pediatrics (AAP) and American Heart Association (AHA)** partner in the evaluation of resuscitation science through the	• International Liaison Committee on Resuscitation **(ILCOR)**
• After the meeting, each ILCOR member organization develops clinical guidelines based on the ---------- document	2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations **(CoSTR),**
• The NRP Flow Diagram is divided into **5 blocks** beginning with birth and the initial assessment.	• *Initial Assessment,A,B,C,D*
• Throughout the diagram, **diamonds indicate** --- and **rectangles** show ----	• Assessments, actions **Mnemonic** :**D** comes first than **R** so assessment come first than Action

	COMPONENTS	QUESTIONS
	Antenatal **C**ounseling, **T**eam briefing **E**quipment Check	**(Mnemonic :AC To EC)**
	Ask the 4 pre-birth questions **The 4 pre-birth questions are** **i**. What is the expected **gestational age**? ii. Is the **amniotic fluid clear?** **iii. How many babies** are expected? iv. Are there any **additional risk factors**?	*What are the 4 pre-birth questions to ask the obstetric provider before every birth?*
Assemble team.	• Assembles team based on perinatal risk factors **Perform pre-resuscitation briefing.** • Identifies team leader • Discusses possible clinical scenarios and assign roles and responsibilities **Perform equipment check.** • Demonstrates an organized routine to locate the most essential supplies needed for newborn resuscitation	**Assemble team.**
	The components of neonatal resuscitation are (TABCD) – T - Maintain **T**emperature A - Establish **A**irway B - Initiate **B**reathing C - Maintain **C**irculation D- **D**rug	*What are the component of NRP?*
MAINTAIN TEMPERATURE:	• Newly born infants who do not require resuscitation can be generally identified upon delivery by rapidly assessing the answers to the following ***3 questions:*** **T**erm gestation, Good **M**uscle tone, **C**rying or Breathing (**Remember:TMC**). • If the answer to all 3 questions is "yes," the newly born infant may stay with **the mother for routine care.** • **Routine care**: Provide warmth in the form of ***skin to skin(STS) contact by*** *placing baby on*	*What is routine care?What is DCC?*

mothers chest, Assure open airway,Dry ,**Delayed[Q] cord clamping(DCC) for longer than 30 seconds[Q]** ,Ongoing evaluation **(color, activity and breathing)**

- **If the answer to any of these 3 assessment questions is "no," the infant should be moved to a radiant warmer and Initial steps is started.**

AIRWAY:

What are initial steps?

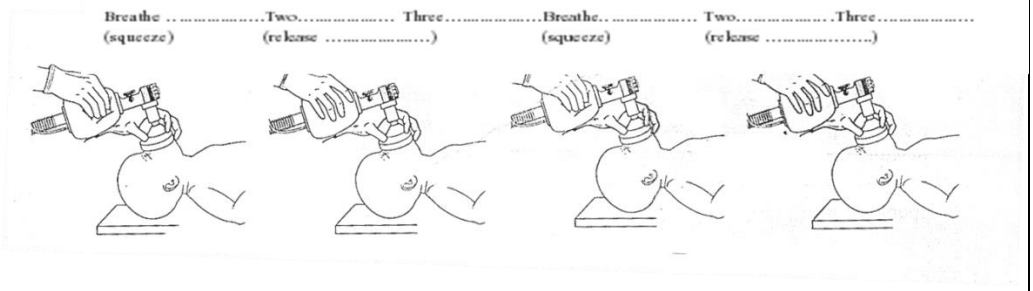
- **Initial steps consists of** (**warm a**nd maintain normal temperature by **radiant warmer**, "**sniffing"**[Q] position, clear secretions only if copious and/or obstructing the **airway**, **dry,stimulate (Gently rub the newborn's back, trunk, orextremities.**)
- **10F or 12F** suction catheter attached to wall suction, set at **80 to 100 mm Hg**
- Avoid both hypothermia* and overheating. During resuscitation and stabilization, the baby's body temperature should be **maintained between 36.5°C and 37.5°C**
- **Stimulationis d**one by Slapping or flicking the soles of the feet,or Gently rubbing the back, trunk or extremities
- Intrapartum suctioning for infants with Meconium stained amniotic fluid(MSAF) , after delivery of head before **delivery of should not advised**
- If an infant born through **meconiumstained amniotic fluid presents** with p**oor muscle tone and inadequate breathing efforts, t**he initial steps of resuscitation should be completed under the radiant warmer.**PPV should be initiated if the infant is not breathing or the heart rate is less than 100/min after the initial steps** are completed. **Routine intubation for tracheal suction in this setting is not suggested**

What is Golden minute?

- Approximately **60 seconds ("the Golden Minute**")[Q] are allotted for completing the initial steps, reevaluating, and beginning ventilation if required . Iit is important to **avoid unnecessary delay in initiation** of ventilation, because **this is *the* most important step for successful** resuscitation of the newly born who **has not responded to the initial steps**

BREATHING :

- **The most important and effective action in neonatal resuscitation is to ventilate the baby's lungs.**
- The decision to **progress beyond the initial steps** is determined by simultaneous assessment of **2 vital characteristics**: **respirations** (apnea,gasping, or labored or unlabored breathing) and **heart rate (less than 100/min).**
- **Auscultation of heart at the precordium is the most accurate** than umbilical cord palpation[Q]
- **Indication on PPV**:*Apnea (not breathing),Gasping,**Heart rate less than 100 bpm**,Oxygen saturation below the target range despite free-flow oxygen or CPAP*
- Once positive-pressure ventilation (PPV) or supplementary oxygen administration is started, assessment should consist of simultaneous evaluation of 3 vital characteristics: **heart rate, respirations, and oxygen saturation, as determined by pulse oximetry(not color)[Q]**
- *During resuscitation of term and preterm newborns, **the use of 3-lead ECG** for the rapid and accurate measurement of the newborn's heart rate **may be reasonable***
- **Increase in HR most sensitive indicator of resuscitation efficacy[Q]**
- ***Resuscitation of both term and preterm(<35 weeks of gestation) should be initiated with low oxygen (21% to 30%), and the oxygen concentration should be titrated to achieve preductal oxygen saturation by attacing probe to right hand or wrist.***
- CPAP in labour room:Spontaneously breathing preterm infants with respiratory distress may be supported with **continuous positive airway pressure** (CPAP)**initially[Q]** rather than with routine intubation for administering PPV.
- *Assisted ventilation should be delivered at a rate of **40 to 60 breaths per minute to promptly** achieve or maintain a heart rate >100 per minute*

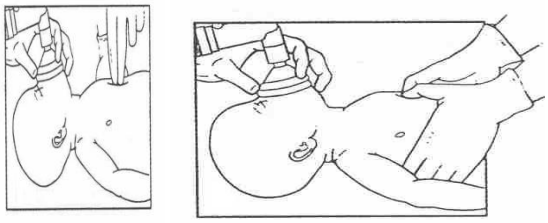


- *PPV can be delivered effectively with a -**self-inflating bag, flow-inflating bag,or T-piece resuscitator***
- ***Confirmation of endotracheal tube placement -Exhaled CO2 detection** is recommended except in cardiac asystole where direct laryngoscopy may have to be done*
- *Laryngeal mask airway(**LMA):-may be used for infants >2000g and ≥ 34** weeks in case bag and mask is ineffective and tracheal intubation is unsuccessful or not feasible*
-

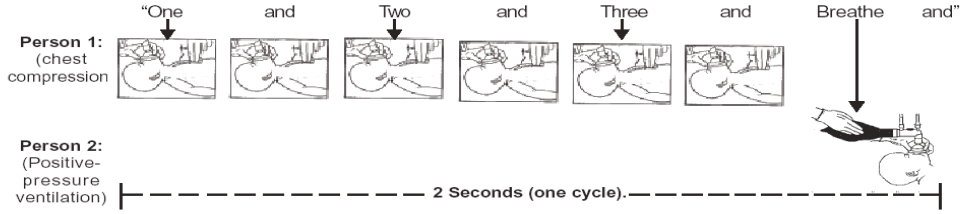
CIRCULATION:

Chest compression:

- **Indication: Heart rate less than 60 bpm despite 30 sec of effective positive-pressure ventilation**[Q]



- **Ratio** of compression **3:1** [Q] **with 90 compressions and 30 breaths per minute unless** cardiac arrest is due to a clear **cardiac etiology** where ratio of **15:2 may be** Considered
- **Two thumb**[Q] **technique** better than **two finger** technique(2 FINGER NO LONGER NEEDED)
- The compression is applied at the **lower one third of sternum**[Q]
- The **depth of compression** should be **one-third**[Q] **of the** antero-posterior diameter of the chest



- Use 100% oxygen whenever chest compressions are provided.
- It is reasonable to wean the oxygen concentration as soon as the heart rate recovers.

Q.When and how should chest compressions be performed during neonatal resuscitation?

DRUGS:

Indication and routes of Adrenaline and volume expander:

What are the Indication of Adrenaline and volume expander

• Indication	• Epinephrine is indicated if the baby's heart rate remains below 60 bpm after • At least 30 seconds of PPV that inflates the lungs (moves the chest),and Another 60 seconds of chest compressions coordinated with PPV using 100% oxygen.
• ***Preferred route.***	• ***IV administration by Umbilical venous catheter(UVC).Dose of adrenaline*--0.1 ml/kg toO.3 ml/kg diluted(l:10,000)**
• Alternate route (Less effective)	• ***Endotracheal tube-if I.V access is not obtained.Dose of adrenaline-*** *higher dose* ***0.5 to 1 ml/kg*** **diluted(l:10,000)** *, but the safety and efficacy of this practice have not been evaluated*
• ***Volume expansion by isotonic saline or blood should be considered***	• ***Considered when*** blood loss is known or suspected (pale skin, poor perfusion, weak pulse) and the infant's heart rate has not responded adequately to other resuscitative measures.
• ***Intravenous glucose infusion*** [Q]	• *should be considered as soon as practical after resuscitation, with the goal of avoiding hypoglycemia*
• **Naloxone**	• **is not recommended**[Q] as part of initial resuscitation in babies with respiratory depression

Therapeutic Hypothermia:

- Therapeutic hypothermia (whole body or selective head cooling) recommended for infants ≥ **36weeks with** moderate to severe hypoxic ischemic encephalopathy
- In resource-limited settings, use of therapeutic hypothermia may be considered

What is therapeutic hypothermia?

DNR(Do not *resuscitate):*

In general withhold care for:

- **Gestational age < 23 weeks,Birth weight <400 grams, Anencephaly[Q], Major chromosomal anomalies (eg. Trisomy 13)**

What are the conditions in which we Do Not Resuscitate(DNR) the baby?

Discontinuation of resuscitation:

- Infants with an **Apgar score of 0 after 10 minutes of resuscitation,** if **the heart rate remains undetectable**, it may be reasonable to stop assisted ventilation

When should we **discontinue resuscitation?**

CRUX:

MAJOR CHANGES IN UPDATED GUIDELINES- 2015

Delayed cord clamping(DCC) after 30sec	• For **both term and preterm** infants **who do not require** resuscitation at birth. • Routine use of cord milking (outside of a research setting) for infants born at **less than 29 weeks** of gestation is not recommended
" *Routine intubation for tracheal suction is no longer recommended" for* non-vigorous baby	• Neonates born **through meconium-stained amniotic fluid** and who are non-vigorous at birth, should be placed under **a radiant warmer and PPV should be initiated if needed. " *Routine intubation for tracheal suction is no longer recommended".*** Intubation and suction of the airway may be used as needed for ensuring oxygenation and ventilation.
Assessment of heart rate	• Use **of a 3-lead ECG for assessment** of heart rate in first minute may be used. However, the use of the ECG should not replace the need for pulse oximetry to evaluate the newborn's oxygenation.
Administration of oxygen in preterm baby	• Resuscitation of preterm newborns **of less than 35 weeks** of gestation should be initiated with low **oxygen (21% to 30%) and the oxygen titrated** to achieve pre-ductal oxygen saturation approximating the range achieved in healthy term infants.
CPAP	• **CPAP may be offered** to spontaneously breathing preterm infants with respiratory distress in place of **routine intubation** for administering PPV.
Use **of 100% oxygen**	• Recommendation to use **of 100% oxygen** whenever **chest compressions are provided**
Temperature	• Temperature of newly born non-asphyxiated infants be maintained between **36.5°C and 37.5°C after birth** • In resource-limited settings, use of **therapeutic hypothermia** may be considered under clearly defined protocols and in facilities with the capabilities for multidisciplinary care and follow-up.
Task training	• **Neonatal resuscitation task training** should be **done more frequently** than the **current 2-year interval**.

APGAR score	**0**	**1**	**2**
Respiratory efforts:	None	slow, irregular	good, crying
HR:	Absent	< 100	> 100
Color:	Blue or pale Extremity blue	Body pink,	pink
Muscle tone:	Flaccid	some flexion	actively moving the extremities
Reflex stimulation:	No response	Grimace	Cries, coughs, Sneezes

Apgar score is taken at 1, 5 & 10 minutes of birth
Apgar score at 5 minutes is more important than one minute score.
As at 5 minutes < 4 → is very low
4-8 → is moderately low
> 8 → is normal

Management of infant born through MSL

Vigorous baby
- HR > 100/min
- Strong respiratory efforts
- Good muscle tone

Absence of any single sign would mean a non vigorous baby

For non vigorous babies
- Place the baby under radiant warmer
- The trachea should be then intubated & meconium suctioned from lower airways .(INTRATRACHEAL SUCTIONING WITH NEGATIVE PRESSURE)

Neonatal reflexes

• Neonatal reflexes appear at particular age and then disappear at particular age. Some may persist for life.
• Absent Neonatal reflexes in general means depression of central or peripheral motor function.
• Abnormal persistence of neonatal reflex is pathognomic of central motor lesions. Asymmetrical neonatal reflex is abnormal.

Rooting, sucking and swallowing reflexes: Full term sucks vigorously.
Rooting reflex: When breast is brought into contact with infant's cheek, he/she seeks the nipple.
• It appears at 32 weeks; fully develop by 34 week, less prominent after 1 month.
• Feeble in sick and preterm infants.
• Absence suggest developmental defect.
Sucking and swallowing reflex: By introducing a washed, clean finger into the infant's mouth; Note Strength, Rhythm, and Regularity of sucking.
• Well developed at 34 weeks of gestation.

Moro's reflex: Hold the baby at an angle of about 45 from couch and then suddenly let the head full backs a short way. Reflex consists of:
1. Abduction and extension of the arms; appears at 28 weeks.
2. Opening of hands; appears at 32 weeks
3. Followed by adduction of arm and flexion of forearms; appears at 36 week
• It is vestibular reflex. Disappear by 3-4 months.
***** *Abnormal if persists for more than 6 months*.
***** If absent: Suggests severe hypotonia, cerebral damage, mother sedated heavily. If exaggerated suggests cerebral irritability.
***** If Asymmetrical: Suggests Erb's palsy, # clavicle or humerus or hemiplegia.

Reflex	Age of appearance	Age of Disapperance
(1) ROOTING	32 wks of gestation	Len prominent after 1 month

(2) MORO	28 – 3 week of gestation	3 – 6 months
(3) PALMAR	28 weeks of gestation	2 – 3 months
(4) ASYMETRIC TONIC NECK	35 weeks of gestation	6 – 7 months
(5) SYMMETRIC TONIC NECK	4 – 6 months	8 – 12 months
(6) LANDAU	3 months	12 months
(7) PARACHUTE	8 – 9 months	Remain throughout life
(8) CROSSED EXTENSOR	28 weeks of gestation	1 – 2 month

Palmer Grasp reflex: When baby's palm is stroked with the examiner's index finger or ulnar side, the baby's fingers close on it and grasp it. As an examiner lifts his finger, term infant can support his whole body wt.

***** This reflex appears at 28 weeks, fully develop at 32 weeks.
***** Disappear by 3 months.
***** Asymmetrical in Hemiplegia or cerebral damage.

Glabellar tap: Normal Habituation occurs after 3-4 taps, after that baby do not blink.
• Abnormal if persist after > 5 taps.
• Present after 32 weeks.

Crossed Extension: When foot is stroked while the leg is held extended at knee; there is rapid flexion, adduction and then extension of the opposite leg.
***** Appears at 32 weeks.
***** Adduction component appears at 37 weeks. This suggest term baby.

Tonic neck reflex (TNR): Types: 1. Asymmetrical **(**ATNR**)**.
2. Symmetrical **(**STNR**)**.

ANTR: Supine infant's head is turned suddenly to one side. This leads to:
• Arm and leg on same side goes into extension.
• Opposite limbs (Arm and leg) go into flexion.
***** Appear at 35 weeks of gestation. Fully develop by 1 month of age.
***** Disappear at 3-4 months.
***** Persistent by 6 month is abnormal; suggest spastic cerebral palsy.
STNR: Evoked by flexion or extension of the neck.
• On raising the head of kneeling child; extensor tone↑ in the arms and Flexor tone increases in the legs.
• If reflex is strong, the child extends the arms and flexes the legs.
• On flexing the neck; there will be opposite response.
• This reflex is seen in normal children when they raise the head and shoulders, in prone position and disappear when they learn to crawl.
***** In cerebral palsy this reflex is usually overactive.
Landau reflex: When child is held is ventral suspension; the head, spine and legs extend.
• When the head is depressed; the hip, knees and elbows flex.
***** This reflex *appears from 3 months of age*.
***** Present till 1 yr of age then disappear.
***** Absence in over 3 months of age suggests motor weakness, Cerebral Palsy and mental sub normally.
Parachute reflex: When child is held in ventral suspension and then suddenly lowering him towards, the couch; the arms extend.
***** Appears at 6-9 months, fully develop by 11-20 month.
***** *Persists throughout life*.
***** In Cerebral Palsy, reflex is absent or incomplete because of strong flexor tone.

Normal findings in infants during 1st week of life

1. **Milia**: Distended sebaceous glands, white dots (on nose and face).

2. **Erythema toxicum**: On D2-D3, discrete, erythematous papules, appear on trunk and face. Scrapping from lesions shows eosinophilic infiltration.
3. **Cephalhematoma**.
4. **Caput Succedaneum**.
5. **Subconjunctional hemorrhages**.
6. **Epstein pearl**:
• Palatal: Inclusion cysts, Whitish spots on hard palate.
• Prepucial: White in color, on tip of prepuce at 6 O'clock position.
7. **Natal teeth**: Present at birth or erupt shortly. It should be removed if causing injury to breast.
8. **Breast engorgement**: Full term babies of both sexes on D3-D4.
While or creamy white liquid from breast, due to transparently acquired maternal hormones.
9. **Peeling of skin**: Frequent in post term infants.
10. **Stork bites**: Pinkish gray capillary hemangiomata. Disappear after few months.
11. **Mongolian spot:** Usually disappear before the first birthday.
12. **Vaginal bleeding**: On *D3-D7 due to withdrawal* of maternal hormones.
13. **Vaginal mucoid discharge**: Thick, white viscid vaginal discharge due to effect of transplacentally acquired estrogen on vaginal mucosa.
14. **Physiological phimosis**: In 80% of male neonates.

Cephalhematoma	**Caput succedaneum**
• Subperiosteal Hemorrhage: Parietal or temporal.	• Edema of scalp that follows local Pressure and trauma during delivery.
• More frequent after forceps delivery or instrumentation i.e. vacuum extraction etc.	• It is present on Presenting part.
• Soft and fluctuant.	• Boggy swelling.
• Well define outline, along sutures	• Circumscribed. Not outline by suture line.
• Usually not cross midline: if cross midline it suggests underlying #.	• Cross midline.
• May appear after 12-24 hr • Disappear within 12-24 hr.	• Present at birth • Disappear over longer duration.

Hypothermia

Normal temperature: 36.5-37.5°C
Cold stress: 36.5-36.0°C
Moderate hypothermia: 36-32°C
Severe hypothermia < 32°C

Neonates are more prone for hypothermia because of:
• Large surface area/body weight.
• Decreased subcutaneous and brown fat /body weight.
• Immature/thin skin.

Brown fat is site of heat production (*Non-shivering thermo genesis*).
It is present at:
• Around adrenal glands • Kidneys • Nape of neck
• Inter scapular region • Axillary regions
(Blood flowing through the brown fat becomes warm and through circulation transfer heat to other parts of the body).

Loss of heat: it is by:
• Evaporation (evaporation of amniotic fluid from surface)
• Conduction (in contact with cold objects)

• Convection (by air current)
• Radiation (to colder solid objects)

Effects of hypothermia are metabolic acidosis, hypoglycemia, and respiratory distress.
Thermo-neutral range of temperature is temperature range in which
• Basal Metabolic Rate is minimum.
Oxygen utilization is less.
• Baby thrills well.

Incubator: Principal mode of heat exchange is: *forced convection*.
Management

- Rewarming as soon as possible
- i/v 10% dextrose
- Oxygen

Assessment of gestational age

Term infant	**Preterm infant**
Skin – is smooth, pink with visible veins	is friable, red transparent to translucent
Hair – silky & black in aappearance	Brownish black fuzzy or wooly appearance
Lanugo- very little lanugo	Abundant lanugo hair
Sole creases –present over the entire sole	Single deep crease over ant 1/3rd of sole or no deep crease ; sole may be full of superficial creases
Breast nodule – of 5 – 10 mm is present	Is <5 mm or imperceptible
Ear cartilage – shows instant recoil	Ear cartilage defecient so poor recoil
Genitals	
Males – testes are descended with deep rugae on scrotum	Testes at or above ext inguinal ring with few rugae on scrotum
Females – labia majora cover clitoris and minora	Labia majora is widely separated exposing the minora and clitoris hypertrophied

Premature/preterm infants

• Born < 37 weeks of gestation. They are smaller in size.
• Head is relatively large; sutures are widely separated, large fontanel
• Small face; decreased buccal pad of fat, decreased S/c fat.
• Skin: thin, pinkish. *Abundant lanugo* and little vernix caseosa.
• Small breast nodule < 5mm. Ears: *soft and flat, deficient cartilage*.
• *Testis: not descended into scrotal sac*. Labia majora appears widely separated.
• *Soles: deep creases not well developed*. Neonatal reflexes are sluggish.

Neonatal sepsis

Early: Onset with in 72 hrs of life; organism prevalent in the maternal genital tract or in delivery area are causative agents.
Late: Onset after 72 hrs of life; organism in external environmental or in hospital are causative agents.
Sepsis Screen includes: **1**. µ ESR (Not ESR). µ ESR of > 10 or 3+Days of life is significant i.e. favors sepsis.
2. Absolute neutrophil count (ANC) including band cells.
3. Polymorph in gastric aspirate (> 5 is significant).
4. C-reactive protein (CRP > 1:1titre is significant).
5. Immature: Total (I: T) ratio (>0 .2 is significant).
Maternal risk factor: • Maternal fever.
• Rupture of membrane > 24 hrs • Choriamnionitis
• Perterm baby
Causes of Neonatal sepsis: Community acquired: E. coli. Others are listeriosis etc.
Hospital acquired: *klebsiella pneumonia*. Others are staphylococcus, pseudomonas etc.
Clinical Features: Varied and Non-specific.
• Most Common is refusal to suck/ lethargy.
• Sclerema is more specific.
***** In Late onset sepsis: Always does CSF examination.
***** In Early onset Sepsis: Do LP in symptomatic infants and those with blood culture positive.
Treatment: Warmth, fluid resuscitation (as TABC).
• Treatment of hypoglycemia, Vit K 1 mg.
• Antibiotics: Local nursery flora
• Exchange Transfusion (DVET) for sclerema.

Intrauterine infections: TORCH

Rubella

Clinical features: Sensorineural deafness, Cataract, corneal opacity.
• Microopthalmia, salt and pepper type of Chorioretinitis.
• Cardiac defect: PDA, Peripheral PS.
• Microcephaly, IUGR.
• Hepatosplenomegaly, jaundice, petechiae, rash, thrombocytopenia.
• Metaphyseal lesions: linear radiolucent areas, periosteal reaction.
Diagnosis: By any one of below-
• Isolation of rubella virus (oropharynx, urine).
• Detection of rubella specific IgM in cord or neonatal blood.
• Persistent rubella specific titers over time**.**
Treatment: No specific treatment.

Cytomegalovirus (CMV)

Clinical features: Neonatal hepatitis, Hepatosplenomegaly.
• Periventricular calcification, Microcephaly, psychomotor retardation.
• Chorioretinitis: Cottage cheese with ketchup appearance.
(*****Peripheral and with spacing of macular)
Diagnosis: Spin enhanced culture or `shell viral´.
• CMV Ag (PP65) • CMV DNA PCR • IgM ELISA
• Infants with congenital CMV infection may excrete CMV in the urine for several years.
• An IgG antibody test is of little diagnostic valve because a positive result also reflects maternal antibodies, although a negative result excludes the diagnosis of congenital CMV infection. In general, IgM tests lack sensitivity and specificity and are unreliable for diagnosis of congenital CMV infection.
Treatment: Gancyclovir/forcarnet for chorioretinitis.

Toxoplasmosis

Clinical features: Central destructive chorioretinitis **(*** involving macula**),** optic atrophy, cataract
• Hydroceplalus or microcephaly
• ***** Diffuse nodular cerebral calcification
• Hepatosplenomegaly, thrombocytopenia.
Diagnosis: Sabin-feldman dye test • ELISA - IgM, IgA
• Immunosorbent agglutination assay (ISAGA).
Treatment: Pyrimethamine + sulfadiazine for 1 yr + Folic Acid (to decrease pyrimethamine toxicity).

Congenital syphilis

• Hutchison's triad: Interstitial keratitis, 8th nerve deafness and pegged central upper incisors.
• IUGR is uncommon. Periosteitis, chondritis, deafness.
• May present as hydrops fetalis.
• Meningoencephlitis, Rashes, snuffles, depressed nasal bridge.
Diagnosis:
1. Non-treponemal test:
• RPR (rapid plasma reagin) test • VDRL
2. Treponemal test:
• FTA-ABS (fluorescent treponemal antibody absorption test)
• TP-PA (Treponemal pallidium particle agglutination test)
• TPI (Treponemal pallidium immobilization test).

Treatment:
• Primary, secondary and Early latent syphilis (without neurosyphilis) → Benzathine penicilin G 24 lakhs (2.4 million) units 1/m stat.
• For late latent and Tertiary syphilis (without neurosyphilis)
→ Benzathine penicillin G 24 lakhs 1/m weekly, for 3 weeks.
• For Neurosyphilis → Aqueous crystalline penicillin G 18-24 million units daily as 3-4 million units 1/v every 4 hours for 10-14 days.
OR procaine penicillin 2.4 million 1/m daily + probenecid 500 mg daily 6 hrly for 10-14 days.

Herpes simplex

Clinical features: Vesicular lesions, Pneumonitis, HSM.
Diagnosis:
• PCR • Vesical fluid/CSF culture • IgM ELISA
Treatment: Acyclovir for 14-21 days.

Small for Gestational age (SGA) infants

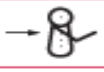
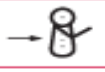
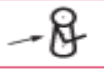
Asymmetrical/malnourished SGA infants –
- Commonest variety of SGA
- Head circumference (HC) and brain weight are unaffected
- Prognosis for subsequent physical growth is relatively better.
- Growth retardation is due to reduction in cell size but not in cell number

Symmetrical/hypoplastic SGA infants –
- Growth arrest occur in early part of pregnancy
- Baby is proportionately small including head size
- There is reduction in the number of cells
- Cause can be intra-uterine infection, genetic defects of chromosomal aberrations
- Prognosis for subsequent physical growth and mental development is poor
- Ponderal index <2. [PI = Weight in grams/(length in cm)^3 X 100]

- PI > 2

Brain, heart & lungs are least affected by intrauterine malnutrition

Neuromuscular Maturity

Score	–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 and/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 40–50 mm: –1 < 40 mm: –2	> 50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases anterior 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: –1 tightly: –2	Lids open; pinna flat; stays folded	Slightly curved pinna; soft; slow recoil	Well curved pinna; soft but ready recoil	Formed and 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	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and 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

Assessment of gestational age—new Ballard score.

The Ballard scoring system is accurate to ±2 wk

CLINICAL PROBLEMS	PRETERM	TERM SGA
Intrauterine hypoxia	+	+++
Respiratory difficulties		
Birth asphyxia	+	+++
Aspiration in utero	+	+++
HMD	+++	0
Apneic attacks	+++	0
Feeding difficulties		
Inability to suck& swallow	+++	0

Aspiration of feeds	++	0
Functional obstruction & NEC	++	+
Symptomatic hypoglycemia	+	+++
Hypothermia	+++	+
Polycythemia	+	+++
Hyperbilirubinemia	+++	+
Susceptibility to infections	+++	++
Congenital malformations	+	+++
Hemorrhage		
Intraventricular	+++	0
Pulmonary	+	+++
Prognosis		
Immediate	High mortality	Better prognosis
Future physical & mental development	good	poor

Respiratory Distress

Respiratory Distress: Any two of the following signs are present:
• Tachypnea (RR > 60/min) • Grunting • Chest retraction

Causes:

Respiratory causes: Meconium aspiration syndrome (MAS), Hyaline membrane disease (HMD), Pneumonia, transient tachypnea of newborn (TTNB).

Non Respiratory causes:
• Cardiac: Congestive heart failure, Cong. H. disease etc.
• Metabolic: Metabolic Acidosis, hypothermia, hypoglycemia etc.
• CNS: Birth asphyxia, Cerebral edema, Hemorrhage, meningitis etc.
• Chest wall: Spinal Muscular Atrophy etc.

Cardiac causes present with severe cyanosis (central), Hepatomegaly, O/E: Murmur, shock.

Metabolic causes: Predisposing factors are sepsis, diarrhea, Asphyxia etc.

Monitoring of respiratory distress: Downe's score

	0	1	2
RR/min	<60	60-80	>80
Cyanosis	Absent	Absent with upto 40% O2	Requires >40% O2
Retractions	Absent	Mild	Mod-severe
Grunting	Absent	Audible with steth	Resent
Breath sounds	Good	Decreased	Barely audible

Silverman Anderson retraction score [2]

Score	Upper chest retraction	Lower chest retraction	Xiphoid retraction	Nasal dilatation	Grunt
0	Synch	None	None	None	None
1	Lag on inspiration	Just visible	Just visible	Minimal	Stethoscope only
2	See-Saw	Marked	Marked	Marked	Naked ear

A score of >6 is indicative of impending respiratory failure.

Hyaline membrane disease (HMD/RDS):

• Almost always in preterm babies often < 34 weeks of gestation.

Risk factors:

• Prematurity • Asphyxia • Acidosis

• Maternal diabetes • Cesarean section

Pathogenesis: It is due to surfactant deficiency.

• Surfactant deficiency → alveoli collapse during expiration → Inadequate O2 and increase work of breathing → Hypoxemia and acidosis → pulmonary vasoconstriction → Ischemia damage to alveoli → Exudation of protein.

***** Surfactant is produced by type II alveolar cells.

***** Surfactant is Lipoprotein containing: Phospholipids like phosphatydylcholine/Phosphatydyl glycerol and Protein.

Clinical feature: Respiratory Distress usually occurs within 6 hrs.

Diagnosis: It is based on clinical and CXR findings; CXR shows:

• Small volume lung. • Ground glass appearance.

• Reticulogranular pattern. • Air bronchogram.

Shake test positive: Take 0.5 ml gastric aspirate + 0.5 ml absolute alcohol. Shake for 15 second and look for bubbles formation. No bubbles formation means surfactant deficiency.

Prenatal Diagnosis: Lecithin: Spingomylin (L: S) ratio < 2.

Treatment: NICU care.

• IVF, O2 (not 100%), ventilation (CPAP, S1MV).

• Surfactant administration.

Prevention: By prenatal corticosteroids:

Benefits: - 50% decrease in RDS.
- 50% decrease in Intra Ventricular Hemorrhage.
- 40% decrease in mortality.

Indications:

• All mothers at risk of preterm delivery at 24-34 week of gestation.

• Cases of premature rupture of membrane at < 32 weeks of gestation, in absence of overt clinical chorioamnionitis.

Contra Indications: – Clinical chorioamnionitis

Monitoring: For hyperglycemia and Hypertension.

Treatment schedule: Betamethasone 12 mg i/v OD for 2 days.
OR Dexamethasone 6 mg i/m BD for 2 days.

Timing of effect: Optimal effect occur 24hrs of initiating treatment.

• Effect of one course last for 7 days.

Meconium aspiration syndrome (MAS)

• Meconium staining of liquor occurs in 10-14% of pregnancies.

• Usually occur in post mature and small for Date baby.
Pathogenesis: Meconium can be:
1. Thin meconium lead to → Chemical pneumonitis.
2. Thick meconiun → Block airway →leads to Atelectasis, Emphysema, Pneumothorax.
Clinical Features: Respiratory Distress with in 24 hrs.
CXR: Hyperinflation, Patchy infiltrates
Treatment:
• IVF • Surfactant replacement • O2 • Ventilation support
***** No role of steroids.
Prevention:.
Immediately after delivery, ET suctioning should be done.

Transient Tachypnea of newborn (TTNB)

• Present with tachypnea with mild respiratory distress.
• Benign self limiting disease.
• Usually occur in term neonates, born of cesarean section.
• Due to delayed clearance of lung fluid.
CXR: *Prominent vascular marking* and prominent *interlobar* fissure.
Treatment: O_2.

Tracheosophagial fistula (TEF)

Type I (Esophageal Artesia with lower esophagus communicating bronchus) *is most Common* type. It occurs in 87% cases.
VACTERL association: Vertebral, **A**norectal, **C**ardiac, **T**rachael, **E**sophageal, **R**enal / **R**adials anomalies, **L**imb anomalies.
Clinical Features: Frothing and bubbling at the mouth and nose; and episodes of coughing, cyanosis and RD associated with feeding.
• Aspiration of gastric contents.
Diagnosis: Early onset respiratory distress.
• Inability to pass a Nasogastric tube in Esophageal Atresia.
• Maternal *polyhydramnios*.
• ***X-ray with feeding tube*** in the esophageal pouch and/or air distended stomach.
H type TEF: Present later in life with chronic respiratory problems,
Refractory bronchospasm, Recurrent Pneumonias.
Pure EA: Present as scaphoid, Airless abdomen.
Treatment: Prone positioning (for maintaining airway and preventing aspiration of secretion.
• Esophageal suctioning minimizes aspiration from blind pouch.
• Surgery: Ligation of TEF and primary end to end anastomosis of esophagus.

Congenital diaphragmatic hernia (CDH)

Types:
1. Hiatal (esophageal)
2. Para esophageal (adjacent to hiatus)
3. Morgagni (retrosternal)
4. Bochdalek (posterolateral)

Bochdalek hernia :
• It is *most common CDH*. Defect is on left side in 70-85%.
Associated with: *Lung hypoplasia* and Malrotation of intestine.
Others: CNS lesions, esophageal atresia, Omphalocele, cardiovascular lesions, trisomy 21
Etiology: Failure of closure of posterolateral pleuroperitoneal canals.
Clinical Features:– Severe respiratory distress with in Ist hr of life.
– Scaphoid abdomen.
– Heart sound on right side.
Diagnosis: In ANP: Maternal Polyhydraminos. On USG

After birth: Clinical features and on CXR-AP and lateral views.

Treatment: ECMO (extracorporeal membranous oxygenation)
• Initial resuscitation (T, A, B, C) and stabilization: Temp maintenance, volume resuscitation, dopamine, HCO3 to maintain (PH > 7.50)etc.
• Gentile ventilation with Permissive hypercapnia.
• Repair of diaphragms at 24-72 hr, after stabilization.
Others: Surfactant administration, Nitric Oxide (inhaled).
***** BPL: **B**ochdalek is **P**ostero **L**ateral in position.
***** ECMO with paralysis and *Nasogastic suction may produce a dramatic reduction of the volume* of herniated viscera.

Neonatal Apnea

Definition: Cessation of respiration for ≥ 20 sec with or without bradycardia and Cyanosis **Or** shorter period if it is associated with cyanosis or bradycardia.
Types: **1**. Central (due to sepsis, metabolic; Hypoglycemia, hypocalcaemia etc).
2. Obstructive (improper position, airway secretions etc).
3. Mixed (Most Common type).
Apnea of prematurity: In Preterms it is due to immaturity of developing brain. It presents on D2-D5 of life.
• It is diagnosis of exclusion.
***** Best way to detect breathing/apnea is *impedance technique*.

Neonatal jaundice

• Jaundice occurs when the liver cannot excrete sufficient bilirubin from the plasma.
Production: 75% from senescent RBC.
• 25% from non HB heme proteins.
Pathophysiology:
Heme ring ——————→ Biliverdin ——————→ bilirubin.
Heme oxygenase Biliverdin reductase
• Iron and CO are produced during biliverdin formation.
• 1 gm Hb produces 34 mg of bilirubin.
• Unconjugated bilirubin ————→ Conjugated bilirubin.
UDPG -T
***** UDPG-T: Uridine Diphosphate Glucuronyl Transferase. This enzyme is induced by phenobarbitone.
***** Jaundice progresses in cephalo-pedal progression.
• Face = 5 mg% • Upper trunk = 10 mg %
• Lower trunk and thigh = 12 mg % • Till ankle = 15 mg %
• Sole staining > 15 mg %
Causes: Time wise presentation includes:
With in 24 hrs: Hemolytic disease of Newborn: Rh, ABO, Minor blood group Incompatibility.
• Intra Uterine infections: TORCH, HBV, bacterial infections.
• G6PD deficiency, pyruvate kinase deficiency.
• Drugs: Large amount of Vit K, salicylates, sulfaxazole.
• Hereditary spherocytosis, α thalassemia.
• Crigler-Najjar syndrome, Lucey-Driscoll syndrome.
24-72 hrs of age: Immaturity, Birth Asphyxia, acidosis, hypothermia, hypoglycemia.
• Drugs, Cephalhematoma, concealed Hg, bruising, polycythemia.
• Breast feeding, hypothyroidism.
> 72 hrs to 2 weeks: Septicemia.
• Neonatal hepatitis including Intra uterine infection.
• Metabolic causes: Galatosemia, tyrosinemia, fructosemia, organic academia, α_1 Anti tripsin deficiency.
• Pyloric stenosis, intestinal obstruction, extra hepatic biliary atresia.
• Breast milk jaundice.

Pathological Jaundice:

- Clinical jaundice with in 24 hrs.
- Total serum Bilirubin > 12.9 mg% in term and > 15 mg% in preterm.
- Conjugated bilirubin > 1.5 % or > 20% of Total serum Bilirubin.
- Total serum Bilirubin increasing by > 5 mg% day.
- Clinical jaundice persisting for > 1 week in terms and > 2 weeks in preterm.

Unconjugated hyperbilrubinemia	Conjugated hyperbilrubinemia
1. Hemolytic diseases of newborn RH, ABO & other bld. gp. incompatibility	1. Biliary Atresia/cholestasis
2. RBC enzyme defect G6PD/ Pyruvate kinase deficiency	2. Neonatal hepatitis
3. RBC membrane defect Hereditary spherocytosis/elliptocytosis/others	3. Intrauterine infections viral/syphilis/toxoplasmosis
4. Hemoglobin defects & thalassemia	4. Sepsis
5. Criggler Najjar syndrome I & II	5. Metabolic disorders Cystic fibrosis α - 1 antitrypsin deficiency tyrosinosis galactosemia hemochromatosis
7. Lucey Driscoll syndrome	
8. Hypothyroidism, Cephalhematoma 9. GILBERT Syndrome 10. Hepatocellular disease: viral / drug induced hepatitis,CIRRHOSIS	6. Impaired secretion of conjugated bilirubin in BILE - Dubin johnson syndrome - Rotor syndrome

Breast feeding jaundice

- Due to decrease intake of milk ↑enterohepatic circulation.

Breast milk jaundice

- Due to pregnanediol that interferes with conjugation

ABO incompatibility

- Seen in O' bld. gp. mothers with 'A' or 'B' bld. group fetus
- Usually milder disease

Rh incompatibility

- Disease worsens with increasing pregnancy
- The affected infant may have severe anemia, hepatosplenomegaly or hydrops fetalis , hypoglycemia, leukopenia, thrombocytopenia
- Jaundice within a few hours of birth.
- DCT is positive
- If there is concomitant feto-maternal ABO incompatibility, some protection is achieved against RH-HDN because fetal Rh-positive cells get destroyedby maternal antibodies of ABO system before they get a chance to stimulate anti-D antimody protection

KERNICTERUS –Acute bilirubin encephalopathy

1. Phase I – Poor sucking, lethargy, hypotonia, depressed sensorium
2. Phase II – seizure, hypertonia, opisthotonus
3. Phase III – high pitched cry, convulsion Death

Long term survivors demonstrates choreo-athetoid cerebral palsy, upward gaze palsy, sensorineural hearing loss and mental retardation

Drugs aggravating jaundice

- ❖ Hemolysis – vit K
- ❖ Competing with glucuronyl transferase

- Moxalactam - Gentamicin
  - o Chloramphenicol
- ❖ Prevent binding of bilirubin to albumin
- ❖ - Salicylates - Indomethacin

- Sulfonamides - Kanamycin
- Furosemide

Criggler Najjar Syndrome
Gilbert syndrome

- Autosomal dominant condition
- Hepatic biochemical test – normal – hepatic histology is normal
- Exception some patient ↑↑ lipofusin deposition
- Due to underactivity of the conjugating enzyme system bilirubin-uridine diphosphate glucuronyl transferase there is also ↓↓ uptake of bilirubin
- May be precipitated by dehydration, fasting, menstrual periods, or stress, such as an intercurrent illness or vigorous exercise.
- These episodes resolve spontaneously, and no treatment is required, except supportive care.

Dubin Johnson syndrome (DJS)

- Rare autosomal recessive condition
- Characterized by conjugated hyperbilirubinemia with normal liver transaminases [normal LFT]
- Cardinal feature of DJS is the accumulation in lysozyme of centrilobular hepatocyte of dark, coarsely granular pigment (thought to be derived from epinephrine metabolites]. As a result liver is black in colour.
- Conjugated hyperbilirubinemia results from defective transport of bilirubin glucuronide across the membrane that separates the hepatocyte from the bile canaliculi.Membrane Carrier Defect [Canalicular multi drug resistant protein – 2 MRP – 2]

Rotor syndrome

- Conjugated hyperbilirubinemia
- It has many things in common with Dubin-Johnson syndrome except that in Rotor Syndrome, the liver cells are not pigmented.

NEONATAL CHOLESTASIS

- Neonatal cholestasis is defined as prolonged elevation of serum levels of conjugated bilirubin beyond the 1st 14 days of life.

Treatment:
1. Phototherapy: Most effective lights for Phototherapy are those with energy output near the maximum absorption peak of bilirubin (i.e. 425-475 nm).
• Special blue lamps are most effective: peak output is at *425-475nm.*
Photochemical reactions: These are 3 types:
a. Photoisomerization: It occurs is extravascular space.

• Unconjugated bilirubin is converted to less toxic isomer (4 Z, 15E) and this diffuses into the blood and is excreted into bile without conjugation.
•This occurs at low dose phototherapy (6 μw/ cm²/nm).
• This reaction is reversible.
b. Structural isomerization: bilirubin is converted to lumirubin, which is rapidly excreted in bile and urine without conjugation.
• This reaction is *Irreversible*.
• It is *most important pathway*.
• It is strongly related to dose of phototherapy (6-12 uw/ cm²/nm).
c. Photoxidation: Least important pathway.

2. DVET: Double volume exchange transfusion.
Complications of DVET

- Hypoglycemia – high glucose content in CPD bld may stimulate insulin release
- Hypocalcemia, hypomagnesemia – citrate in CPD binds Ca & Mg, Citrate bind Ca/Mg
- Hyperkalemia
- Acid base imbalance – citrate is metabolized to alkali – metab alkalosis
- Infections – HIV, HBV, HCV and bacterial sepsis, NEC
- Bleeding –d/t thrombocytopenia and deficient clotting factors
- Cardiovascular complications e.g. –Umbilical vein or portal vein perforation, thrombosis, embolism, arrhythmias etc.
- Graft vs host disease
- Hypothermia/hyperthermia/NEC

3. I/v albumin.
4. I/v Immunoglobulin.
5. Double surface Phototherapy (Bili blankets).
6. Drugs: Phenobarbitone. Metalloporphyrins: These *inhibit heme oxygenase*.

Breast-milk jaundice

• It is late onset. Occur in term infants, in 2-4% cases.
• Present by D4. Instead of fall, bilirulin continues to rise and may reach 20-30 mg% by 14 days of age. Then it falls. If breast feeding is stopped bilirubin level falls rapidly.
• Recurrence late is 70% in future pregnancy.
Mechanism: Not known. But it may be due to:
1. Unidentified factors (3-α, 20-beta pregnandiol and free FA) in breast milk interfering with bilirubin metabolism, is thought to be causative agent.
2. Increased enterohepatic circulation in breast fed infants. Because they ingest β- glucoronidase (this enzyme convert conjugated Bilirubin to unconjugated bilirubin) present in breast milk.
• Colonization of gut is also delayed.
***** Intestinal bacteria can prevent enterohepatic circulation of bilirubin by converting Conjugated Bilirubin to urobilinoids, which are not substrates for β-glucoronidase.

Breast feeding Jaundice

• Those who are exclusively breast fed.
• Main factor responsible for breast feeding jaundice is decreased intake of milk that leads to increased enterohepatic circulation.

Prolonged/Persistent unconjugated jaundice
• Jaundice persisting for >14 days.
Causes:
• Immaturity, Hypothytroidism.

• Hemolytic disease of the newborn: ABO, Rh incompatibility etc.
• Pyloric stenosis and conditions associated with organic or functional intestinal stasis.
• Breast milk jaundice, Criglar-Najjar syndrome.
• Concealed hemorrhage, Malaria, UTI, Sepsis.

Neonatal Cholestatis

Definition: Elevated conjugated bililrubin for >14 days of life i.e. conjugated bilirubin > 2 mg% or > 20% of the total bilirubin for >14 days of life.

Types: It can be: **1**. Intrahepatic Neonatal cholestatis.
2. Extrahepatic Neonatal cholestatis.
Intrahepatic (neonatal hepatitis) **causes are**:
• Infections: I/U infections, bacterial infections, toxins, hepatitis B, C.
• Metabolic: Tyrosinemia, glactosemia, α_1 Anti tripsin deficiency, hypothyroidism, cystic fibrosis, Gaucher's disease, Nieman-Pick disease.
• Syndromes: Alagille's syndrome, Byler's syndrome.
• Toxic: TPN, drugs, idiopathic.

Extrahepatic causes are:
• EHBA (Extrahepatic biliary atresia) • Choledochal cyst.
• Bile duct stenosis. • Inspissated bile syndrome.
Clinical Features: Persistent jaundice, Dark colored urine, Clay colored stool, staining of cloths, Hepatomegaly.
Investigations: USG (*first investigation to be done*).
• HIDA scan • Liver biopsy
Treatment: depends on cause. See below.

Neonatal Hepatitis:
• Baby usually is small for date. Present at 4-6 weeks of age.
• Symptoms may be intermittent.
• Increased association with infection.
• 1/2 to 1/3 with persistent obstructive jaundice do not have biliary atresia.
Liver biopsy: Presence of *altered lobular architecture, focal hepatocellular necrosis* cholestatic inflammatory process with giant cell transformation, in the *absence of bile duct* proliferation.
Treatment:
Medical treatment: Medium chain triglycerides. These are more water soluble and do not require bile salts for absorption.
• Multi vitamins: fat soluble vitamins are given at 5 times RDA; water soluble vitamins are given at 2 times RDA.
• Ursodeoxycholic acid (UDCA): 15mg/kg/day.
• Treatment for cause: e.g. thyroxin for hypothyroidism etc.

EHBA (Extra hepatic biliary atresia)
• Baby usually is full term, appropriate for age, looks healthy.
• May present with continuation of physiological jaundice.
• Clay colored stool from D4-5 of life.
• Anemia and fat soluble vitamin deficiencies set in.
Liver biopsy: *Bile plugs in dilated ducts, fibrosis* and ductal proliferation, inflammatory changes and giant cell transformation.

Treatment:
1. Surgery: if done *with in 2 months of life* has better prognosis.

***** On HIDA scan, if absence of tracer activity → exploratory laparotomy with operative cholangiography is done → If no correctable lesion i.e. atresia is there → *Hepatoportoenterostmy* (**kasai procedure**) is done.
***** HIDA scan sensitivity is 100%; specificity is 55-85%.
2. Liver transplantation.

Differences between Neonatal hepatitis and EHBA

	Neonatal hepatitis	EHBA
Gestation, look:	Pre term, sick	Term, Appropriate for Gestational age, active
Onset:	Anytime during neonatal period	End of first week
Jaundice:	Mild-Mod	Mod-severe
Stool:	Variable in color	clay colored
Activity of feeding:	Normal to slow	Normal
Hepatosplenomegaly:	Early	Late
Urinary Urobilin:	Present	Absent
Stercobilin in stool:	Present	Absent
↑Serum Alkaline Phosphatase:	+	++
SGOT/SGPT:	Severe derangement	Mild-mod
Serum αFP:	May be raised	Absent
α_1-anti tryspin:	May be deficient	Generally normal
HIDA Scan:	Radioactivity seen in intestine	Not seen
Liver biopsy:	see above explanation	
Operative cholagiogram:	Normal	Block will be there

Neonatal Hypoglycemia

• Blood Sugar < 40 mg%.
Causes: Inadequate substrate: Small for Gestational Age, Preterm.
• Hyperinsulinemia: Infant of diabetic mother (IDM), β- cell hyperplasia (Nesidioblastoma), adenoma of β cells.
• Increased utilization: Erythroblastosis fetalis (hyperplastic islets of langerhans)
• Secondary to Polycythemia, Hypothermia, sepsis, Asphyxia, respiratory disease.
• Deficiency of hormones: Glucagon, GH, epinephrine, Adrenal, ACTH deficiency.
• Metabolic diseases: Glycogen storage Disease, fructose intolerance
Ketotic hypoglycemia, galactosemia etc.
• Maternal drugs: β-Sympathomimetics (salbutamol, terbutaline), Chlorpropamide.
• Rebound Hypoglycemia: After exchange blood transfusion (Citrate PD blood).
• Beckwith -Weidemann syndrome (Macrosomia, mild microcephaly, omphalocele, Macroglossia, hypoglycemia and visceromegaly).
***** Insulin: glucose > 0.4 is suggestive of hyperinsulinemia.
Clinical Features:
Related to increased epinephrine: Sweating, jitteriness, tachycardia
Related to decreased blood sugar: Lethargy, irritability, seizure.

Treatment:
• Breast Feeding as soon as possible (with in 1hr). *****except in cases of suspicion of metabolic defect.
Symptomatic: Give 2ml/kg of 10% dextrose. Start dextrose infusion rate 6 mg/kg/min. gradually increase to 12 mg /kg/min.
• If hypoglycemia not controlled (dextrose requirement > 12 mg/kg/min).
Then give: - Prednisone/Hydrocortisone: 10 mg/kg/day as I/v BD.
- Glucagon: 0.3 mg/kg as 1/m.
- Diazoxide: 15mg/kg/day 8 hrly as oral.

- Somatostatin analogues–Octreotide.
- Calcium channel blockers.

***** Surgery for nesidioblastoma and treatment of the cause.

Infant of diabetic mother (IDM)

• Baby will present as: *Macrosomia* (wt > 4 kg) in 30-40%, also organomegaly.
• Birth trauma, asphyxia, increases chances of Caesarian Section.
• RDS, Hypoglycemia, hypocalcemia, hypomagnisemia.
• Hyperbilirubinemia, polycythemia, renal vein thrombosis.
• There is ↑Chances of congenital anomalies.
Cardiac: VSD, Conotrunkal defects (6-8%), HOCM, PDA, PPHN Cardiac regression syndrome (sacral agenesis).
Neural Tube Defect: Anencephaly, microcephaly.
• Cardiomegaly is seen in 30%.
• Small left colon syndrome.
• IDM has 1- 9% incidence of diabetes in later life.
***** *Most common congenital anomaly is cardiac defect and is VSD*.
*****Isotropic agents are contraindicated in HOCM (Hypertropic obstructive cardiomyopathy).
***** Renal vein thrombosis will present as: Flank mass, Hematuria, Thrombocytopenia.
***** Can present as IUGR (if occurs it is due to maternal placental vascular insufficiency).
***** Small left colon syndrome is due to transient delay in development of left side of colon.

Pathogenesis: Maternal hyperglycemia → Fetal hyperglycemia → Fetal pancreatic β cell hyperplasia → ↑Insulin by the fetus → Insulin C peptide plasma concentration of fetus is increased → *Macrosomia* → *Large fetal size* is due to accumulation of fat.
***** Hyperinsulinemia→ Block cortisol induction of lung maturity → RDS.
Treatment: Treatment of hypoglycemia and other metabolic complications; and respiratory support.
***** No anomaly is specific for IDM, although *half of all cases of caudal regression syndrome* are seen is in IDM (infant of diabetic mother).

Necrotisng enterocolitis

- **Risk factors are** - Prematurity
  - **Early feeding**
  - **Formula feeding**
  - **Apnea**
  - **Infection**
  - Age of onset is inversely related to gestational age.
  - The 1st signs of impending disease may be nonspecific including lethargy and temperature instability or related to gastrointestinal pathology such as abdominal distention and gastric retention.

Signs and Symptoms Associated with Necrotizing Enterocolitis

GASTROINTESTINAL	SYSTEMIC
Abdominal distention	Lethargy
Abdominal tenderness	Apnea/respiratory distress
Feeding intolerance	Temperature instability
Delayed gastric emptying	"Not right"
Vomiting	Acidosis (metabolic and/or respiratory)

GASTROINTESTINAL	SYSTEMIC
Occult/gross blood in stool	Glucose instability
Change in stool pattern/diarrhea	Poor perfusion/shock
Abdominal mass	Disseminated intravascular coagulopathy
Erythema of abdominal wall	Positive results of blood cultures

- **Clinical features** – Sepsis + abdominal distension + vomiting + blood in stools
- **Blood studies** - Thrombocytopenia, persistent metabolic acidosis & severe refractory hyponatremia
- **X-ray** – Pneumatoses cystoides intestinalis, pneumobilia dilated bowel loop, portal or hepatic vinous air, pneumoperitoneum
  - ❖ The finding of pneumatosis intestinalis (air in the bowel wall) confirms the clinical suspicion of NEC and is diagnostic;

- **Management - A**ll oral feeding witheld
- - Fluid & electrolytes
  - nasogastric decompression
  - Careful attention to respiratory status, coagulation profile, and acid-base and electrolyte balance are important**.**

Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia

Indications for surgery

- evidence of perforation on abdominal roentgenograms (pneumoperitoneum)
- positive abdominal paracentesis (stool or organism on Gram stain from peritoneal fluid).

- Ideally, surgery should be performed after intestinal necrosis develops, but before perforation and peritonitis occurs.
- The role of **peritoneal drainage** in lieu of laparotomy may be helpful for patients in extremis with peritonitis who are too unstable to undergo surgery.
- Peritoneal drainage tends to be more successful in patients with isolated intestinal perforation
  - lower birthweight,
  - less likely to be receiving oral feeding,
  - prone to perforation at an earlier postnatal age than are patients with perforation related to NEC**.**

Neonatal seizures

Types:

1. Subtle: *Most Common type*. e.g. Tonic eye deviation, oro-bucco-lingual movements, pedaling, Eye blinking etc.

2. Clonic: Characterized by fast contraction phase and a slower relaxation phase. Common causes are trauma, subarachnoid hemorrhage and Metabolic.

3. Tonic: Characterized by sustained periods of muscle contraction. Causes include Intra ventricular hemorrhage.

4. Myoclonic: Characterized by fast contractions and nonrhythmic character. Causes are asphyxia, inborn error of metabolism, cerebral dysgenesis, and major brain trauma.

Causes of seizures:	Frequency
Cerebral hypoxia –Ischemia	50-50%
Intra Cranial Hemorrhage	10-15%

CNS infection	5%
Metabolic–Transient and IEM	5%
Cerebral dysgenesis	5%
Syndrome	2 %
Unknown	10%

***** Neonatal seizure is *disorganized convulsive activity* and lack of orderly seizure propagation is due to *Undermyelination of axons* and *underdeveloped organization of cortex*.

Difference between Seizure and Jitteriness:

Seizure	**Jitteriness**
It is of many types.	It is symmetrical tremors of the extremities.
It is rarely stimulus sensitive.	It is physical or photic Stimulus sensitive.
It Cannot be abolished by passive restraint.	It can be abolished by passive restraint.
It is associated with autonomic changes e.g. uprolling of eye ball.	It is not associated with autonomic changes.
Rate of movement: Has fast and slow phase of movement in clonic seizure.	Movement is identical in either direction.
Prognosis depends on type of seizure	Prognosis is generally good.

Treatment: Stabilization of vitals. Treatment of cause: Of hypoglycemia, hypocalcemia, hypomagnesemia.
• Seizure control: *Phenobarbital*: total 40mg/kg as I/V. others are:
Lolazepam: 0.05 mg/kg as 1/V.
Phenytoin: total 30 mg/kg as 1/V.
Pyridoxine: 50-10 mg/kg 1/v for refractory seizures.
Prognosis: Best: *hypocalcaemia (late)* has 100 % normal outcome.
• SAH has 90% normal outcome.
Poor: Cerebral dysgenesis. It has 0% normal outcome.
• IVH has 10% normal outcome.
***** Hypoglycemia has 50% normal outcome.

Neonatal Meningitis

Etiology: Group B streptococcus (*streptococcus agalactiae*), E. coli, klebsiella, salmonella, pseudomonas, staph aureus.
***** *Streptococcus agalactiae* is most common cause of early onset neonatal meningitis.
Clinical Features: Non specific: sepsis, apnea, poor feeding etc
CNS: seizures

Normal CSF findings:

	Term babies	Preterm babies
Inspection	Clear	Clear
WBC count (cell/µL)	0-32	0-29
Protein (mg %)	20-170	65-150
Glucose (mg %)	34-119	24-63

***** < 60% of total WBC count is polymorph cells.
***** < 170 mg % of protein is normal.
***** CSF sugar is 2/3 of blood sugar.

Abnormal CSF findings:
•On inspection: Xanthochromatic in Hyperbilirubinemia, Carotenemia,
Sub arachnoid hemorrhage, marked elevated protein
• On WBC count > 60% of total are polymorph cells.
• Protein > 170 mg %.
• Glucose < 1/2 of blood sugar level.
• Culture positive.

Treatment: Antibodies: Ampicillin and Amikacin or 3rd generation cephalosporins for 3 weeks.
• Phenobarbitone for seizure control.
***** BERA is done at 3 months of age to detect any auditory problem in all meningitis cases.

Birth asphyxia

Definition – Presence of either of the following is suggestive of birth asphyxia

- Persistence of Apgar score of 0-3 for >5 minutes
- Scalp or cord blood pH < 7.0
- Evidence of multi-organ system dysfunction in immediate neonatal period
- Neurological manifestations – seizures, hypotonia, coma, HIE in immediate neonatal period

Modified Sarnat Stage *			
STAGE **	**Stage 1**	**Stage 2**	**Stage 3**
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular Control			
Muscle Tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration (extension)
Stretch Reflexes	Overactive	Overactive	Decreased or absent
Complex / Primitive Reflexes			
Suck	Weak	Weak or absent	Absent
Moro (startle)	Strong; low threshold	Weak; incomplete; high threshold	Absent
Tonic Neck	Slight	Strong	Absent
Autonomic Function			
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex; fixed; dilated
Heart Rate	Tachycardia	Bradycardia	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)

* Sarnat H.B., Sarnat M.S.: Neonatal encephalopathy following fetal distress. Arch Neurol. 33:698-705. 1976.
** STAGE 0 = Normal

IMMUNITY AND IMMUNIZATION VACCINES

Vaccination: it is administration of any vaccine or toxin.

Immunization: it is process of inducing immunity artificially by either vaccination (passive immunization) or administration of antibody (passive immunization)

Types of vaccines:

Type of antigen	**Vaccine**
Live bacteria, attenuated	BCG, Ty 21 a
Live virus, attenuated	OPV,MMR, Yellow fever

Killed bacteria	Pertussis, S. Typhe
Killed virus	IPV, Rabies, HAV
Toxiod	DT,TT
Capcular polysaccharide	Typhoid Vi, Hib, Meningococcal, Pneumococcal
Viral sub unit	HB s Ag
Bacterial subunit	Acellular pertussis

Live vaccines:
• BCG • OPV • MMR
• Yellow fever • OPV • Influenza • Plague.

Both Live and killed vaccines:
• Polio • Typhoid • Influenza • Plague.

BCG: Bacillus Calmette Guerin vaccine.
• Live attenuated strain of mycobacterium bovis.
• Two common strains used are Danish 1331 and Pasteur.
• Freeze dried (lyophilized) form. It is constituted with normal saline.
•To be administered with in 3 hrs of constitution
• Dose: 0.1 ml 1/D.
• Changes at I/D site:
2-3 weeks → papule formation.
4-5 weeks → maximum size.
6 weeks → ulcer formation.
6-12 weeks → healing for scarring.
• BCG protects form progressive primary and disseminated TB including meningitis.
Mantoux test: 0.1 ml I/D; WHO advocate a preparation PPD -1 T.U with RT 23 Tween 80(strain).
• The result is read after 48 hrs (3rd day) i.e. induration.

Polio vaccine:
1. Oral polio vaccine: It is a suspension of over 1 million particles of polio virus types 1, 2 and 3.
• It is supplied with a stabilizing agent, magnesium chloride.
• OPV should be stored at -20 c.
Adverse reaction: it has been associated with occurrence of *vaccine associated paralytic poliomyelitis (VAPP).*
• Risk of VAPP would continue as long as we use OPV.
• Most VAPP cases are associated with the type 2 OPV strain.
2. Inactivated polio vaccine: it is formaldehyde killed poliovirus grown in monkey kidney cell/human diploid cells containing 20, 8 and 32 D antigen units of types 1, 2 and 3 polioviruses respectively.
• Enhanced potency IPV (eIPV) which is now available contains 40,8 and 32 D antigen units.
• It is highly immunogenic.

Diphtheria vaccine: used as combined vaccine as triple antigen.
• Protective level for diphtheria is > 0.1 Iu/ml.

Pertussis:
Types: **1**. Inactivated Whole cell Pertusis vaccine (DwPT)
2. Acellular Pertusis vaccine(DaPT): less reactogenic

1. DwPT: Used in immunization programme. Mactrods
• Protective efficacy is 80%

Side Effects:
• Local pain and redness.

• Prolonged crying/screening with in 48 hrs, lasting ≥ 3 hrs.
• Hypotonic-Hyporesponsive state with in 48 hrs.
• Seizure with in 72 hrs.
• Fever > 40.5°C with in 48 hrs.
Contra indications: Above side effects and any allergic reaction.
• Progressive neurological disease (*not static neurological disease*).

2. DaPT: Protective efficacy is same: 80%.
• Less reactogenic. Given in children with above contraindications.
Pediatric preparation: DPT/DT; diphtheria toxoid 25-30 Lf, tetanus toxoid 5-10 Lf.
Adult prepration (> 12yrs): adap; it contains diphtheria toxoid 2Lf, tetanus toxoid 5 Lf, and three acellular pertussis namely- pertussis toxoid 8 ug, filamentous hemagglutinin 8ug and pertactin 2.5 ug.

Measles vaccine:
• Live attenuated measles virus vaccine. It is supplied in freeze dried state.
• Strains used are: • Edmonston jagreb • Mortan • Schwartz
• Given at 9 months as S/C along with vitamin A.
• Once reconstituted, should be used in 3-4 hrs.
• Also given as MMR at 12-15 months.

Mumps vaccine:
• Strain used is jeryl lynn.
• Given along with MMR at 12-15 months.
• Not given in pregnancy.

Rubella:
• Strain used is RA 27/3
• Also used as MMR.
• MMR is contraindicated in pregnancy and immunosuppression.
***** *National strategy for prevention of congenital rubella should be*:
→ start with selective rubella vaccination of adolescent girls and women in child bearing age group, followed by →immunization of pre-school and adolescent girls and → then universal immunization of pre-school boys and girls.

Hepatitis B vaccine: It is Recombinant vaccine. Use HBsAg as antigen. Vaccination schedule: Can follow any of below
• 0, 6, 14 weeks
• 6, 10, 14 weeks (as with combined vaccine).
• 0, 1, 6 months
Dose: 10 µg for children (< 10 yrs); 20 µg for adults.
***** Immunocompromised children should receive twice the dose.

Typhoid vaccine:
Types:
1.Heat inactivated phenol Whole cell salmonella vaccine (TAB).Not used now.
2. Vi polysaccharide (contain Vi Ag): Given as single dose to children >2 yrs and booster at every 3 yrs.
3. Oral Ty 21a (as capsule): Given on three alternate days 1, 3, 5 to children >6 yrs. Immunity last for 3-5 yrs.

Hemophilus influenzae type b vaccine:
• Hib vaccine (conjugated vaccine). It is conjugated with carrier protein (This is T cell dependent protein Antigen).
• Not given after 5 yrs of age.

Carrier protein used: Diptheria Toxoid (PRP-D), Diptheria Toxoid like protein (PRP-Hboc), Tetanus Toxoid (PRP-T) and Meningococcal outer membrane protein (PRP-OMP).
• PRP is type b capsular polysaccharide-polyribosylribitol phosphate.
Varicella vaccine: Live attenuated strain used is OKA Strain.
Pneumococcal vaccine: Types: 23 valent and 7 valent.
• Given in children > 2 years.
Indications are:
• Undergoing splenectomy • Asplenia • Sickle cell disease
• Nephrotic syndrome • Cerebrospinal rhinorhea
• Chronic lung/heart disease • diabetes mellitus • CRF
• After transplant • Malignancy • HIV • Immunosuppression
Dose: 0.5 ml 1/M at 0, 1, 6 months.
Meningococcal vaccine: 1.Unconjugated meningococcal vaccine : These are based on combinations of group-specific capsular polysaccharides- bivalent (A and C) or tetravalent (ACY and 135).
• Age >18 months; single dose I/m or s/c; revaccinated after 3-5 yrs.

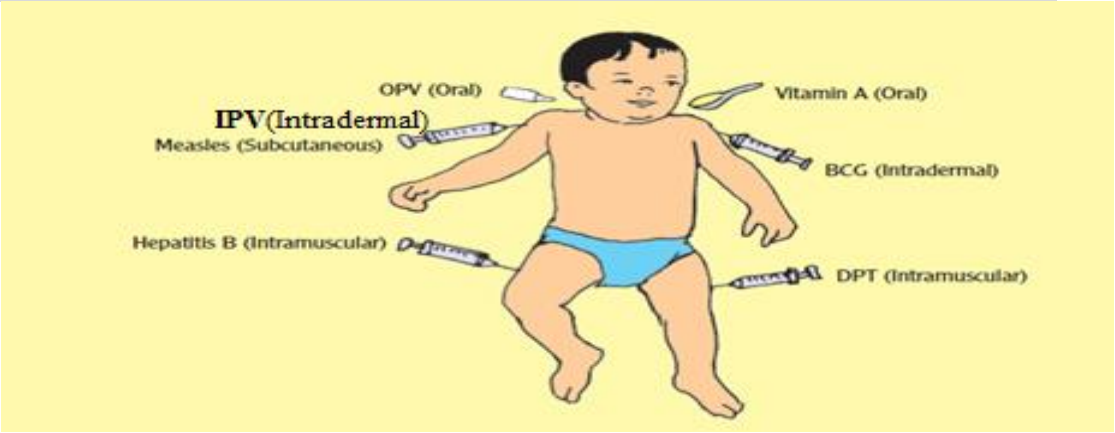
2. Conjugate group C vaccine. Not marked in India.
Indications for use: • Close contacts of patients
• Children with complement deficiency
• Prior to splenectomy
• Sickle cell anemia
• During disease outbreaks
• Prior to travel to the high endemicity meningococcal belt
• All Haj Pilgrims

Influenza vaccine:
• Influenza virus is orthomyxovirus. There are tree antigenic types (A, B and C) with several subtypes of each based on two surface antigens- hemagglutinin and neuraminidase.
• Current inactivated influenza vaccines are produced from virus grown in embryonated hens' eggs and are of *three types*: whole virus, split-product, subunit surface-antigen formulations.
• Vaccines are usually trivalent. Containing 15 ug each of two influenza A subtypes (H1N1 and H3N2) and one influenza B strain.
• Vaccines elicit a relatively strain-specific humoral response, have reduced efficacy against antigenically drifted viruses, and are ineffective against unrelated strains.
• Vaccine is effective for only a short period, usually 6 months to I yr, and a new vaccine is brought every year.
Doses: in children 6 months to 8 yrs- 2 doses as I/M; > 8 yrs only one dose is sufficient.
Indications: only in high risk children and adolescents.
• Individual with chronic pulmonary and cardiac disease
• Sickle cell disease • Immunodeficiencies • HIV infection
• SLE • Diabetes mellitus • those on prolonged aspirin therapy

Expanded programme on immunization (EPI – 1978)
Target population: < 5 yrs children and pregnant women.

Universal immunization programme-(UIP-1985)
Target population: infants < 1 yr of age.

Latest National Immunization schedule(NIS)



National Immunization Schedule (NIS) for Infants, Children and Pregnant Women

Vaccine	When to give	Dose	Route	Site
For Pregnant Women				
TT-1	Early in pregnancy	0.5 ml	Intra-muscular	Upper Arm
TT-2	4 weeks after TT-1*	0.5 ml	Intra-muscular	Upper Arm
TT- Booster	If received 2 TT doses in a pregnancy within the last 3 yrs*	0.5 ml	Intra-muscular	Upper Arm
For Infants				
BCG	At birth or as early as possible till one year of age	0.1ml (0.05ml until 1 month age)	Intra-dermal	Left Upper Arm
Hepatitis B - Birth dose	At birth or as early as possible within 24 hours	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
OPV-0	At birth or as early as possible within the first 15 days	2 drops	Oral	Oral
OPV 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks (OPV can be given till 5 years of age)	2 drops	Oral	Oral
Pentavalent 1, 2 & 3	At 6 weeks, 10 weeks & 14 weeks (can be given till one year of age)	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
Rotavirus#	At 6 weeks, 10 weeks & 14 weeks (can be given till one year of age)	5 drops	Oral	Oral
IPV	Two fractional dose at 6 and 14 weeks of age	0.1 ml	Intra dermal two fractional dose	Intra-dermal: Right upper arm
Measles /MR 1st Dose$	9 completed months-12 months. (can be given till 5 years of age)	0.5 ml	Sub-cutaneous	Right upper Arm
JE - 1**	9 completed months-12 months.	0.5 ml	Sub-cutaneous	Left upper Arm
Vitamin A (1st dose)	At 9 completed months with measles-Rubella	1 ml (1 lakh IU)	Oral	Oral
For Children				
DPT booster-1	16-24 months	0.5 ml	Intra-muscular	Antero-lateral side of mid-thigh
Measles/ MR 2nd dose $	16-24 months	0.5 ml	Sub-cutaneous	Right upper Arm
OPV Booster	16-24 months	2 drops	Oral	Oral
JE-2	16-24 months	0.5 ml	Sub-cutaneous	Left Upper Arm
Vitamin A* (2nd to 9th dose)**	16-18 months. Then one dose every 6 months up to the age of 5 years.	2 ml (2 lakh IU)	Oral	Oral
DPT Booster-2	5-6 years	0.5 ml.	Intra-muscular	Upper Arm
TT	10 years & 16 years	0.5 ml	Intra-muscular	Upper Arm

- *Give TT-2 or Booster doses before 36 weeks of pregnancy. However, give these even if more than 36 weeks have passed. Give TT to a woman in labour, if she has not previously received TT.
- **JE Vaccine is introduced in select endemic districts after the campaign.
- *** The 2nd to 9th doses of Vitamin A can be administered to children 1-5 years old during biannual rounds, in collaboration with ICDS.
- #Phased introduction, at present in Andhra Pradesh, Haryana, Himachal Pradesh and Orissa from 2016 & expanded in Madhya Pradesh, Assam, Rajasthan, and Tripura in February 2017 and planned in Tamil Nadu & Uttar Pradesh in 2017.
- $ Phased introduction, at present in five states namely Karnataka, Tamil Nadu, Goa, Lakshadweep and Puducherry. (As of Feb' 2017)

INFECTIOUS DISEASES
DAY OF ONSET OF RASH WITH FEVER

Remember by **V**ery **S**ick **P**erson **M**ust **T**ake **D**ouble **T**ea.
V: Varicella rash on D1 of fever.
S: Scarlet fever rash on D2 of fever.
P: Measles rash on D3 of fever.
T: Typhoid rash on D4 of fever.
D: Dengue rash on D5 of fever.
T: Typhus rash on D6 of fever.

Erythema infectiosum

• Fifth disease. Usually no prodromal period or it is minimal.
• Fever ± (not high grade).
• Characteristic Slapped cheek appearance.
• Caused by Parvo virus B19.

Exanthem subitum

• Sixth disease. Start with URI like symptoms.
• High fever for 2-4 days.
• Fever comes done with appearance of rash.
• Caused by Herpes Virus 6.

Chickenpox (Varicella Zoster)

• Rash appears on day 1 of the illness.
• Rash is *centripetal (Starts on abdomen*) and *pleomorphic*.
• Caused by *Varicella zoster virus* (Herpes virus family).
• Man is only reservoir.
• Crust/scabs are not infective
• Period of infectivity is 1 day prior to illness to 5 days after onset.
• Secondary attack rate is 90%.
• Latent infection is established in dorsal root ganglia. It reactivates to herpes zoster.
• Incubation period is 14-16 days (2 weeks - 2 ½ week).
• Vesicles are *not umbilicated*.

Treatment: Symptomatic.

Prevention:
1. Live vaccine with Oka strain: Indicated in adults, adolescents and immunocompromised subject, who are at risk of contacting chicken pox (e.g. no chicken pox in childhood) to be given with in 3 days of exposure.
2. Varicella zoster immune gammaglobulin: 125 U/kg to be given in 96 hrs of exposure, to those who are at risk.

Measles

• It is caused by RNA virus, paramyxovirus family.
• Man in only reservoir of infection.
• Maculopapular rash appears on D4-D5 of the illness. Rash first appear behind the ear. *Koplik spot* is present in pre-eruptive phase.
• Period of infectivity is 4 days before and 5 days after the appearance of rash.
• Incubation period is 7-14 days.
• *Koplik spot*: It is present on 2^{nd} and 3^{rd} day of the illness. Appear on the inner side of cheek, opposite the second molars as grayish or bluish white grains surrounded by reddish areola. Disappear by 2^{nd} day of rash.
• Mortality is high in malnourished children. Cell mediated immunity is depressed.
• Hemorrhagic measles: Presents as high fever, convulsion, delirium stupor, coma and bleeding.
Complications:
1. Respiratory: Pneumonia, otitis media, flare up of tuberculosis, Bronchiectasis etc.
2. Encephalitis: May occur early, usually with in week after the onset of rash. It is due to direct invasion of measles virus or autoimmune response.
3. SSPE: Subacute sclerosing panencephalitis presents as Myoclonic jerk, mental retardation. It has fatal course.
• It is late complication, occurs after 3-8 yrs of primary infection.
• It is due to persistent of measles virus infection in CNS.
4. GIT: Persistent diarrhea.

Prevention: live attenuated measles vaccine at 9-12 months. MMR vaccine at 15-18 months.
Treatment: Symptomatic.

Erythema infectiosum (fifth disease)

• It is caused by human parvovirus B 19 (HPV B 19).
• Erythema infectiosum is most common manifestation of human papilloma virus (HPV) infection.
• Incubation period is 4-14 days.
• Characteristic skin lesions occur in 3 stages:

1. Cheeks appear erythematous : *Slapped cheek appearance*.
2. Itchy erythematous or maculopapular rash over trunk and extremities, Sparing the palms and soles.
3. Rash fades from centre-*reticular or lacy pattern*.
• *Prodromal period is absent, there is no fever*.
• Rash disappears in 2 weeks without desquamation.
• Most common complication is arthritis.

Other manifestations of HPV B19 infections are:
• Aplastic crisis in sickle cell anemia, spherocytosis, β-thalassemia, Auto immune hemolytic anemia.
• In pregnancy as hydrops fetalis. • Severe anemia. • Acute arthralgia

Exanthem Subitum/Roseola Infantum (sixth disease)

• It is caused by human herpes virus 6 (HHV-6).
• Age group is 6 month-3 yrs. Incubation period is 5-15 days.
• *Prodromal period is present* and is characterized by high fever, irritability, coryza for 2-4 days.
• *Fever comes down with the appearance of rash*. Rash starts from trunk.
• Occipital and post auricular glands are enlarged.

Mumps

• It is benign viral infection of the salivary glands with systemic manifestations. *Parotids are mainly enlarged* but submaxillary and sublingual glands may be enlarged.
• Caused by RAN virus, paramyxoviridae family.
• Age of presentation is 5-15 years.
• *Infant protected by transplacentally acquired maternal antibodies*.
• Man is only reservoir of infection
• Period of infectivity is 7 days prior to 9 days after the appearance of the parotid or salivary glands swelling.
• Incubation period is 18 days (2-4 weeks).

Clinical features: Salivary manifestation: Pain near ear lobe, difficulty in chewing. Parotid swelling (initially unilaterally and then bilaterally) is present, stensen's duct appear red.
Extra salivary manifestation: 1. Aspetic meningitis: occurs in 10% cases, usually with in 1 week prior to 3 weeks after the onset of parotitis. *It may occur in absence of parotitis.* It is most common complication in children.
• CSF pleocytosis (lymphocytic).
2. Encephalitis: It is less common than meningitis and may develop before, with or after appearance of parotid swelling.
Early: It is due to mumps infection of brain (with in 1-2 weeks of onset of swelling).
Late: It is through due to demyelinating and autoimmune in origin. It has good prognosis.

3. Cerebella ataxia, Transverse myelitis, LGBS etc.
Complications: Orchitis and or epididymitis. On healing atrophy of testis occurs. It is more frequently in adolescents.
• Pancreatitis • Oophoritis • Nephritis
• Others are Myocarditis, thyroiditis, mastitis, arthritis, uveokeratitis.
Prevention: Active immunization with MMR vaccine at 15-18 months. *Strain used is Jeryl lynn strain.*

Hepatitis B

• Hepatitis B virus is DNA containing double-shelled virus.
• HBs Ag is called Australia antigen (surface antigen).
• HBc Ag is HB core Ag. HBe Ag is associated high infectivity.

Modes of infection:
1. Parental, contaminated blood transfusion
2. Contaminated injection usage
3. Vertical transmission (Mother to child)
4. Sexual contact

• Vertical transmission usually occurs at during delivery. Only 5-10% newborns are infected in utero.
• If mother is HBs Ag and Hbe Ag Positive, then transmission rate is 90% but only 10 to 15% of anti-HBe Ag positive mothers transmit the infection to offspring.
• Incubation period is 1-6 months. Man is only reservoir.
• Jaundice is present in 25% patients, usually begins about 8 week after exposure. Period of infectivity is during acute illness.
• Child is *chronic carrier* if HbsAg is + ve for 6 months. It occurs in 10% cases. Chronic hepatitis and hepatocellular carcinoma is seen hepatitis B and C infection.
• Fulminant hepatitis is seen in 0.1-1%.

Extra hepatic manifestations of hepatitis B are:
• Serum sickness like syndrome-rash and arthralgia.
• Essential mixed cryoglobulinemia. • Poly arthritis nodosa.

• Membranous or MPGN. • Severe aplastic anemia.
• Pleural effusion, myocarditis, pericarditis.

Sequence of appearance of serological markers: HBs Ag → HBe Ag →anti HBc (HBc Ag antibodies) →Anti HBe →Anti HBs.

Serological patterns in hepatitis B infection:
1. Acute hepatitis B infection with high infectivity: HBs Ag +, anti HBc Igm +, HBeAg +.
2. Chronic hepatitis B infection: HBs Ag +, anti HBc IgG +.
3. Post HBV infection and cured: Anti HBs Ag ±, anti HBc IgG +.
4. Recent HBV infection and cured: Anti HBs Ag +, anti HBc IgG +.
5. Post Vaccine: Anti Hbs Ag + (also seen in remote past infection).

Prevention: HB vaccine is DNA recombinant vaccine. Dose is 0.5 ml. Schedules are: **1**. At 0, 1, 6 months.
2. At 0, 10, 14 weeks.
3. At 6, 10, 14 weeks with combined vaccines.
• Give double dose (1 ml) for older children (> 10 years).

Vaccination in HB infected (HBs Ag) Mother: HB vaccine is to be given within 12-24 hrs as 0.5 ml I/M at 0, 1, 6 months and HB immunoglobulin 0.5 ml I/M with in 24 hrs.
• Post vaccination testing for HBs Ag and Anti HBs Ag to be done at 9-15 months. Further interpretation is as follows:

a. If anti HBs positive: Child is immune.

b. If only HBs Ag positive: Child is to refer to hepatologist

c .If both HBs Ag and Anti HBs negative: Complete second hepatitis B vaccine series is to be administered.

Treatment of chronic hepatitis B: α-interferon or lamivudine.
1. α-interferon for 4-6 months.

2. Lamivudine for 1-2 years.

Candidates for antiviral therapy:

Features	**Interferon**	**Lamivudine**
Detectable markers of HBV replication:	Yes	Yes
Elevated ALT activity:	Yes	Yes
Chronic hepatitis on biopsy:	Yes	Yes
Immunocompetence:	Yes	Yes
Immunosuppressant:	*No*	Yes
Acquisition of infection in adulthood:	Yes	Yes
Acquisition of infection in childhood:	*No*	Yes
Compensated liver disease:	Yes	Yes
Decompensated liver disease:	*No*	Yes
"Wild type" chronic hepatitis B:	Yes	Yes
Pre-core mutant hepatitis B:	*No*	Yes
Prior non-response to interteron:	*No*	Yes

HIV infection

• It is caused by RNA, enveloped virus, lentivirus subfamily, retrovirus family.
• Genome of HIV contains: gag, pol and env genes.
• Important proteins are: gp 120 (surface protein), gp 41 (envelope protein) and P 24 (core protein).
• It is inactivated by sodium hypochlorite (0.2%).
• Probability of transmission of HIV from mother to infant is 25-35%.

Mode of transmission:
• Vertical transmission (Mother to child) in 90%.
• Horizontal transmission (exposure to blood, sexual contact etc) in 10-15%.

Mother to child transmission: In utero: 30-35%; During delivery: 60-65%; Breast feeding: 10-15%.

• Chances of transmission: Mixed breast feeding > Exclusive breast feeding > Not breast feed.

Case definition: Child < 18 months: Positive results on two separate determinations from one or more of following tests:
1. HIV culture
2. HIV specific PCR: RNA or DNA
3. HIV Ag (p 24) or
4. Meet clinical criteria

• IgG antibody test cannot be used for diagnosis of HIV in children age < 18 months, as these can be due to passive transfer of maternal antibodies.
Child > 18 months: HIV antibody positive by repeated ELISA and confirmatory (western blot, immunofluorescence assays) test positive.

Treatment: Two NRTI + one protease inhibitor (Zidovudine (ZN) and lamuvidine + Ritonavir / Lopinavir) is preferred thearpy.
• NRTI (Nucleotide reverse transcriptase inhibitor).
• NNRTI (Non nucleotide reverse transcriptase inhibitor) are:

1. Efaviranz: Only capsule form available. So it is given in children > 3 years of age.

2. Nevirapine: It is used in < 3 years of age.

Prevention: Two drugs used in prevention of HIV transmission from mother to baby are Zidovudine and Nevirapine.

Strategies for prevention of HIV transmission from mother to baby:

1. ACTG 076 Trial: Mother is given zidovudine 100 mg 5 times a day, from 14 weeks of gestation onwards.
• During labour: 2 mg/kg/hr for 1 hr as I/V and then 1mg/kg/hr till birth • Newborn is given as 2 mg/kg/dose Q ID for 6 weeks.

2. HIV Net: Single dose of nevirapine to mother during labour and single dose to baby after birth.
• Both these protocols ↓ HIV transmission by about 50%.
• Live vaccines are not given to HIV positive (symptomatic) baby except BCG.

DISEASES OF GASTROINTESTINAL SYSTEM
CONGENTIAL HYPERTROPHIC PYLOIC STENOSIS

• Usual age of presentation is 3-6 weeks.

• Usually affected is Ist born male baby, who present with non-bilious vomiting.

• Vigorous peristaltic waves can be seen moving from left hypochondrium to umbilicus. Small mass may be palpable.

• Pylorus is thickened and elongated. Lumen is narrowed.

Biochemical abnormality:
• *Hyponatremia, Hypochloremia and Metabolic alkalosis*.
***** Serum potassium level is usually maintained.

Diagnosis: Clinical presentation, Palpable mass.
• USG abdomen (confirm diagnosis) will show thickened pyloric sphincter.

• Barium meal will show: - *Elongated pyloric channel*.

Shoulder sign: Bulge of pyloric muscle into the antrum.

Double tract sign: Parallel streaks of barium seen is the narrowed channel

Treatment: Medial: correction of dehydration and electrolytes imbalance.
Surgery: Ramstedt's operation (pyloromyotomy).

Hirschprung's disease

• Congenital absence of ganglionic cells in the submucosal and myenteric plexuses.

• Distal rectum is always aganglionic. It extends proximally to usually rectosigmoid colon (transition zone).

• Aganglionic segment is not relaxed → obstruction. ***** Proximal portion to aganglionic segment is dilated.

• Most important association is with Down syndrome.

• There may be History Of: ***** *Delayed passage of meconium*.

***** Constipation or diarrhea.

P/R examination: Empty rectum and on removal of finger it is followed by rapid expulsion of faces.

Diagnosis:
Barium anema; and full thickness rectal biopsy done for confirmation.
Rectal biopsy will show *Aganglionic colon* and *Hypertrophied nerves.*

Treatment: Surgery: Pull through, Swenson, duhamel operation.

Acute diarrhea

Etiology: *Mostly viral*.
Viruses: Rota virus, Calici virus, eco virus etc.
Bacteria: E.Coli (enterotoxigenic), Vibrio cholera, Salmonella, Shigella, Campylobacter Jejuni, Yersenia.

Assessment of dehydration in patient with diarrhea:

Look at:

Condition:	Well, alert	Restless*****, irritable*****	Lethargic/ unconscious*****
Eyes:	Normal	Sunken	Very shrunken and dry
Tears :	Present	Absent	Absent
Mouth and tongue:	Moist	Dry	Very dry
Thirst:	Drinks normally Not thirsty	Thirsty*****, Drinks eagerly*****	Drinks poorly***** or Not able to drink*****

Feel:

Skin pinch:	Goes back quickly	Slowly*****	Very slowly*****
Decide:	No signs of dehydration	If the patient has two or more signs including at least one ***** sign, there is **Some dehydration**	If the patient has two or more signs, including at least one ***** sign, there is **Severe dehydration**
Treat:	PLAN A	PLAN B	PLAN C

PLAN A: Give ORS and home based solutions as needed.

PLAN B: Give 75 ml/kg ORS over 4 hrs →Reassess if no dehydration →start Maintenance.

PLAN C: Start 1/V fluid.

	First give	Then give
For < 12 months:	30 ml/kg in 1 hr	70 ml/kg in 5 hours
For 1-5 yrs:	30 ml/kg in 30 minutes	70 ml/kg in 2½ hours

***** After ORS/fluid therapy, again reassess and decide next plan of therapy.
***** *Fluid of choice is ringer lactate solution*. *An ideal solution would be ringer lactate with 5% added dextrose*. However, it is not available.
***** If ringer lactate is not available, normal saline solution can be used.

WHO ORS:	Grams	mmol/L	**Low Osmolarity ORS (**mmol/L)
Glucose:	20	111	75
NaCl:	3.5	Na - 90	Na - 75
Trisodium citrate:	2.9	Cl - 80, Citrate - 10	Cl - 65
KCl:	1.5	K - 20	K - 20
Water:	1 L		
Osmolarity	311		245

MALIGNANCIES IN CHILDHOOD LEUKEMIAS

• Leukemias are most common childhood malignancy. It accounts 30% of all cancers in < 15 years. It is a genetic abnormality of hemopoietic cell that give rise to a clonal proliferation of cells.

Types: ALL, AML, CML. ALL occurs in 77%; AML in 11%; ACML in 1-3%; JCML in 1-2% of leukemias.

Acute lymphoblastic leukemia (ALL): It accounts for ¼ of all childhood cancers, ¾ of all newly diagnosed leukemia (77%). It is more common in males. Age group is 3-5 years. Among identical twin risk is more in second twin if first develops leukemia (may be 100%).
Etiology: not known. Multiple factors are implicated:
Genetic syndromes associated with ALL:
A: Ataxia telengiectasia, B: Bloom's syndrome, D: Down's syndrome, F: Fanconi's anemia, Klinefelter's syndrome, Neurofibromatosis, Immunodeficiencies, Diamond blackfan syndrome, Schwachman syndrome.
Ionizing radiations: in utero or in childhood.
Toxic chemicals: Nitros urea, benzene exposure, epipodophyllotoxins.
Therapeutic radiations: Secondary AML after aggressive chemotherapy with alkylating agent and epipodophyllotoxins.

Classifications:
1. Morphological (FAB classification):
(i) L_1 Lymphoblast: It is most common type. It accounts for 80-85%. Lymphoblast has scanty cytoplasm and inconspicuous nuclei.
It has better prognosis.
(ii) L_2 Lymphoblast: It accounts for 15%. Lymphoblasts are Large and more pleomophic; has abundant cytoplasm and prominent nuclei.
(iii) L_3 Lymphoblast: These are Large, deep cytoplasmic basophilia, have prominent cytoplasmic vacuolation. It accounts for 1-2%. These are similar to Burkitt's lymphomas.
***** Lymphoblasts are PAS (periodic acid-schiff) and tdt (terminal deoxynucleotidytransferase) +ve.
***** Myeloblasts are Myeloperoxidase, Enolase (NSE), Suddan black and Auer rods +ve.

2. Immunophenotye: Panel of monoclonal antibodies is needed for immunophenotypic analysis. Flow cytometery is for identification of cell surface antigen, after the cells are labeled with monoclonal antibodies.
(i) Precursor B-cell: It includes CD_{19}, CD_{20}, CD_{22}, and CD_{79}.
(ii) Mature B-cell: These are characterized by immunoglobulin on their surface.

(iii) T-cell ALL: These carry immunophenotypes CD_3, CD7, CD5 or CD_2. The specific myeloid markers include CD_{13}, CD_{14}, and CD_{33}.

Clinical features:
Non specific: Anorexia, fatigue, irritability, low grade fever, Bone pain.
Sign and symptoms of bone marrow failure: Pallor, fatigue, Bruising, epistaxis, fever/infection etc.
On examination: Pallor, Bleeding manifestations (Mucosal, Skin), lymphadenopathy, hepatosplenomegaly, bone tenderness, joint swelling, CNS involvement (↑ intracranial pressure-2.5%), mediastinal mass (mass lesion). Rare presentation includes ↑ ICP, cranial nerve palsy and retinal hemorrhage.

Diagnosis: Peripheral blood film shows: Anemia, ↓ Platelet, Leukemia cells are often not observed-atypical lymphocytes.
• Bone marrow aspiration/ bone marrow biopsy: This will show > 25% of bone marrow cells as homogenous population of lymphoblasts.
CSF is done for staging.

Prognostic factors: Important prognostic factors are age, initial leukocyte count and response to treatment.
Bad factors are: Age > 10 years or < 1 year, TLC > 50,000/1lakh,
t (9; 22)- philedelphia chromosome, slow response to treatment, hypodiploidy (chromosome no < 45/ cell), t (4;11)- infantile leukemia, t (8;14)- B cell leukemia, mediastinal mass at diagnosis, CNS disease
Good prognostic factors are: Age 1-10 years, TLC < 5000/µL, rapid response to treatment, hyperdiploidy (chromosome no > 50)

Treatment: Induction phase (4 weeks): It includes VAMP (Vincristine, L-asparaginase, methotrexate, prednisolone).
Remission means < 5% blasts in marrow, return of neutrophil and platelet count to near normal level.
Intensification (consideration) phase
CNS therapy: It is given intrathecal as prophylaxis. Likelihood of later CNS relapse < 5%.
Irradiation to brain and spinal cord is given if lymphblast present in CSF or ↑ CSF leukocytes.
Maintenance phase: It is of 2-3 yrs.
Supportive care: It includes management of tumor lysis syndrome,
Support for severe myelosuppression, treatment of febrile neutropenia, prophylactic treatment of pneumocystis carinii and nutrition support.

Relapse: Bone marrow: It occurs in 15-20% cases. Treatment is intensive chemotherapy followed by allogenic stem cell transplantation.
CNS: It occurs in 5% cases. It presents as ↑ ICP, cranial nerve palsy, retinal hemorrhage or leukemic cells on CSF.
Testicular: It occurs in 1-2% cases as painless swelling of one or both testis. Diagnosis is by biopsy. Survival is good.
***** Allogenic bone marrow transplantation is done for those who enters second remission after hematological relapse.
***** Long term survival is 60% after 5 years.

Late effects of treatment:
CNS irradiation (particularly if given at young age): Cognitive/ intellectual impairment, CNS neoplasm (Secondary AML after etoposide- epipodophylotoxin).
Endocrine dysfunction: Short stature, obesity, Growth retardation, thyroid dysfunction, Precocious puberty, osteoporosis.
Anthracyclins (Doxorubicin/Daunorubicin) induced cardiac toxicity.

Acute myeloid leukemia (AML)

• AML accounts for 10% of all cases of leukemia in childhood.
• More during adolescence, but can occur at any age.

• AML: ALL = 1:4
• Congenital leukemia (< 4 week of life) is mostly AML. M: F is equal.

Classification:
1. FAB classification:
M_0: Minimally differentiated leukemia
M_1: Amyeloblastic leukemia without maturation.
M_2: t (8; 21). AML with maturation.
M_3: t (15; 17). Acute promyeloblastic leukemia. 5-10%
M_4: inv (16). Acute myelomonocytic leukemia.
M_5: t (9; 11). Acute monocytic leukemia.
M_6: Erythroleukemia.
M_7: Acute megakaryocytic leukemia. It is strongly associated with Down syndrome. It is related to platelet specific antigens CD_{41} and or $CD_{61.}$
***** M_1 and M_2 constitute 30-40%; M_3 constitute 5-10%; M_4 and M_5 constitute 30-40% of AML.
***** M_1, M_3 and M_4 have Favorable prognosis.
2. Immunophenotypic classification.
3. Chromosomal classification: Most important for pretreatment Prognostic information.
4. Molecular classification: Have revealed genes that may be involved in leukemiogenesis.

Pathogenesis: Characteristic feature include > 30% of myeloid-monocyte- megakarocyte series of blood cells on bone marrow aspiration/ bone marrow biopsy or ≥ 20% myeblasts in bone marrow (WHO).
• If characteristic features e.g. Auer rods, of myeloblast is not present then Myeloperoxidase reaction in > 3% of blasts may be the only feature distinguishing AML from ALL.
• FAB classification was used until 2000. Current practice also use flow cytometery and chromosomal and molecular genetic techniques.

Predisposing factors: Ionizing radiation,
Drugs- Alkylating agents, epipodophylotoxins, topoisomerase II inhibitors, chloramphenicol, phenylbutazone, less common with chloroquine, methoxypsoralen.
Genetic syndromes:
A- Ataxia telengiectasia, B- Bloom's syndrome
D-Down syndrome, Diamond blackfan syndrome
F- Fanconi's syndrome,
K- Kostmann syndrome, Klinefelter's syndrome
P- Patau syndrome
Chemicals: Benzene, Smoking & exposure to petroleum products, paints, embalming fluids, ethylene oxide herbicides, & pesticides

Clinical features: Due to replacement of bone marrow by malignant cells and leading to secondary bone marrow failure. Signs/symptoms are similar to ALL.
Other features includes: *Subcutaneous nodules or blueberry muffin lesion*, infiltration of gingival in M_5, DIC in $M_{3.}$
• Discrete masses called *chloromas or granulocytic sarcomas* (localized collection of leukemic cells) are seen in $M_{3.}$
• Unlike ALL, bulky lymphadenopathy (LAP) and massive hepatosplenomegaly is not very common. However infants and toddler with AML- more organomegaly, ↑ WBC and CNS disease is seen (M_4 and M_5 subtypes).
• Sign and symptoms of mass lesion.

Diagnosis: This is on bone marrow aspiration/ bone marrow biopsy.
Special stains – Myeloperoxidase (MPO).

Treatment: Aggressive multiagent chemotherapy.

Drugs used in induction are: Cytosine arabinoside, Anthracyclic (doxorubicin or daunorubicin), others are Etoposide and Thioguanine.
Drugs used in consolidation are: Cytosine arabinoside, Etoposide or Bone marrow transplantation.
M_3 (promyelocytic leukemia): It is characterized by a gene rearrangement involving the *retinoic acid receptor,* is very response to retinoic acid with anthracyclines.
• Pml-Rar α fusion protein tends to suppress gene transcription and block differentiation of cells. Pharmacological dose of tretinoin, relieve the block and promote differentiation of leukemic cells bearing the t (15; 17).
• Patients refractory to tretinoin: *Arsenic trioxide* produces response in 85% of patients.

Complete remission: It is by blood and bone marrow examination:
Blood neutrophil ≥ 1500/uL, Platelet count ≥ 1 lakh, Circulating blasts should be absent, bone marrow cellularity should be > 20% with trilineage maturation, bone marrow < 5% blast, Auer rods should be absent , Extramedullary leukemia should not be present.
• Hb is not considered in complete remission.

Prognostic factors:
• Advancing age- bad prognosis
• INV (3) or – 7 have very poor prognosis.
• Factors associated with lower complete remission rate and shorter survival time have bad prognosis.
• t (8;21), INV (16), or t (15;17) have good prognosis

Retinoic acid syndrome: it occurs after at least 3 weeks of treatment. It is related to adhesion of differentiated neoplastic cells to the pulmonary vascular endothelium.
• Features include fever, dyspnea, chest pain, pulmonary infiltration, Pleural and pericardial effusion and hypoxia.
Treatment is Glucocorticoids, Supportive measures and Chemotherapy.

Chronic myeloid leukemia (CML)

• It is one of the groups of disease called myeloproliferative disorders.
• It is disease of middle age- 4^{th} and 5^{th} decade, but May occur at any age.

Types:
1. Clinically and hematologically comparable with **adult form of CML (ACML)**. It occurs in > 4 yrs of age.
2. **Juvenile CML (JCML)**: it occurs in < 4 yrs of age.

JCML: Now termed *Juvenile myelomonocytic leukemia* (JMML). It is uncommon (< 2%).
• Like ACML, it is clonal panmyelopathy involving pleuripotent stem cells. Neurofibromatosis is high risk factor of JCML.
On Bone marrow: Myelodysplastic pattern and blast < 30% of cells.
Treatment: Stem cell transplantation.

	JCML	ACML
Age of onset	< 4 yrs	> 4 yrs (10-12 yrs)
Splenomegaly	Variable	Marked
WBC at diagnosis	< 100,000	> 100,000
Response to Busalfan	Poor	Good
Colony production from peripheral blood	Monocytosis	Granulocytes
Facial rash	Present (eczema, xanthomas)	Absent
Lymphadenopathy	Frequent	Rare
Bleeding manifestations	Frequent	Absent
Thrombocytopenia	Frequent	Uncommon

Monocytosis	Present	Absent
Fetal Hb	15-50%	Normal
Immunoglobulins	Increased	Normal
Median survival	9 months	2.5-3 years
Philadelphia chromosome t(9; 22)	Absent/Monosomy7 is present in 30% of patients.	Present
Leukocyte alkaline phosphate score	Normal or low	Decreased (↑during blast crisis)

ACML: it accounts for 2-3% of leukemia. 99% patients have specific translocation t (9; 22) - Philadelphia chromosome.
• In initial chronic phase, there is *massive splenomegaly*, leukocytosis, mild anemia and ↑platelets.
• Accelerated or blast crisis phase: After 3-4 yrs, WBC count increases rapidly leading to *tumor lysis syndrome*.

Diagnosis: Peripheral blood film and bone marrow shows myeloid cells with differentiation to mature form.
• Confirm by cytogenetic studies for Philadelphia chromosome.
• Molecular techniques include BCR- ABL gene rearrangement.
Treatment: *Interferon α*, Bone marrow transplantation, *Imatinib mesylate* (inhibit BCR - ABL tyrosine kinase).
• Others include Hydroxyurea, Busalfan (used earlier): Useful only in chromic phase.

Down syndrome and Acute leukemia

• Acute leukemia is 15-20 times more common in Down syndrome.
• ALL: AML is same as in general population.
• Down syndrome with ALL, expected outcome of treatment is same.
• *Down syndrome with AML*: Patients have much better outcome than does of non Down syndrome population.

Neonates with Down syndrome

• They are prone to develop *transient leukemia or myelpoliferative syndrome* (↑WBC, blast cells and Anemia, ↓platelet)
• These neonates require close follow up.

Infant leukemia

• It occurs before 1 yr.
• In 2/3 of cases, there is a rearrangement of MLL gene – on chromosome 11.
• It has poor prognosis and very high relapse rate.
• *Leukemia cutis* (subcutaneous nodules) and tachypnea due to diffuse pulmonary infiltration by leukemia cell is common finding in infants.

Lymphoma

• 3rd Most Common group of malignancies, accounting 10-15%.
• In western world - Hodgin's Lymphoma - 40%
- Non-Hodgkin's Lymphoma - 60%
• But it is reverse in India.

Types:
1. Hodgkin's Disease: Progressive enlargement of lymph n. • Unicentric in origin (Lymphoid tissue).
• Predictable pattern of spread (contiguous nodes) in orderly fashion.
• Bimodal distribution: In developing countries: Before adolescence.
-In developed countries: At 20-30 years and > 50 years.
• Males > Female; Ist degree relative 3-7 fold more chances of Hodgkin's lymphoma.

Cause: Not known. Certain viral infections implicated are- *EBV, Herpes virus, CMV.*
• More common in individuals with immunodeficiency: *-Ataxia- telangiectasia, Diseases of lymphoreticular system, AIDS.*

Involvement: Lymph Node (Most Common site).
• Liver, spleen, B.M. or Lung (Hematogenous spread).

Pathology: *Excision biopsy* is preferred (Not FNAC).
• Characteristic *Reed stein Berg cell* (RS) is seen: Large, multinucleated giant cell, abundant cytoplasm, Owl eye appearance.
• RS cell is not pathognomic of Hodgkin's lymphoma. It is also seen in: *Reactive lymphoid hyperplasia, Non-Hodgkin's lymphoma, Non-Lymphoid malignancies, Infection mononucleosis.*

Types:
1. Lymphocytic predominance: best prognosis.
2. Lymphocytic depletion: worst prognosis.
3. Nodular sclerosis: In developed countries it is most common.
4. Mixed cellularity: Most Common.
5. Lymphocytes rich type.

Clinical Features: Painless cervical LAP (80%) or supraclavicular LAP.
• Lymph nodes are firm, rubbery in consistency.
• Mediastinal LAP (50%).

B Symptoms *on Ann Arbor staging criteria are:*
• Fever > 38°C (due to interleukin 1 or 2). • Night sweats
• Weight loss > 10% (due to TNF).
• Sign /Symptoms depends on site of involvement - lung involvement, Pricardial effusion, Mediastinal widening etc
***** *HSM (clinically detectable) rarely seen*.

Diagnosis: Lymph Node *Excision biopsy* is diagnostic.
• CXR - Mediastinum widening (> 33% of intrathoracic diameter).
• CT chest, Abdomen, Pelvis.
• *ESR, serum Copper and serum ferritin* are of prognostic value.
*****Bone marrow is done in advanced stages (III and IV) or B symptoms
***** Staging laparotomy is not done.

Classification: *Ann Arbor Staging:*
Stage I: Single L.N. region OR Single extralymphatic organ or site.
Stage II: 2 or > L.N. region on same side of diaphragm OR Localized extralymphatic organ or site and one or more L.N. regions on same side of diaphragm.
Stage III: Involvement of L.N. regions on both sides of diaphragm, with or without localized involvement of extralymphatic organ or site or *spleen*.
Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated LN enlargement.
A: Absent of B symptoms.
B: Presence of B symptoms.

Bulky disease:
• Mediastinal mass (> 33% of thorax diameter).
• L.N. mass ≥ 10 cm in diameter **Or** • 4 or more L.N. region involved.

Treatment regimens: chemotherapy includes:
MOPP: Nitrogen mustard, Oncovir (Vincristine), Procarbazine and Prednisone.
ABVD:Adriamycin(Doxorubicin),**B**leomycin,**V**inblasitine, **D**acarbazine
COPP: **C**yclophosphamide, **O**ncovir (Vincristine), **P**rocarbazine and **P**rednisone.
Favorable Prognosis: Stage I and II A (i.e. without B symptoms).

2. Non-Hodgkin's Lymphoma:
• Pediatric lymphomas are high grade lymphoma. M: F=3:1.
Geographic variation: In equatorial Africa 50% of lymphomas are Burkitt's lymphoma.
• In U.S. and Europe - 1/3rd are Lymphoblastic, 1/2 are small, non cleaved cell lymphoma (Burkitt's and non Burkitt's or Burkitt's like).
Rest are Large cell Lymphoma.
***** In India - Lymphoblastic Lymphoma is most common.

Classification:
1. Lymphoblastic Lymphoma (T. cell): Most common in India.
2. Small Noncleaved cell Lymphoma (SNCCL) - B. cell type.
Types: a. Burkitt lymphoma: Most common in Africa.
b. Non Burkitt lymphoma.
3. Large cell Lymphoma:
Types a. Diffuse lymphoma.
b. Anaplastic lymphoma.

Pathogenosis: EBV → Burkitt's lymphoma.
• Congenital and Acquired immunodeficiency e.g. *Weskit-Aldrich syndrome, Ataxia telengiectasia, X-Linked lymphoproliferative disorder, HIV* are associated with Non-Hodgkin's Lymphoma.
• Following: Chemotherapy for Hodgkin's disease;
immuno suppressive therapy or post transplantation.

Chromosomal translocations: Burkitt type: t (8; 14), t (8; 22), and t (2; 8) .There is dysregulation of *Myc-gene*.
Clinical Features: Different lymphoma has different site involvement.
1. Lymphoblastic Lymphoma (LL): Mediastinal mass (***** Extranodal disease), Cervical, axillary LAP.
2. Small noncleaved cell Lymphoma (SNCCL): *Abdominal mass* in 80% in US. (Present as distension, obstruction, GIT bleed).
• CNS, Bone Marrow involvement, LAP.
• *Jaw involvement* -70% in equator and Africa. Less than 20% in US.
3. L**arge cell Lymphoma (LCL):** Many sites: Abdomen;
• Mediastinal: dyspnea, Superior Vena Cava syndrome.

Diagnosis: Multiple needles biopsy specimen or large wedge of tumor is required.

Classification: *St. Jude staging systems*.
Stage I: Single nodal or extranodal site excluding mediastinum and abdomen.
Stage II: More than stage I and on same side of Diaphragm; Primary GIT tumor.
Stage III: Present on both sides of diaphragm; Mediastinal tumour, throracic, pleural, thymic; Extensive intrabdominal; Para spinal or epidural tumour.
Stage IV: Any of above with CNS or Bone Marrow involvement.
Treatment: Stage I and II: For all lymphoblastic lymphoma ALL regimen is used.
• For others COMP, COPA chemotherapy regimens are used.
Stage III and IV: For Lymphoblastic lymphoma ALL regimen is used.
• For SNCCL (B cell): CDET + cyclophosphamide.
*** CDET**: **C**ytarabine, **D**oxorubicin, **E**toposide and **T**hioguanine.

*** COMP**: **C**yclophosphamide, **V**incristine, **M**ethotrexate, **P**rednisone.
*** COPA**: **C**yclophosphamide, **V**incristine, **P**redinsone, **A**driamycin.

Neuroblastoma

• Most Common intra-abdominal solid tumor in children.
• It is tumour of Autonomic nervous system arising from Neural crest.
• 50% present at < 2 years, 90% present at < 6 years.
Etiology: not known
Association with: Neurofibromatosis, Hirschprung Disease, Friedreich's Ataxia, Fetal hydantoin and Fetal alcohol Syndrome.

Clinical Features: Are related to localization and metastasis.
• Most common site is adrenals (30%).
• Paravertebral retroperitoneum (28%).
• Can occur in Sympathetic chain any where from neck to pelvis.
• Can present as-*Asymptomatic mass*: Intra thoracic, retroperitoneal, Abdominal.
• *Symptomatic* - Diarrhea, HT, Sweating, emaciated with metastasis.
• In Spinal cord as *Dumb-bell tumour* → paraplegia.
• Metastasis to Bone - facial and skull (60-70%), *Opsoclonus* (dancing eyes).
Stages: Stage I: Tumour confined to organ of origin.
Stage II: Extend beyond organ of origin but do not cross midline.
Stage III: Tumour crosses midline.
Stage IV: Disseminated to distant sites: Bone, bone marrow, distant LN, other organs.
Investigations: Complete blood count (CBC), Urinary catecholamine metabolite secretions- *Homovanillic acid,Vanily mandelic acid(HVA, VMA).*
• Bone marrow examination, Liver biopsy.
• Nuclear scan- I^{123}, I^{131}; MIBG (to detect metastasis accurately).
For prognostication: Neuron specific enolase (NSE), Serum ferritin, Amplification of N-Myc oncogene.
Favorable features: Age < 1.5 yrs; Stage I, II and IV-S; Normal Serum ferritin; Favorable histology.
***** IV-S means tumour in liver, skin or BM without bone involvement i.e. otherwise be Stage 1 or 2. And age < 1 year.
Unfavorable features: Age older, Stage III and IV, Serum ferritin > 150 mg/ml, Unfavorable histology.
Treatment: OPEC chemotherapy.
OPEC: **O**ncovir, Cis**p**latinum, **E**toposide, **C**yclophosphamide.

Wilms Tumor/ Nephroblastoma

• It account for 6-7% of all malignancies.
• Deletion in the region of *chromosome 11 p13*.
• Most Common malignant tumor of kidney.
• 2nd Most Common intra-abdominal tumour of children.
• 80% occur in < 5 year. 6% are B/L.
• 1% is familial. B/L disease is more common in familial type.
• 6% have genitourinary abnormality: Horse shoe kidney, renal dysplasia, Cystic kidney disease, Cryptorchidism, Hypospadius etc.
Associations:
• *WAGR syndrome*: **W**ilm's tumor, **A**niridia, Mental **r**etardation, **G**enitourinary abnormality.
• *Beckweith-Wiedmann syndrome*: Hemihypertrophy, Macroglossia, Visceromegaly.
• *Denys-Drash syndrome*: Male pseudohermaphroditism, renal failure (Mesangial sclerosis), Wilm's tumour.

Clinical Features: Asymptomatic Abdominal Mass (*Most common*).
• Hematuria (10-25%). • Hypertension (25%).
• Other presentations: Abdominal pain, Fever, Hemi-hypertrophy Aniridia, Genital abnormality.
***** One Wilm's tumour gene mutation seen is *WT_1 gene* located on chromosome 11.

Diagnosis: Is by biopsy. Other investigations are USG, CT/MRI.
Staging: Stage I: Tumour is confined to kidney; is completely excised with capsule surface intact.
Stage II: Tumor is confined to kidney but capsule is penetrated i.e. present in peri-renal soft tissue.
Stage III: Tumor has post surgical residual. Non-hematogenous extension is present. (Spread is confined to abdomen, peri-renal bed, draining LN, surrounding tissue)
Stage IV: Hematogenous metastasis is present: Lungs, Liver etc.
Stage V: B/L renal involvement.

Treatment: Surgical extirpation, Chemotherapy and Radiotherapy.
• **For Stage I and II with favorable histology**: Vincristine and Actinomycin D chemotherapy is used.
• **For Stage III with Favorable histology**: Vincristine, Actinomycin D and Doxorubixin AND Radiotherapy to tumor bed.
• **For Stage IV and V with favorable histology**: Above chemotherapeutic agents AND Radiotherapy to metastasis sites.
Or surgical resection for liver metastasis.
• **For Unfavorable histology**: All 3 chemotherapeutic agents with cyclophosphamide AND Radiotherapy to tumor bed and metastasis sites.
***** Patency of IVC should be established before the resection (Surgery). If IVC not patent give chemotherapy.
Prognostic factors: *Tumor size* (most important), Stage, Histology.
Poor prognostic factors: Larger tumor (> 500gm), Advanced stage (III and IV), Unfavorable histology, Hyperdiploid tumors.

Differences between Neuroblastoma and Wilm's tumor:

	Neuroblastoma	Wilm's tumour
Age:	< 2 years	2-5 years
Calcification:	Often contains Calcification and Hemorrhage	Usually does not calcify.
Mass:	Crosses midline (Stage III and IV)	Usually not cross (but may cross).

Rhabdomyosarcoma

• Most common soft tissue sarcoma in children. Male >Female.
Associated with:
• Li-fraumeni syndrome • Neurofibromatosis • Fetal alcohol syndrome
Pathology: Small round cell tumor.

Classification:
1.Embryonal (60%).Occur at Head and Neck (common) and Genito-urinary tract.
2. Aveolar (20%).
3. Pleomorphic and undifferentiated.
***** Embryonal has good prognosis
***** Aveolar at extremities, perineal sites and old children has Worst prognosis.

Clinical Features: Mass lesion without any H/o trauma.
• Sign and symptoms are related to site of tumor.
• Most common site is *head and neck* (striated muscle).
• Next common sites are genitourinary tract, extremities, trunk and retroperitoneum.
• Most Common non-ocular orbital tumor in young children presenting with proptosis.
• In genitourinary tract present as Pelvic mass, bladder and prostate enlargement, *Polypoid mass in vagina*.
• Most Common sites for metastasis are Lung, Bone marrow and bone.
Treatment: Chemotherapy, Surgery and Radiotherapy.
Chemotherapy agents: Actinomycin D, Vincristine, and Cyclophaplamide with or without Doxarubicin.

*** Other small round cell tumours are:** RROMENN
R: Rhabdomyosarcoma; **R**: Retinoblastoma, **O**: Oat cell carcinoma
M: Medulloblastoma; **E**: Ewings sarcoma; **N**: Neuroblastoma
N: NHL, Lymphoma.

Retinoblastoma

• Most Common primary ocular tumor arising from embryonic neural retina.
• 20-30% of Retinoblastomas are B/L.
• 10% have family history of retinoblastoma and all have mutation in the RB1 gene (Retinoblastoma) on chromosome 13.
• 10% of U/L has a germ line mutation of the Rb gene as well.
• It is inherited as Autosomal dominant disease with high penetrance rate (80% to100%).

Clinical Features: Most common sign is white reflex (*leukokoria*)
• Strabismus, Painful glaucoma, Redness of eye, decreased vision.
Diagnosis: CT scan head with orbital cuts.
Others: BM biopsy, CSF examination.
Treatment:
For Intraocular: Enucleation in unilateral cases.
• In B/L cases, Enucleation for if **(i)** with local loss of vision.
(ii) High risk for extraocular spread.
• In remaining B/L cases**:** local therapy for individual lesion; with Cryotherapy, Photo (laser) coagulation, Brachytherapy and/or External beam radiotherapy.
For Extraocular: Chemotherapy OPEC and bone marrow transplantation.
OPEC: **O**ncovir, Cis**p**latinum, **E**toposide, **C**yclophosphamide.
***** *Rb gene mutation* is associated with increased *risk of developing secondary malignancy* e.g. Osteosarcoma, Soft tissue sarcoma.

BRAIN TUMORS

- *** Second most frequent malignancy in childhood and adolescence**
- *** Most common solid tumors in childhood**
- *** ASTROCYTOMAS are the most frequent pediatric brain tumors**
- *** Embryonal tumors or primitive neuroectodermal tumors (PNET) are the most common group of malignant CNS tumors.**
- *** Medulloblastoma accounts for 90% of embryonal tumors.**

Leptomeningeal Metastasis is seen in → Glioma, Medulloblastoma, Ependymomas, Primary CNS Lymphomas

EPIDEMIOLOGY:
5 categories:
1. Juvenile pilocytic astrocytoma
2. Medulloblastoma/primitive neuroectodermal tumor
3. Diffuse Astrocytoma
4. Ependymoma
5. Craniopharyngioma

Constitute 80% of all brain tumors.
Children: Predominance of infratentorial location.

1 – 10 yr **Infratentorial tumors**:
High incidence of juvenile pilocytic astrocytoma and medulloblastoma
> 10 yr &<1 yr **Supratentorial tumors**: Diffuse astrocytoma

Hereditary syndromes associated with Brain Tumours

Syndrome	Gene	CNS Neoplasm
Neurofibromatosis Type 1	NF 1 (17q)	Neuroma, Schwannoma, Meningioma
Tuberous Selerosis	TSC 1 (9q) TSC 2 (16q)	Astroyctoma
Neuro Fibromatosis Type II	NF2 (22q)	Schwannoma, Glioma
Li-Fraumeni	P53 (17p)	Malignant Glioma
Turkot Syndrome	APC (5q)	Medulloblastoma
Von-Hipple Lindau	VHL (3p)	Hemangio Blastoma of Retina cerebellum, Spinal Cord
Werner Syndrome (MEN-1)	MEN 1 (11q)	Pituitary Adenoma, Malignant Schwanoma
Retinoblastoma	RBI (13q)	Retinoblastoma, Malignant glioma

CLINICAL MANIFESTATIONS:
Classic triad: headache, nausea and/or vomiting and papilledema
associated with midline or **infratentorial tumors**.
Supratentorial tumors are more commonly associated with **focal disorders.**
Infants may present with hand preference.

DIAGNOSIS : For primary brain tumors, MRI is the neuroimaging standard.

WHO GRADING OF TUMORS :

Grade I : Circumscribed, moderate cellularity reflecting slow growth.
Grade II : Moderate cellularity, margins poorly defined or diffuse.
Grade III : One or more "anaplastic" foci that have developed with in a pre-existent low grade tumor(I or II).
Grade IV : Very marked anaplasia that may be generalised (up to the margins of tumor mass) or focal (with in a pre-existent tumor of lower grade)

MEDULLOBLASTOMA:

* 90% OF EMBRYONAL TUMORS
* Predominantly males, 5-7 years
* Second most frequent posterior fossa tumor in the pediatric age group.
* Most prevalent brain tumor in children less than 7 years of age.
* Majority in **midline cerebellar vermis**
* Truncal ataxia, early papilledema, unsteadiness in sitting position tendency to walk with a broad base
* Most common cytogenetic abnormality involves chromosome 17p deletions.
* Most radiosensitive Brain tumour

CT: A solid homogenous, contrast medium enhancing mass in the posterior fossa causing 4th ventricular obstruction and hydrocephalus.
Homer Wright rosettes : cells surround small stellate areas of fibrillarity without a central lumen or blood vessel.
Immunopositivity for synaptophysin
Tumour dissemination is most important prognostic factor.

INVESTIGATION
MRI with administration of Gadolinium DTPA

diagnostic test of choice
MULTIMODAL TREATMENT:
* Surgery cornerstone
* Both chemotherapy sensitive and irradiation sensitive.

Chang classification staging system

* M0 - No gross subarachnoid or hematogenous metastasis
* M1 - Microscopic tumor cells found in CSF
* M2 - Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in the third or fourth ventricles
* M3 - Gross nodular seeding in spinal subarachnoid space
* M4 - Extraneuraxial metastasis

With the risk based approach to treatment, children with high risk medulloblastoma receive full dose cranial-spinal radiation with chemotherapy during and after radiation therapy.

Most common childhood brain tumor to metastasize extraneuronally. [Bone, Lymph node, Liver]

ASTROCYTOMA

Most cases occur in the first decade of life,
with the peak incidence occurring in children aged 5-9 years

Juvenile pilocytic astrocytoma most common WHO grade I tumor

CLINICAL:
* Common in cerebellar hemisphere.
* Ataxia & incordination more on the side of the lesion
* Nystagmus is observed on lateral gaze of the child to the affected side.
* Areflexia and hypotonia are present.
* The head is tilted to the side of lesion to relieve the increased intracranial pressure caused by herniation of tumor or cerebellar tonsils through the foramen magnum.

Cerebellar astrocytoma is the most common posterior fossa tumor of childhood and has the best prognosis.
Neuroradiological finding:
Contrast medium enhancing nodule within the wall of a cystic mass
Microscopically:
Rosenthal fibres

Management : **Surgery as the primary treatment**
as well as radiation therapy and chemotherapy.

JPA of optic nerve and chiasmal region common finding in patients with NF – 1.

Astrocytoma is the most frequent CNS tumor in children with Li Fraumeni syndrome

→ PET/ SPECT done to distinguish tumour recurrence from radiation necrosis.

CRANIOPHARYNGIOMA (WHO Grade I)

* 7 to 10% of all childhood tumors.
* One of the most common supratentorial tumors in children.
* **Adamantinomatous variant** predominated.:

reticular epithelial masses resembling the enamel pulp of developing teeth

* Solid with cystic components, occur in **suprasellar region**.
* Arise from remnants of craniopharyngeal duct and/or

Rathke's pouch

CLINICAL:

Peak age 5 to 10 years , later peak 50-60 years

Growth failure

* Bitemporal hemianopsia, asymmetric or unilateral visual field defect.
* Signs of raised intracranial pressure.
* Endocrine abnormalities: Diabetes Insipidus and delayed puberty.

Most common endocrinopathy → reduced GH secretion

CT scan: Calcification in (~ 90%) associated with solid and cystic wall components.

PRIMARY TREATMENT:

Surgery with gross total resection → Curative in small lesions.[Trans cranial / Trans sphenoidal surgical resection]

No role of chemotherapy followed by radiation therapy.

Histiocytoses

• It is rare tumor. Its types are:

Class I: Langerhans cell histiocytosis (LCH).Previously called Histiocytosis X.

Class II: Hemophagocytic lymphohistiocytosis.

Class III: Acute monocytic leukemia; True histiocytic lymphoma

LCH: Characterized by accumulation of abnormal histiocytes along with lymphocytes, eosinophils and normal histiocytes to form infiltrates.These infiltrates causes osteolytic lesions and other organs involvement.

• Most Common involvement is skeleton (skull, long bones, spinal vertebrae, mastoid and mandible) - 80%. Bony lesions are usually painless but can present with pain and localized swelling.

• Vertebral collapse/fracture of long bones and spinal compression.

• Seborrheic skin rash in scalp and back (50-60%).

• Chronic ear discharge, LAP (30%), Hepatosplenomegaly (20%), lung infiltration (15%).

• Hallmark of LCH is *Birbeck granules* (Tennis racket shaped) on E/M examination. It is Positive for *S-100 protein and CD 1a positively*.

• It is rapidly progressive disease.

• It has recurrence and spontaneous regressions and resolutions.

• Systemic symptoms includes: Fever, wt loss, malaise, failure to thrive, liver failure.

X-ray: Sharply defined lytic lesions with non-healing border (*punched out lesions*).

***** If localized to Skin and bone: good prognosis.

***** Multiple organ involvement: has bad prognosis.

• It can present with **Pituitary dysfunction**: Growth retardation, Diabetes Insipidus, Panhypopituitarism.

• Rare presentations: Liver-Cirrhosis; Bone marrow involvement-anemia, thrombocytopenia.

***** BMA is done to rule out infiltration.

Treatment: Localized disease or single bony lesion: Curettage and Low dose radiation.

• Multi system disease: Chemotherapy: Vinblastin and Prednisolone.
LCH types: Reflect different extent of disease:

1. Eosinophilic granuloma: Characterized by expanding, erosive accumulation of Langerhans cells, usually in medullary cavities.
• Most commonly involved bone is *Calvarium*. Others: Ribs, Femur.

2. Lietteree-Siewe disease: Usually occurs in < 2 yrs.
• Cutaneous lesions: Seborrheic eruption. HSM, LAP, Pulmonary infiltrates.
• Destructive osteolytic bone lesions.

3. Hand-Schuller-Christian disease: triad is *Calvarial bone defect, Diabetes Insipidus* and *Exophthalmos* (Due to B/L infiltration of retroorbital area).

GENETICS AND INBORN ERROR OF METABOLISM

Gene: The portion of a chromosome, which codes for a character, is called a gene. Two genes on the chromosomes for same character all called alleles. Genes are made up of DNA.
• Basic unit of DNA is nucleotide. This is made of: Nitrogenous base, Sugar (deoxyribose) and Phosphate.
• Nitrogenous base can be **Purines**: A (Adenine) and G (Guanine).
or **Pyrimidines**: T (Thymine) or U (Uracil) and C (Cytosine).
• Thymine is present in DNA and Uracil in RNA.
Homozygous state: If alleles code for the same trait.
Heterozygous state: If alleles code for different trait e.g. one code for blue iris and other code for black iris.
Dominant gene: If an allele clinically manifests even in heterozygous state.
Recessive gene: If an allele clinically manifests only when allele present on both chromosomes in pair i.e. Homozygous state.

Patterns of inheritance

Genetic disorders are caused completely or partially by altered genetic material.
Pedigree means family free.
First degree relatives: Individuals who share ½ of genetic material with the proband (patient) e.g. brothers, sisters, children, parents.
Second degree relatives: Those who share ¼ of genetic material with the proband e.g. grand parents, grand children, aunt, uncle, niece, nephews.
Third degree relatives: Those who share 1/8th of genetic material with the proband.

Autosomal Dominant Disorders: It is characterized by: Single gene in heterozygous state is sufficient to cause the phenotype.
• Vertical transmission pattern (from parents to child).
• Any child has 50% risk of inheriting the disorders.
• Normal Individual does not transmit the disease.
• Males and female are equally affected.
• Significant proportion of cases all due to new mutation.
***** Variable expressivity of the mutant gene can cause reduced penetrance. Cause for this is not known.

Autosomal Recessive Disorders: It is characterized by:
•Two copies of the mutant gene in the homozygous state are necessary.
• The child of two heterozygous presents has a 25% chance of being homozygous (i.e. 1 in 2 from each presents= $1/2 \times 1/2 = 1/4$).
• Males and females are equally affected.

• The affected individuals are almost always born in only one generation of the family.
• The children of the affected (homozygous) person are all heterozygous.
• Horizontal pattern in pedigree (among brother and sister).
***** Consanguinity is important factor in transmission of disease.

Autosomal Recessive Disorders are: Remember by mnemonic **BSC HAWXI**
B: β-thalassemia; **S**: Sickle cell Anemia; **C**: Cystic fibrosis
H: Hemochromatosis; **A**: Albinism; **W**: Wilson's disease
X: Xeroderma pigmentosa; **I**: Inborn error of metabolism

X-linked Recessive Disorders: It is characterized by:
• Incidence of the condition in much higher in males than in female
• Heterozygous females are carrier and are asymptomatic
• Gene from affected man is transmitted to all of his daughters and any of his daughter's sons has a 50% chance of inheriting the gene
• From carried female, sons have 50% chances of inheritance
• Never transmitted from father to son
• New mutations are response for sporadic cases
***** In turner syndrome: X0, 45. She is homozygous for all genes on X chromosome.

X-linked Recessive Disorders are: Remember by mnemonic **BCD FGH**
B: Bruton's Agammaglobulinemia
C: Chronic granulomatous disease, Color blindness
D: Diabetes insipidus (primary nephrogenic), Dystrophies (DMD and BMD)
F: Fragile X syndrome, Fabry's disease; **G**: G-6PD deficiency
H: Hemophilia A and B, Hunter disease, Hydrocephalus (congenital); Hypoxanthine guanine phosphoriboxyl deficiency (Leisch-Nyhan syndrome).

X-liked dominant Disorders: It is characterized by:
• From affected father, all the daughters will be affected and none of the sons will have the condition.
• From affected females, both male and female have 50% chances of inheriting the disease.

Multifactorial inheritance/Polygenic inheritance: e.g. Neural tube defect, D.M, Cleft palate, Club feet, Congenital Hypertrophic pyloric stenosis etc.

Mitochondrial inheritance: It is characterized by:
•They result from mutations in mitochondrial DNA.
• Material genetic transmission.
• All offspring born to an affected female will be affected.
• Sons will be affected but will not transmit the disease.
***** Mitochondria are present only in ovum and not in sperm.
e.g. Kearns-Sayre disease (**KSS**), Leigh disease (Subacute Necrotizing encephalomyopathy), Leber Hereditary Optic Neuropathy (**LHON**), Mitochondrial encephalomyopathy, Lactic Acidosis, Stroke like syndrome (**MELAS**), Myoclonus epilepsy and Ragged-Red fibers (**MERRF**), ATPase Subunit 6 Mutation (**NARP**), Pearson marrow/Pancreas syndrome.
Genomic imprinting: It is characterized by:
• It takes place in the germ line. Certain regions of the genome are being inherited differently, depending on the parent of origin.
• Genes in the relevant region are functionally inactivated (imprinted) during gamete formation. Examples include:

1. Prader-willi syndrome: Micro-deletion of chromosome 15, on **P**aternally delivered chromosome and relevant gene/genes are silenced on maternal chromosome 15.

***** If no micro-deletion found, then both alleles/chromosomes are inherited from mother called **Uniparental disomy** (inheriting both homologous chromosome from a single parent, here is mother). It occurs in 60% of Prader-Willi syndrome.

2. Angelman syndrome: Micro-deletion of chromosome 15 is on maternally derived chromosome and gene/genes are silenced on parental chromosome 15.
***** If no micro-deletion found, then both chromosomes/alleles (silenced) are inherited from father called **Uniparental disomy.** It occurs in 5% of Angelman syndrome.
***** Numbers of chromosomes are normal.

Prader-willi syndrome	**Angelman syndrome**
• Severe hypotonia	• Hypotonia
• Obesity, hypogonadism	• Fair hair, mid face hypoplasia
• Short stature	• Seizures, Jerky ataxic movements
• Small hands and foots	• Uncontrollable bouts of laughter (Happy puppets)
• Mental retardation	• Severe MR

Down's syndrome

• Commonest chromosomal disorder occurring with frequency of 1: 800 to 1: 1000.
Risk of occurrence: among newborn is 1:1500 if maternal age is 15-29 years; 1:800 if maternal age is 30-34 years; 1:270 if maternal age is 35-39 years; 1:100 if maternal age is 40-44 years; 1:50 after 45 years.
Cytogenetics:
• Trisomy 21 occurs in 95% of cases (that is Non-familial).
• Translocations (unbalanced) in 4% of cases.
• Mosaic in 1% of cases.
Translocations: This occurs in Between group D (13, 14, 15) and group G (21, 22) chromosomes. Of these 75 % are denovo and 25% are familial translocation.
• Balanced translocation if between G/G groups.
Risk of recurrence: In trisomy 21, If mother age < 35 yrs then recurrence is 1%. If mother age >35 yrs then recurrence is > 1%
• In translocation, if mother is carrier then recurrence is 10%. If father is carrier then recurrence is 5%
• If balanced translocation (21:21) then recurrence is 100%.
***** If child karyotyping is trisomy 21, then to know recurrence there is no need of karyotyping of parents as Trisomy 21 occuring in 95% of cases is non familial type.
***** If child karyotyping is having translocation, then to know recurrence karyotyping of parents is done to know carrier status of parents.

Clinical Features: Mental and physical retardation.
• Flat facies, mongoloid slant of eyes and epicanthal folds.
• Oblique palpebral fissure.
• Brachycephaly, Small nose, flat nasal bridge, Protuding tongue.
• Hands: Short and broad, Clinodactyly (fifth finger), Simian crease, Distal Triradius, Preponderance of ulnar loops on fingers.
• Foot: Sandle gap.
***** Diagnostic signs in neonatal periods: Hypotonia, Flat facies and small dysplastic ears.

Systemic abnormalities:
1. Cardiac: Congenital heart disease (CHD) in 50%. 50% of CHD have Endocrinal Cushing defect. Next common is VSD.
***** Major cause of early mortality in congenital heart disease.
***** Echocardiography is indicated as early as possible or with in 9 months of age.
2. GIT: *Duodenal atresia* in 10% (Also ileal and jejunal atresia).
Associated conditions are *Hirschprung's disease, Celiac disease*
3. Hearing: Conductive hearing loss in 90%.
4. Vision: *Brushfield spots* on the iris (*speckled iris*), Cataract, Myopia, strabismus.

5. Endocrinology: Hypothyroidism in 15-30%.
6. Atlantoaxial instability: in 15-30%.

Evaluation: *Echocardiography* for Heart disease. *Eye examination* at Birth, 3 months, 6 months and at 1 year then yrly. *Hearing assessment* to be done at 3 months.
Antenatal diagnosis: Triple test: ↑β HCG, ↓ Alfa feto protein and ↓Estriol.
• Aminocentesis at 16-18 weeks: FISH on uncultured cells
• CVS at 9-11 weeks: Culture and Karyotyping
• Cordocentesis at 18 weeks: Culture and FISH
• USG at 11-20 weeks: *Nuchal fold thickness > 4 mm*; *Double-bubble* (Duodenal atresia) in abdomen; Short femur, Macroglossia.
• Fetal echocardiography: Endo-cardial cushion defect.

Edward syndrome (Trisomy 18)

• Second Most Common autosomal trisomy.
• Baby born is usually post mature, Low Birth Weight.
Clinical Features:
• Hypertonia, Elongated skull (prominent occiput), microcephaly
• Malformed and low set ears, Micrognathia, Short sternum
• Rocker-bottom feet, closed fists with overlapping of digits
• CHD: VSD, PDA; renal malformations.

Patau Syndrome (Trisomy 13)

• Microcephaly, Microopthalmia, ocular hypotelorism.
• Holoprosencephaly (Incomplete development of forebrain, olfactory and optic nerve), Cleft lip, Cleft palate, Polydactyly.
• These children have Ectodermal scalp defect.

Trisomy 8

• Long face, high prominent forehead
• Wide upturned nose, thick everted lower lip
• Microretrognathia, low-set ears, high arched some times cleft plate
• Osteoarticular anomalies are common.

Turner's syndrome (45, XO)

• 45, XO chromosome: Loss of whole or short arm of the X chromosome → Ovarian dysgenesis and somatic features.
• Loss of long arm of the X chromosome →Only ovarian dysgenesis.
Clinical Features: In Newborn: Lymphoedema of the dorsum of hands and feet, Loss of skin folds at the nape of neck.
In Older children: Short stature, Short webbed neck, Low posterior hair line, High arched palate, small mandible
• Chest: Broad shield like, widely spaced hypoplastic nipples
• Elbow: Increased carrying angle (Cubitus valgus)
• Knee: Medial tibial exostosis
• Fourth metacarpal and metatasal are short. ***** No mental retardition
Puberty: Delayed secondary sexual characteristic, Height < 145 cm.

Congenital defects:
Kidney: Horse-shoe kidney, pelvic kidney
Heart: *Coarctation of Aorta, Bicuspid Aortic valve* (abnormality)
Ear: Conductive hearing loss
Normal fetal ovary has 7 million oocytes.
At birth: 2 million oocytes (1 million active follicles);

By menarche: 4-5 lakhs oocytes; At menopause: 10,000 oocytes
***** In Turner's syndrome this process is accelerated and all oocytes are gone by 2 yrs. ***** *Ovaries are `streaks'.*
*****Antithyroid antibodies, thyroid peroxidase or thyroglobulin antibodies are in 30-50%.
***** Abnormal glucose tolerance and insulin resistance is also seen.
Treatment: BP monitoring and echocardiography for correction of defect. • HT monitoring •Thyroid function test
• Growth hormone replacement
• Ovarian hormone replacement and should be stated at 12-14 years of age (Esterogen and Cyclical therapy of progesterone)
• Hearing assessment. • USG for Renal and Ovaries.
***** Prophylatic gonadectomy is done in turner syndrome in patient with Y chromosome as there are increased chances of gonadoblastoma.

Differences in Noonan's syndrome (when compared with Turner Syndrome).
• Normal chromosomes; 46, XX or 46, XY (i.e. male or female)
• Mental retardation is present.
• Common Cardiac defects are: Pulmonary stenosis; ASD (rather than aortic defect).
• Usually normal sexual maturation (But may delayed by 2 years)
• *No infertility*.

Klinefelter's syndrome

• 47, XXY genotype. Small testis with hyalinized seminiferous tubules
• Failure of development of secondary sexual characters with raised Gonadotrophins.
• Mental Retardation, Tall and underweight
• Hypospadius/cryptorchidism, Infertility, Gynaecomastia
• Behavioral/ psychiatric problems
***** Boys with Mental Retardation and large testis → **Fragile X syndrome**
Treatment: Testosterone replacement to be start in middle adolescence.

Marfan's Syndrome

• Disorder of connective tissue (elastic).
• Gene implicated is fibrillin on chromosome 15.
• Tall, Slender with long and thin Extremities (fingers and toes).
• It is Autosomal Dominant disease. Sporadic cases can occur.
• Muscles: Hypotonic; Joints: Hyper-extendible.
• Eyes: Sublaxation of lens (upward and lateral), Cataract, Coloboma
•Aortic cystic medionecrosis: Aortic dilatation and valvular abnormalities.
• Intelligence is normal.

Homocystinuria

• It is Autosomal Recessive disease. Methionine
Type I: ↓↑ Methyl transterase
• Due to deficieney of *cytathionine* Homocysteine → Homocytine
synthetase in the liver. Serine +↓ *Cystathionine synthetase*
• Homocysteine accumulates Cystathionine
in the tissues. ↓
• It is rapidly oxidized to homocystine. Cysteine ↔ Cystine
• ↑ Homocystine →*Homocystinuria*
Clinical Features: Age of presentation is 3-4 years.
• Marfanoid features, Subluxation of lens is medial and downward.
• Deficiency of cystine →lesions of the lens.

• Mental Retardation (due to ↑ methionine level in brain)
• Cystine deficiency →defective collagen formation →generalized osteoporosis.
• Plasma folate ↓ (Because of more conversion of Homocysteine to methionine).Recurrent thromboembolic episodes.
Diagnosis: Homocysteine in urine (***** by cyanide nitroprusside test).
• ↑Serum methionine and homocystine.
Treatment: Large doses of pyridoxine and FA (1-5 mg/day).

Phenyl ketonuria (PKU)

• It is Autosomal Recessive disease.
• It is due to deficiency of phenylalanine hydroxylase or Cofactor tetrahydrobiopterin (BH_4).
• ↑Phenylalanine level in blood, CSF and tissues
• Phenylalanine is converted into: *Phenyl pyruvic acid*, *Phenyl-lactic acid* and *o-hydroxyphenyl-acetic acid*.
• Cells are not able to effectively utilize other amino acids because of very high phenylalanine.
• Phenylalanine metabolities are not directly toxic to brain.
• Brain cells are deprived of amino acids which are essential for maturation and Myelination → CNS manifestations.

Phenylalanine
Tyrosinase ↓ *Phenylalanine hydroxylase*
Melanin ← Dopamine ←————Tyrosine
↓ Transaminase
Homogentisic acid
↓ *Homogentisic acid oxidase*
Meleyl-aceto acetic acid
↓
Fumaric acid and acetoacetic acid

Clinical Features: Infant will be normal in first few months.
Neurological signs: Irritability, tremors, seizures, hyperkinesis, muscular hypertonia, Microcephaly, mental retardation, brisk DTR.
• ↑↑Phenylalanine levels →Competitive inhibition of tyrosinase. So tyrosine is not converted to Melanin → Blond hair, blue iris and fair skin, skin rash
***** Characteristic *musty body odor* is due to phenylacetic acid.
Diagnosis:
• On normal diet, phenylalanine > 20 mg% on two occasions.
• Blood tyrosine level > 5 mg%.
• Abnormal urinary metabolites of phenylalanine detected by *Guthrie test* (*******Bacterial inhibition assay*) and *Ferric chloride test*.
Treatment: Phenylalanine *restricted diet* (*****not eliminated) to maintain serum level 2-6 mg%.
• Mental Retardation is preventable. Improvement in neuroloical symptoms/signs changes occur weeks after treatment.
• Dietary restriction is for 8-10 yrs (but can be for life).
Maternal PKU: Offspring with *Mental Retardation*, *Microcephaly*, *Congenital heart disease*.
Treatment: Phenylalanine restricted diet before and during pregnancy.

Tyrosinemia

• It is Autosomal Recessive disorder.
Type I: It is due to deficiency of enzyme fumarylacetoacetate hydrolase.
Clinical Features: Major organs affected are:
• Liver: hepatic crisis
• Peripheral nerves: acute peripheral neuropathy (pain in legs, hypertonia, weakness, paralysis)
• Kidneys: Fanconi's like syndrome (Rickets, Failure to thrive), Nephrocalcinosis
Treatment: Diet restricted in phenylalanine, tyrosine and methionine →There will be some improvement
Type II: Oculocutaneous tyrosinenia: Due to deficiency of tyrosine aminotransferase.

Clinical Features: White and silky hair, Photophobia, Irish is blue/pinkish.
***** Liver and kidney functions are normal.
Treatment: Same as above.
Type III: It is due to deficiency of 4-hydroxyphenylpyruvate dioxygenase (4HPPO). It is rare.

Alcaptonuria

• It is due to deficiency of *homogentistic acid oxidase* (HGO) in liver and kidney. Homogentisic acid is excreted in urine and is accumulation in connective tissue.
• *Black pigment* (polymer of homogentisic) is deposited in the sclera (between cornea and canthi), Ear and Nose cartilage (**onchronosis**).
• Deposition in articular cartilage leads to degeneration → osteoarthritis. In intervertebeal disks →degenerated, spaces are narrowed and calcification occurs.
• Ochronotic arthritis is common in *hips and shoulders joints*.
• In Kidney →Renal stones, Nephrosis.
***** *Urine becomes dark on standing*.

Inborn error of metabolism(IEM*)*	**Urine odor**
Phenylketonuria	Mousy or Musty
Multiple carboxylane defi	Tom cat urine
Maple syrup urine disease	Maple syrup
Glataric academia (type II)	Sweaty feet, acrid
Hawkinsinuria	Swimming Pool
Isovaleric academia	Sweaty feet, acrid
Hyper Methioninemia	Boiled Cabbage
Oasthouse urine disease	Hops-like
Trimethylaminuria	Rotting fish
Tyrosinemia	Boiled cabbage, rancid butter.

Maple syrup urine disease

• Impaired activity of branched chain 2-oxo-acid dehydrogenase complex (BCOD-DH) **or** branched-chain-α- keto acid dehydrogenase.
• Increased Serum *Branched chain amino acids* (**VIL**) i.e increased *Valine*, *Isoleucin* and *Leucine.*
• Branched chain amino acids are also increase in CSF and Urine.
• Increased Serum Branched chain amino acids → Disturb the transport of other amino acids across the cell membrane.
Clinical Features: Neurotoxic effects: Ataxia, seizures, spasticity, Degeneration of nervous.
• *Maple syrup smell* due to ketoacids.
• Hypoglycemic attacks, due to ↑↑ levels of leucine in the blood.
Diagnosis: Ferric chloride test →Navy blue color with urine.
• DNPH (2-4, dinitrophenyl hydrazine) test → Yellow precipitate with urine.
• Guthrie's test.
• ↑ Serum Branched chain amino acids (Valine, Isoleucin, Leucine).

Glycogen storage Disease

Type I (Von Gierke): Due to Glucose 6 phosphatase deficiency.
Type II (Pompe's): Due to Lysosomal α 1, 4 glucosidase deficiency.
Type III (Limit dextrinosis or cori or forbes disease): Due to Debranching enzyme deficiency.
Type IV (Anderson): Due to Branching enzyme deficiency.
Type V (Mc Ardle): Due to Muscle phosphorylase enzyme deficiency.
Type VI (Hers): Due to Liver phosphorylase enzyme deficiency.
Type VII (Tarui): Due to Phosptopeuctominase enzyme deficiency.
***** Mainly liver (liver glycogenosis) is affected in: Type I, III, IV, VI, IX
***** Muscle glycogenosis occur in: Type II, V, VII (**2 5 7**).
***** Type II also has liver glycogenosis.
Pompe's disease: Onset 0-6 months.

• Presents with Hypotonia, Coarse facies, Hepatomegaly,
***** Cardiomegaly
*** ECG**: high voltage QRS, short PR interval.

Wilson Disease

• It is Autosomal Recessive disease.
• Gene is located on chromosome 13.
Defect: Lysosomal copper is excreted in insufficient amount in bile.
Or the binding of copper by metallothionine is increased.
Affects: Liver: Cell damage →Acute or Chronic Liver Disease.
• RBC: Hemolysis (Coomb's negative hemolytic Anemia).
• Proximal Renal tubules: Bony deformities, fanconi's syndrome.
• Brain: Neurological disturbances, psychiatric problems
• Eyes: *Kayser-Fleischer* (**KF**) *rings*.
Clinical Features: Age of presentation is 6-15 years.
• Jaundice and Hepatomegaly
• Basal ganglia involvement: Rigidity, tremers, difficult speech, abnormal posture, poor handwriting
• Deteriorating school performance. Ataxia -Parkinsonism like.
• **KF rings**: Rusty Brown, *at border (in cornea*) detected on slit lamp examination.

Diagnosis: Low Serum ceruloplasmin level, < 20 mg%.
• Low Serum copper, < 20 µg%. 24° Urinary copper > 100 µg.
• Liver copper > 250 µg/gm of dry wt.
***** On d-penicillanine challenge test 24° Urinary copper > 1000 µg.

Treatment: Decrease intake of copper rich food e.g. liver, shell fish, nuts, chocolates etc.
• d-penicillamine before meals 10-15 mg/kg BD. • Zinc
• Triethylene tetra-amine dihydrochloride (Trien) may be tried.

RENAL SYSTEM

Neonatal Kidney: GFR of child do not approximate adult values until the 3rd year of life. Significant tubular maturation (Tubular transport capabilities of neonates) occurs during infancy.
• By end of 2 years: Renal function approach adult value.
Plasma Osmolality: $2\,(Na) + \frac{B\ Sugar}{18} + \frac{BUN}{2.8}$

Juxtaglomerular apparatus (JGA): Specialized muscle (renin activity) cells of *afferent arterioles* + macular densa in *distal tubule* + afferent arterotis + *lacis cells* located in the Δ space b/w these structures.
Pyuria: Leukocytes in urine →suggest infection. It is > *10 leukocytes/HPF* in uncentrifuged sample and > *5 leukocytes/HPF* in centrifuged sample.
• But infection can occur in the absence of pyuria. Pyuria can be present without UTI. Pyuria is more confirmatory than diagnostic.

Kidney function tests (Radionuclide imaging)

1. Those rapidly eliminated by the kidney: Those for evaluation of filtration and drainage function:
• 99 mTc-DTPA (Diethylene Triamine-Pentacetic acid)
• 99 mTc-MAG-3 (Mercaptoacetyl-triglycine)
• 99mTc-LL-Ec (LL-Ethylene cysteine dimer)
DTPA: *Purely glomerular agent*. It is excreted chiefly by glomerular filtration.
MAG-3: Tubular agent. It is excreted principally through active renal tubular transport.
LL-EC: It is also tubular agent.

2. Those concentrated in the renal parenchyma. For detailed mapping of functioning renal parenchyma (Renal cortical scintigraphy).
• 99Tc-DMSA (Dimercaptosuccinic acid)
• 99Tc-GHA (Glucoheptonate)
DMSA: Excellent method for visualization of renal parenchyma. It is procedure of choice for evaluating patient with UTI. Also anatomical details: Cysts, Cortical scars, renal malpositioning etc.
GHA: Fairly good visualization of the collecting system.
Examine the abnormality of both cortical and collection system.
Diuresis renogram: Frusemide is used to produce rapid diuresis. It helps to differentiate obstructive from non-obstructive dilatation.
Captopril renogram: Captopril temporarily dilates the efferent renal arterioles → reducing the renal blood flow and the GFR → reducing renal BF and the GFR. Thus it increases its sensitivity for diagnosis of renal artery stenosis.

3. Those used for clearance studies:
• 51 Cr- EDTA for GFR.
• 99Tc- DTPA for GFR.
• 131 I-hippuran for effective renal plasma flow (ERPF)

Hematuria

• Hematuria is ≥ 5 RBC/HPF in urine.
Causes of hematuria:

1. Glomerular causes:
a. Hereditary causes: Hereditary nephritis (*Alport syndrome*), Thin glomerular Basement Disease, SLE nephritis, IgA nephropathy.
Others: PCKD, Urolithiasis, Sickle cell disease etc.
b. Acquired: Post streptococcal glomerulonephritis (PSGN), Henoch-Schein purpura (HSP), Hemolytic uremic syn. (HUS), Vasculitis etc.

2. Extraglomerular causes:
a. Upper Urinary Tract causes (Glomeruli, PCT, DCT, interstitium):
Pyelonephritis, interstitial nephritis, Acute Tubular Neprosis, Nephrocalcinosis, Tumours, Trauma etc.
b. Lower Urinary Tract causes (pelvo-calyceal system) and below:
Cystitis, Arthritis, Urolithiasis, Trauma etc.
• Hematuria from glomerulus: It produces Brown-cola colored urine
Proteinuria > 100 mg%, *RBC casts*, *Dysmorphic RBC's* in urine.
• Hematuria from from tubules: Presence of WBC or renal tubular epithelial cell casts.
• Hematuria from Lower tract: Normal RBC morphology, Minimal proteinuria (< 100 mg), Gross/terminal hematuria (relative).

IgA Nephropathy or Berger Nephropathy

• Most common chronic glomerular disease.
Clinical features: *Recurrent episodes of gross hematuria*, after precipitated by upper RTI or gastrointestinal infection.
• In between attacks: Microscopic hematuria, mild proteinuria.

• May present with Acute nephritic; Acute nephrotic syndrome or combined nephritic-Nephrotic syndrome.
• *Serum C3 levels are normal* (***** in post-streptococcal GN it is ↓)
• Recurrence of disease is frequent.

Pathology: **Light M/E**: Focal and segmental mesangial proliferation. IgA is predominant immunoglobulin deposited in mesangium.
Electron M/E: Mesangial deposits in subendothelial and Subepithelial regions of Glomerular basement membrane (GBM).

Treatment:
• BP control. ACE inhibitors and Angiotensin II receptor antagonist decrease proteinuria and may retard the rate of renal progression.
• Immunosuppressive therapy: Corticosteroids or more intensive multidrug therapy.
• Prophylactic antibiotics and tonsillectomy may reduce the frequency of gross hematuria. • Renal transplantation

Post Streptococcal Glomerulonephritis (PSGN)

• It present as acute nephritic syndrome (90%).
• It is characterized by sudden onset gross hematuria, Edema, Hypertension, and renal insufficiency.
• *Common cause of gross hematuria* (*after IgA nephropathy*).

Clinical features: Follows infection of throat or skin by Gr. A β hemolytic streptococcus. Age is 5-12 yrs.
• 1-2 wks after prior streptococcal pharyngitis (strains 4 and 12).
• 3-6 week after prior streptococcal pyoderma(strain 49).
• Microscopic/gross hematuria. Varying degree of edema, Hyper-tension and oligouria, depending on severity of renal involvement.
• May develop encephalopathy or/and heart failure.
• Nephrotic syndrome may develop in 10-2% cases.
• Resolution may take 6-8 weeks.
• Microscopic hemituria may persistent for 1-2 years.

Pathology: **Light M/E**: Diffuse mesangial cell proliferation.

Immunofluorescence M/E: *Lumpy-Bumpy deposits* of immunoglobulin (IgG) and complement on GBM.
Electron Microscopy: *Election dense deposits or humps on sub epithelial* side of GBM.
Diagnosis: On clinical presentation
• Urine examination: RBC, RBC casts, proteinuria, WBC.
• ↓ *Serum C3 level*, returns to normal level in 6-8 weeks.
• Positive throat culture →support diagnosis or carrier state
• Rising antibody titer after pharyngitis to streptococcal antigen (s) e.g. (ASO) Confirm diagnosis. DNase B (deoxyribonuclease B) antigen-antibody after cutaneous infection.

Treatment: treatment of acute renal insufficiency
• Control of Hypertension: Na restriction, diuretics, calcium channel blockes, ACE inhibitors.
•10 days course of penicillin to limit the spread of the nephritogenic organism. *Antibiotic therapy does not affect the natural history of GN*.

Prognosis: Complete recovery occurs in > 95 % patients.
• Recurrences all extremely rare.

Pauci-immune crescentric GN

• Rapidly progressive GN (crescents) unifying abnormality is the presence of crescents in the majority of glomeruli.

Classification:
1. Immune-complex mediated forms:

↓ C3 level	Normal C3 level
• PSGN (ASO, anti DNase)	• *IgA nephropathy*
• Bacterial endocarditis	• *HSP*
• Lupus nephritis (ANA, anti-dsDNA)	• Fibrillary GN
• Shunt nephritis	• Visceral abscess

• Idiopathic, MPGN, crescents (after exclusion)
• Cryoglobulinemia (HCV)

2. Anti-GBM mediated GN:
• Good pasture disease • Anti GBM disease

3. Anti-neutrophil cytoplasmic antibody (ANCA) mediated GN:
• Wegener's granulomatosis (WG)
• Renal limited crescentic GN • Microscopic PAN

Pathology: Crescents are present inside bowman capsule.
Clinical features: Acute renal failure, end stage renal failure with in weeks to months associated with nephrotic and/or nephritic syndrome
Diagnosis: Serologic studies: ANA, C3, Anti-DNAase B, ANCA, ASO
• Renal biopsy
Treatment: PIGN: Spontaneous recovery. Excellent prognosis.
• SLE, IgA, HSP: Steroids + cyclophosphamide. Excellent response.
•Other diseases: *Pulse methyprednisolone + cyclophosphamide (particularly in W G*). Less favourable prognosis.
• Plasmapheresis.

Hemolytic uremic syndrome (HUS)

• It is characterized by: Microangiopathic hemolytic anemia, Thrombocytopenia and Acute renal insufficiency.
Types:
1. **Typical** (D+ HUS): Associated with diarrhea prodrome.
• Diarrhea or dysentery illness precedes HUS by 5-10 days. It affects young children < 4 years.
• *Verotoxin (shiga toxin*) producing E. coli (*E. coli 0157: H7*) is responsible in *North America and Europe*.
• *Shigella dysenteriae I* is responsible in *Indian Subcontinent*.

2. **Atypical** (D- HUS): Not associated with antecedent diarrhea.
• It occurs in older children.
• *Bacteria causing it are*: Salmonella, Campylobacter, Streptococcus pneumonia, Bartonella.
• Viruses causing it are: Coxsackie, echo, Influenzae, Varicella, HIV, Epstein-Barr.
• Drugs causing it are: Oral contraceptives, cyclosporine, mitomycin

Pathogenesis: Capillary and arteriolar endothelial injury in kidney → localized clotting → *Intrarenal platelet adhesion or damage* → Thrombocytopenia. Localized clotting also causes mechanical damage to RBC's → *Microangiopathic anemia.*
• Damaged RBC and platelet is removed by liver and spleen → HSM.
LAB INV: Anemia; Peripheral blood film show Fragmented RBC, helmet cells, burr cells; Thrombocytopenia; ↑Urea/creatinine; Leukocytosis; Urine: Microscopic hematuria and proteinuria.

Differential diagnosis: B/L renal vein thrombosis: Also preceded by gastrointestinal disorder associated with dehydration.
• Has pallor, microangiopathic hemolytic anemia, Thrombocytopenia and ARF. But marked renal enlargement and absence of renal vein flow by renal doppler USG favors this diagnosis.

Treatment: Care of fluid and electrolyte balance and nutrition.
• Control of HT. *Early institution of dialysis decreases mortality* (80%→10%). *Plasmapharesis* or FFP may be beneficial.
• *Antibiotics should be avoided* in patients with acute enteritis secondary to E. coli: 0157: H7. May ↑ risk of HUS.
• Silicon dioxide-derived univalent absorbent that binds shiga toxin within intestinal lumen →reduced risk of HUS.

Nephrotic syndrome (NS)

• Its Characteristic features include **1**. *Heavy proteinuria* (> 3.5 gm /24 hrs or > 40 mg/m2/hr in children).
2. *Hypoalbuminemia* (< 2.5gm%) **3**. *Edema* **4**. *Hyperlipidemia*
Etiology:
1. *Idiopathic NS (90%)*: **a**. Minimal change disease (85%)
b. Focal segmental Glomerular sclerosis (10%)
c. Mesangeal proliferation (5%)

2. *Secondary NS (10%*): Related to glomerular diseases:
• Membranous nephropathy • Membranoproliferative GN

Pathophysiology: ↑ Permeability of glomerular capillary wall → Massive proteinuria and Hypoalbuminemia.
Cause of ↑ permeability:
1. In minimal change disease is T-cell dysfunction →*loss of negatively changed glycoproteins* within glomerular capillary wall.
2. In focal segmental glomerulosclerosis is *plasma factor*.

Causes of edema formation: Hypoalbuminemia → ↓ Plasma oncotic pressure →
1. Fluid shifts into the interstitial space.
2. ↓ intravascular volume → Stimulate release of ADH → ↑ Water absorption from collecting duct.
3. ↓ intravascular volume also causes ↓ renal perfusion pressure →
Activation of renin-angiotensin aldosterone system → ↑ Sodium and H2O absorption.

Causes of ↑ Serum lipid levels:
1. Hypoalbuminemia stimulates generalized hepatic protein synthesis, including lipoproteins.
2. Lipid catabolism is ↓ due to urinary loss of lipoprotein lipase.

Clinical features: Age is 2-6 years. Male: Female is 2:1.
• Edema starts from eyes (periorbital edema) and then anasarca.
Diagnosis: Urine analysis: Proteinuria of 3+ or 4 + **or** > 40 mg/m2/hr **or** spot urine protein/creatinine ratio > 2.0.
• Serum Alb < 2.5 gm%. • Serum Cholesterol > 200 mg %
• Normal C3 and C4 levels.
Treatment: Of **Ist episode**: Steroid (60 mg/m2 as TDS) daily × 6 weeks. It is followed by 40 mg/m2 as OD × 6 weeks. Then taper over 3 months.
Relapse: Steroid (60 mg/ m2 as TDS) daily × 2 weeks (extent if no remission). It is followed by alternate day (40 mg/m^2) as OD.
Steroid dependent: Two consecutive relapses on alternate day steroids or within 14 days of discontinuation of steroids.
Steroid resistant: Absence of remission despite therapy with 4 weeks of daily steroids (full dose).
Frequent relapse: 2 or more relapses in 6 months of initial response **or** 4 or more relapses in 12 months of initial response.

These patients (Steroid resistant/ Frequent relapse) and those with steroid facies are candidates of **alternative agents**:
1. Levamisole (2-2. 5 mg/kg/day)
2. Cyclophosphamide (2mg/kg/day)
3. Cyclosporine (5 mg/kg/day). All are given alternate with steroid.
Supportive: Edema control by Salt restriction, diuretics, albumin infusion and infection treatment.

Minimal-change Nephrotic syndrome (MCNS)

Clinical features: Nephrotic Syndrome in 100%.
Hematuria in 10-20%; Hypertension in 10%
• Progression to renal failure does not occur.
Renal pathology: Light microscopy: Normal
Immunofluorescence: Negative
Electron Microscopy: Foot process fusion.
• *Response to steroids is 90%.*

Focal Segmental Sclerosis

Clinical features: Nephrotic Syndrome in 90%.
Hematuria in 60-80%; Hypertension in 20%
Renal pathology: Light microscopy: Focal sclerotic lesions
Immunofluorescence: IgM, C3 in lesions
Electron microscopy: Foot process fusion
• *Response to steroids 15-20%.*
Similar lesion may be seen in:
• HIV infection • Vesicoureteric reflux • 1/V heroin abuse
Indications of kidney biopsy:
• Age < 1 year or > 15 years. • Sustained hypertension.
• Persistent microscopic or gross hematuria (low C3 level, > 2 months as in Acute GN and PSGN).
• Renal failure not attributable to hypovolemia
• *S*uspected secondary cause of Nephrotic syndrome.

Urinary tract infection (UTI)

• **UTI frequency** in < 1 year: M: F is 3-5%; after 1-2 year: M: F is 1:10
• More common in uncircumcised (10-15 times) boys.
• Organisms: E coli, Klebsiella, Proteus
Clinical features:
1. Pyelonephritis (renal parenchyma involvement): Flank pain, fever, nausea, vomiting etc.
2. Cystitis: Dysuria, urgency, frequency, suprapublic pain, incontinence. Excessive crying or straining during micturition.
3. Asymptomatic bacteriuria: No manifestations of infection, positive blood culture, almost exclusively in girls, Benign except in pregnant women.

Pathology: Nearly all are ascending infection. Rarely hematogeuous.
Host risk factors: female, uncircumcised male, *VUR******, toilet training, Voiding dysfunction, obstructive uropathy, urethral instrumentation, Bubble bath, tight clothing, pin worm infestation, Constipation, *P-fimbriated bacteria******, pregnancy, Anatomical abnormality (labial adhesion), neuropathic bladder.
***** Those with risk for clinical pyelonephritis.

Complicated UTI: Child with fever > 38.5°C, Toxicity, Persistent-vomiting dehydration, Renal angle tenderness.

Diagnosis of UTI: Symptoms, Urine R/E and Culture.
> 10 WBC/HPF in uncentrifuged sample.
> 5 WBC/HPF in centrifuged sample.

Sample collection:
1. Mid stream urine collection: Culture growth of > 10^5 colonies/ml of a single pathogen or > 10^4 colonies/ml and symptomatic child.
2. Sterile collection bag: Culture growth > 10^5colonies of single organism and symptomatic child.
3. Supra-pubic (in < 2 years) aspiration: Urinary pathogens of any no
4. Urethral catheterization: Colony count ≥ 50×10^3 /ml

Treatment:
1. for acute cystitis:
• Trimethoprim-sulfamethoxazole • Nitrofurantoin (5-7 mg/kg/24)
• Amoxycillin (50mg/kg/day); all for 5 days.

2. Pyelonephritis: Ceftriaxone • ampicillin + Aminoglycoside
• Pseudominas • Cefixime (oral 3rd gen cephalosporins)
• Ciprofloxacin for persistent micro-organisms; all for 14 days

3. Renal or perirenal Abscess: Surgery or Drainage + antibiotics.
Recurrent UTI: 2 or more UTI

Antibiotic prophylaxis: Is indicated in:
• Reinfection • Neurogenic bladder • Urinary tract stasis
• Urinary tract obstruction • VUR • Calculi
Drugs used once daily: Cotrimoxazole (1- 2 mg/kg/day), Trimethoprim
Nitrofurantoin (1-2 mg/kg/day), Cephalexin (10 mg/kg/kg/day).

Evaluation after treatment:
• Urine culture after 1 week of termination of treatment.
• USG: 2-4 weeks after UTI
• MCU: 4-8 weeks after UTI (In this time is controversial).
• DMSA: 3 months after UTI

Imaging Studies:
1. USG: It is initial investigation.
2. VCUG / MCU: Indicated in:
• All children with UTI < 5 years • Febrile UTI
• School aged girls who had 2 or more UTI (recurrent)
• Any male with UTI
• VUR is found in 40% of patients with UTI.
• Radio nuclide VCUG compare to contrast VCUG (MCU): Has less radiation exposure but does not provide anatomic details like duplex collecting system, Ectopic ureter, Paraureteral diverticulum, Bladder outlet obstruction, and Upper urinary tract stasis.
• Allows precise grading of reflux (more sensitive for detecting VUR). It is good for follow up of VUR.
3. DMSA: This is Technetium labelled DMSA. Presence of photopenia → Pyelonephritis.
• Most sensitive (100) and accurate study for demonstrating renal scar (1/V pyelography has 90%; USG has 50% sensitivity).
• *Cystoscopy is Contraindicated* in UTI.

Acute Hemorrhagic Cystitis

• It is frequently caused by E. coli. Also by Adeno virus type II and 21.

Interstitial cystitis

• It presents with symptoms of UTI, Negative culture.
• Mostly in adolescents girls.
Diagnosis: Cystoscopic observation of mucosal ulcers with bladder distension.

Treatment: Bladder Hydrodistension and Laser ablation of ulcerated areas.

Xanthogranulomatous Pyelonephritis

• Granulomatous inflammation with giant cells and foamy histiocytes.
Clinical features: Renal mass, acute or chromic infection, renal calculi, obstruction, and infection with proteus or E. coli.
Treatment: Total or partial nephrectomy.

Vesicoureteric Reflex (VUR)

• It is retrograde flow of urine from the bladder to the ureter and renal pelvis. It is most common cause of renal scarring.
• Normally ureter is attached to bladder in oblique direction -flap value mechanism.
• It is usually congenital, occurs in families (35% of sibling have VUR), affects 1% of children.
• It may cause renal injury or scarring called *reflex nephropathy*.
• With bladder growth and maturation, there is a tendency for reflex to resolve or improve overtime.
• Mean age of reflux resolution is 6-7 years.

Classifications: Grade I: Reflex into *non-dilated ureter*.
Grade II: Reflex into *upper collecting system without dilatation*.
Grade III: Reflex into *dilated ureter and/or blunting of calyceal fornice*
Grade IV: Reflex into *grossly dilated ureter and blunting of calyceal fornices.*
Grade V: *Significant ureter dilatation and tortuosity and loss of papillary impression.*

Types:
1. Primary: from an anatomic deformity of VU junction, Duplication, ureterocele, malformation of ureterovesical junction etc.
2. Secondary:
a. due to increased intravesical pressure e.g. post urethral valve, Bladder outlet obstruction, neuropathic bladder
b. due to inflammatory processes e.g. cystitis, vesical calculi etc
c. due to surgical procedures involving ureterovesical junction etc.
***** Ureterocele is cystic swelling of the intramural portion of the distal ureter.
Clinical features: Usually discovered during evaluation for UTI (*80% with reflux are female*. Average age of presentation *is 2-3 yrs*.
• Voiding dysfunction • renal insufficiency, HT, Hydronephrosis (Prenatal hydronephrosis: 80% of affected children are males).

Diagnosis: By Contrast MCU/VCUG, Radionuclide VCUG, USG, DMSA.
Treatment: Medical: antibiotic prophylaxis.
Surgery: VCUG/MCU is generally preformed 12-15 months.
• Success rate is 95-98% in primary reflex grade I-IV; for grade V Success rate is 80%.
• Treatment of cause.

• Treatment of VUR depending on grade is as follow:

Grade	Age (yr)	Scaring	Initial treatment	Follow up
I-II	Any	Yes/No	Antibiotic prophylaxis	No consensus
III-IV	0-5	Yes/No	Antibiotic prophylaxis	Surgery
	6-10	Yes/No	U/L: Antibiotic prophylaxis B/L: Surgery	Surgery
V	< 1	Yes/No	Antibiotic prophylaxis	Surgery
	1-5	No	U/L: Antibiotic prophylaxis B/L: Surgery	
	1-5	Yes	Surgery	
	6-10	Yes/No	Surgery	

***** < 1 yr: any grading, with or without scarring → Antibiotic prophylaxis
***** Surgery is for : **1**. Grade III and IV and age 6-10 yrs with B/L VUR.
2. Grade V: age 1-5 yrs and B/L VUR; age 1-5 yrs and Renal scaring; age 6-10 yrs.

Renal Tubular Acidosis (RTA)

• Normal anion gap metabolic acidosis (Hyperchloremic MA).
• Normal anion gap is {Na - (Cl+ HCO_3)} is 8-16. Value < 12 means absence of anion gap (A.G). Value > 20 means presence of AG.

Normal urinary acidification: It occurs in:
1. HCO_3 Absorption in proximal tubules (85% to 90%).
2. Hydrogen ion excretion. in distal tubules.
• In proximal tubules: Secretion of H+ is in exchange of Na^+
• H^+ secretion in distal tubules is mediated by H^+ATPase. There is formation of ammonium (NH_3+H^+→ NH_4) and titrable acids ($Na\ HPO_4 + H^+ \rightarrow Na_2\ H_2\ PO_4$).
Distal (Type I) RTA: There impaired distal tubule H^+ secretion. *Urine PH cannot be < 5.5* (despite severe MA).
• Loss HCO_3 leads to Hyperchloremia and Hypokalemia.
• Hypercalciuria leads to Nephrocalcinosis.
• Bone disease (resulting from mobilization of organic components from bone to serve as buffers) i.e. bone demineralization → Hypercalcimia.
Clinical features: Non anion gap Metabolic acidosis, growth failure, Nephrocalcinosis and hypercalcimia (***** *PO_4 and massive HCO_3 wasting characteristic of Proximal RTA is absent*).

Causes:
1. Primary
2. Secondary: interstitial Nephritis, VUR, pyelonephritis, medullary sponge kidney, Toxins/medications: Amphotericin –B, Lithium etc.
Proximal (Type II) RTA: It is due to impaired proximal tubular bicarbonate reabsorption or as a component of global proximal tubular dysfunction (*Fanconi syndrome*: Proteinuria, Glycosuria, Phosphaturia, Aminoaciduria, Proximal RTA).

Causes:
1. Isolated Proximal RTA.
2. Fanconi syndrome: Cystinosis, lowe syndrome, Galactosemia, Tyrosenemia, fructosemia, Wilsons disease, Dent disease (X-linked nephrolithiasis).

Clinical features: *Growth failure, polyuria, dehydration* (due to Na loss), Vomiting, hypotonia.
• Those with Fanconi syndrome: Rickets (due to PO_4 wasting) and above abnormalities.
• Non anion gap metabolic acidosis, *urine PH acidic < 5.5*.

Hyperkalemic (Type IV) RTA: It is due to impaired aldosterone production (Hypoaldosteronism) Or impaired renal response to aldosterone (pseudo hypoaldosteronism).
(Aldosterone act on H^+ATPase, causes secretion of H^+. Also K^+ secretion in collecting tubules).

Causes:
1. Primary
2. Secondary: Hypoaldosteronism- Addison disease, congenital adrenal hyperplasia; Pseudo Hypoaldosteronism, Interstitial nephritis, obstructive uropathy, Pyelonephritis, Drugs- cyclophosphamide, aminoglycoside, cisplatin etc.

Clinical features: like those of type I and II RTA, Hyperkalemia, Non anion gap metabolic acidosis. Urine ↑Na, ↓K.

Findings	Type I RTA	Type II RTA	Type IV RTA
Urine PH (minimum)	> 5.5	< 5.5	< 5.5
% filtered HCO3 excerted	< 10	> 15	< 10
Serum K	Low	Low	high
Fanconi syndrome	No	Yes	No
Nephrocalcinosis/stones	Yes	No	No
Urine Anion Gap {(Na + K)-Cl}	Positive	Positive	Positive
Daily HCO_3 needs	2-4 meq/kg/day	20 (> 4)	< 4

Treatment: **Type I RTA**: HCO3 replacement: $NaHCO_3$ and Na citrate
• For Nephrocalciuosis: thiazides (↓urine calcium excretion).
• For Bone demineralization: HCO_3
Type II (Proximal) RTA: HCO_3 replacement
• If Fanconi syndrome: PO_4 supplementation.
• For Rickets: HCO_3+ oral PO_4+ Vit D.
Type IV RTA: Treatment of hyperkalemia.

Bartter Syndrome

• It is autosomal recessive disorder with excessive Cl, K and Na wasting in thick ascending limb of loop of Henle. So there will be *Hypochloremic, Hypokalemic metabolic alkalosis with Hypercalciuria*.
• Mutation in Na K 2 Cl transporter (NKCC2), site of action of loop diuretics (furosemide) causes neonatal Bartter syndrome.
• Features *resemble chronic loop diuretic use*.

Types:
1. Neonatal (Antenatal) Bartter syndrome: severe form. There will be *maternal polyhydramnios*, salt wasting, severe dehydration.
2. Classical: Milder form. It presents as failure to thrive, recurrent episodes of dehydration.
Clinical features: above features, failure to thrive, dysmorphic features, *Normal BP, nephrocalcinosis*.
LAB: Hypochloremic, Hypokalemic metabolic alkalosis.
• Increased Urinary calcium, Na and K.
• Increased serum renin, aldosterone and PGE levels.
Histologically: *Juxta Glomerular Apparatus hyperplasia* in kidney.
Treatment: K supplementation (very high doses is required).
• Na supplementation may require.
• Indomethacin, PG inhibitor may also be effective.

Gitelman Syndrome

• It is autosomal recessive disorder. It presents as *Hypokalemic metabolic alkalosis, hypocalciuria and hypomagnesemia.*
• Biochemical features resemble those of *chronic thiazide diuretic use*
• Thiazides acts on NaCl Co-transporter in Distal Convulated Tubules
Treatment: K and Magnesium supplementation.
***** Bartter syndrome: Normal BP, ↓Na, ↓K, metabolic Alkalosis.
***** Liddle's syndrome: ↑ BP, ↑Na, ↓K, metabolic Alkalosis.

Congenital Anomalies

Renal agenesis: Potter syndrome: *B/L renal agenesis, pulmonary hypoplasia, Potter facies* (widely separated eyes, low set ears, receding chin, epicanthic folds, Nose is broad and compressed, limb anomalies). There is history of *maternal oligohydramnios*.
Renal dysplasia, Multicystic kidney: Renal dysplasia is abnormal development of renal parenchyma (primitive structures are present).

• *Multicystic dysplastic kidney is the most common cause* of *abdominal mass in the newborn*. No intervention is usually required.
• These may got infected or cause HT.
• VUR is present in 15% of contralateral kidney.

Obstructive lesions of urinary tract

• Two important causes are Posterior urethral valve (PUV) and pelvic ureteric junction obstruction (PUJ).
Posterior urethral valve: *Most common cause of severe obstructive uropathy* is children.
• Valves leaflets fans distally to external urinary spincter.
• VUR occurs in 50% of Patients. Maternal USG: *oligohydramnios.*
Clinical features: Weak urinary stream, dribbling,
• Bladder is distended, palpable, show diverticuli and trabeculations.
Diagnosis: VCUG
Treatment: Transurethral ablation of leaflets or Temporary vesicostomy →Ablation of leatlets →Closer of vesicostomy.
PUJ obstruction: This is the most common obstructive lesion in childhood. USG shows hydronephrosis without a dilated ureter.

Causes:
1. Intrinsic stenosis
2. Accessory Artery to the lower pole of the kidney.
Clinical features: Maternal USG shows fetal hydronephrosis.
• Palpable renal mass in newborn or infancy (asymptomatic).
• As abdominal, flank or back pain. • As a febrile UTI.
• As hematuria after minimal trauma. • 60% occur on left side.
Investigation: USG, MAG-3/ DPA.
Treatment: Pyeloplasty. Precutaneous nephrotomy tube placement.

ENDOCRINOLOGY

Diabetes Mellitus: Clinical triad: *polyuria, polydipsia, and polyphagia.*

Types: **1**. **Type I:** This is most common endocrine metabolic disorder of childhood. There is β-cell destruction (immune mediated autoimmune destruction) in Genetic susceptible individual. It is acute onset. Median age of onset is 7-15 yrs (<30 yrs).
Autoantibodies: Islet cell cytoplasmic antibodies (ICA), Insulin auto antibodies (IAA), Antibodies to glutamic acid decarboxylase (GADA).
• It has HLA association with DR_3 and DR_4.
• Diabetic ketoacidosis is frequent.

2. **Type II (NIDDM):** Insulin resistance is present at skeletal muscle, Liver and Adipose tissue with varying degree of β-cell impairment.

• It occurs in obese, onset > 30 yrs, insidious in onset.
***** *Acanthosis nigricans* (dark pigmentation of skin creases/flexural area) is a sign of insulin resistance.
• Family history of diabetes mellitus indicates maturity onset (MODM).
• *Glucose tolerance test (GTT)*: 1.75 gm/kg glucose (maxi-75 gm)

	Normal	Impaired GTT	Diabetes mellitus (DM)
Fasting	< 110	110-125	≥ 126
Post prandal (2 hrs)	< 140	140-200	≥ 200

• Commonest cause of juvenile onset of Diabetes mellitus is *fibrocalcific pancreatiopathy.*

Growth Hormone Deficiencies

• *Height is < 3rd percentile* for the age (short stature).
• Appear normal at birth. *Height velocity is < 4 cm/yr*.
• *Bone age< chronological age*.
• *Delayed teeth development*. Delay in sexual development.
• Hypoplastic penis and scrotum.

Diagnosis: Standard provocation test with: Administration of insulin, arginine, glucogon, L-dopa and clonidine.
• Peak level of GH < 10 ug/L (ng/ml) on two procative tests indicates Growth from deficiency.
• Low IGF-1 and IGF BP-3 levels for age.
***** *Laron syndrome* is GH insensitivity. It has ↑ GH, ↓IGF-1 levels.
Treatment: Recombinant GH 0.07-0.1 IU/kg/day as subcutaneous (*GH is also used in CRF and Turner syndrome*).

Diabetes Insipidus (DI)

• It presents as Polyuria, polydipsia.
Types:
1. Neurogenic (central): Causes: Genetic and Acquired.
Neoplasm: Craniopharyngioma, histiocytosis, optic glioma, TBM, encephalitis meningitis, Cong. Malformation, intracranial bleed etc
• Trauma, Infiltrative disease like histiocytosis.
2. Nephrogenic: Causes: **a**. Genetic
b. Acquired: Hypercalemia, hypokalemia. Drugs: Lithium, demeclocycline, foscarnet, clozapine, ampho-B, rifampicin, methicillin
Kidney diseases: CRF, polycytic disease, medullary cystic disease.
3. Psychogenic
***** *Wolfram syndrome or DIDMOD syndrome: Diabetes insipidus*, *Diabetes mellitus*, *Optic atrophy* and *Deafness.*

Diagnosis: Polyuria/polydipsia (i.e. exceeding 2Litre/m2/24 hr)
• Serum osmolality > 300 mosm/kg, ↑Na, ↑K.
• Urine osmolality < 300 mosm/kg and ↓ specific gravity.
***** Diagnosis is unlikely if Serum osmolality < 270 mosm/kg or
Urine osmolality > 600 mosm/kg.
***** If Serum osmolality 270-300 mosm/kg with signs and symptoms: Do water Deprivation test for 6 hrs and check Urine osmolality:

1. Urine osmolality < 300 and Urine specific gravity < 1.005 → DI
2. Urine osmolality = 300-800 → Partial DI
3. Urine osmolality > 800 and Urine specific gravity > 1.015 → DI is ruled out.
***** Psychogenic polydipsia: ↓Serum osmolality and ↓Na.
Treatment: Neurogenic DI: 5-10 ug Desmopressin (analog of ADH) daily as nasal spray.
• Oral Desmopressin (DDAVP): 0.15-0.5ug/kg
Nephrogenic DI: Elimination of cause

• Hydrochlorothiazide: 0.5-1.5 mg/kg/day (it reduces urinary volume as paradoxical effect).
Psychogenic polydipsia: Psychotherapy (↓Serum osmolality, ↓Na)

Hypothyroidism

Types:
1. Central (hypopituitarism)
2. Primary hypothyroidism:
• Defect of thyroid development (dysganesis)- 85%
• Defect in thyroid hormone Synthesis (10%): Thyroid oxidase defect, iodide transport defect, Thyroid peroxide defect, Thyroglobulin synthesis defect, Deiodination defect.
• Iodine deficiency (endemic goiter)
• Maternal antibodies: Thyrotropin receptor-blocking antibodies.
• Maternal drugs: Anti thyroid drugs e.g. propylthiouracil etc.

Clinical features: Mostly asymptomatic at birth (normal birth weight and length). *Prolonged Jaundice* (delayed maturation of glucuronide conjugation), Feeding difficulties, lack of interest, choking spells. Respiratory difficulties: *large tongue*, noisy respiration, nasal obstruction. *Constipation, umbilical hernia*, large abdomen, Subnormal temperature. Skin: cold and molted, dry, scaly. Edema of genitals and extremities, *hypotonic (floppy*). Slow pulse rate, *cardiomeagaly*, asymptomatic pericardial effusion. *Anemia (macro cytic)-often refractory to hematinics*. Retardation of physical and mental growth. *Open and wide fontanel, delayed dentition*, delayed bone maturation. *Short stature*, delayed sexual maturation. *Beaking of the 12th thoracic or 1st or 2nd lumbar vertebra*.

Neonatal screening: Age specific values are important.
It can be done on cord blood sample. But ideal is on D2-D4 of life. It is to be retest to confirm diagnosis. For screening: do *T4 level, if* ↓ then do TSH level. If *TSH level is* ↑, it indicates Hypothyroidism.
Treatment: Na-L- thyroxine: In neonates: 10-15 ug/kg/day.
In children: 4-8 ug/kg/day; in Adolescent: 2-4 ug/kg/day
Side effects of thyroxine: Craniosynostosis, Pseudotumour cerebri.
Endemic Goiter and cretinism: It is due to iodine deficiency.

Clinical features: depends on severity of iodine deficiency: goiter + hypothyroidism features. It can presents as two syndromes:
1. Neurologic syndrome: as mental retardation, deaf, mutism, *disturbances in standing and gait*. Pyramidal signs (e. g. clonus), Babinski sign, Patellar hyper reflexia, normal Pubertal development and adult stature.
2. Myxedematous syndrome: as mental retardation and deaf and have neurologic symptoms, and Delayed sexual development and growth, Myxedema and abscene of goiter, Delayed skeletal maturation.
Treatment: Iodine supplementation.

Congenital adrenal hyperplasia (CAH)

• It is autosomal recessive disorders with ↑ ACTH (due to cortisol deficiency) and overproduction of intermediate metabolites.
• *90% all caused by 21-hydroxylase deficiencies*
• Primary adrenal insufficiency can be Congenital or acquired.
• Acquired is called *Addison disease*.
• Most common cause of adrenocortical insufficiency in infants is *21 hydroxylase deficiency (75%)*. Other causes are Lipoid adrenal hyperplasia, 3β-hydroxysteroid dehydrogenase deficiency.
• All above present as salt-losing symptoms (Not able to synthesis either cortisol or aldosterone).

1. **21-OH deficiency**: Classic form presents with *salt wasting crisis*, Female pseudohermaphroditism, postnatal virilization, severe *vomiting, and dehydration*.
LAB: ↑ ACTH and ↑ 17OH progesterone.↑ Serum androgen and urinary metabolites.
Treatment: Glucocorticoid: Hydrocortisone 10-20 mg/m2/24hr indefinitely for classic 21-hydroxylase deficiency).

• Mineralocorticoid: fludrocortisone 0.1-0.3mg daily. • NaCl
• Vaginoplasty and clitoral recession in female pseudohermaphroditism.
Non classic form: Presents as Precocious pubarche, disordered puberty, menstrual irregularity, hirsutism.
LAB: same as for class form.
Treatment: glucocorticoids.

2. 11 β- Hydroxylase deficiency:
Classic form: female pseudohermaphroditism, Postnatal virilization in males and females, *hypertension*
LAB: ↑ ACTH and ↑ Doc (deoxycortisol), ↑ Serum androgens, ↓ K.
Treatment: Glucocorticoids, plastic surgery of gonads.
Non classic form: same as non classic form of 21-OH deficiency.
LAB: same as classic form.
Treatment: Glucocorticoids.

3. 3β-HSD deficiency: Presents as salt wasting crisis, Male and female pseudohermaphroditism, Precoccious pubarche, Disordered puberty.
LAB: ↑ ACTH, pregnenolone, DHEA (dehydroepiandrosterone).
Treatment: Glucocorticoids, Mineralocorticoids, NaCl, Surgery

4. Lipoid congenital adrenal Hyperplasia: Salt wasting, male pseudohermaphroditism.
LAB: ↓ level of all steroid hormones, ↑ ACTH.
Treatment: as above in 3.

5. 17α OH deficiency: Male pseudohermaphroditism, Sexual infantilism, *Hypertension*.
LAB: ↑ Doc, ↑corticosterone, ↑ ACTH and ↓K.
Treatment: Glucocorticoids and surgery.
• HT is present in 11-β hydroxylase and 17-α OH deficiency.
• *Male pseudohermaphroditism* is seen in: Lipoid congenital adrenal hyperplasia and 17 OH deficiency.
• *Female pseudohermaphroditism* is seen in: 21OH deficiency (*most common cause*) and 11-β OH deficiency.
• *Both Male and female* pseudohermaphroditism is seen in: 3 β HSD deficiency.
• Most common cause of male pseudohermaphroditism is *AIS* (*Androgen insensitivity syndrome*).

Newborn screening:
• 21-OH deficiencies is often undiagnosed in affected males until they have severe adrenal deficiency
• ↑ *17-hydroxy progesterone level* (heal-stick sample, on filter paper). • Same paper can also be used for screening hypothyrodism and phenylketonuria)
Prenatal diagnosis: Chorionic Villous Sampling and Amniocentesis.
Treatment: Recommendations for pregnancy at risk: administration of dexamethasone (steroid readily crosses the placenta) 20 ug/kg or oral dexamethasone 1 mg daily.
• This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. *If started by 6 week of gestation*, this ameliorates the virilization of the external genitalia in the affected female.

Cryptorchidism

• Cryptorchidism is seen is 3-4% of full term infants.
• It is seen in 30% of premature male infants. By 1 yr of age it is present in 0.5-1%. It is B/L in 10% of cases.
Descent of testis is regulated by: hormonal and mechanical factors: Testosterone, dihydrotestosterone, MIF (Mullerian-inhibiting factor), Gubernaculum, Intra abdominal pressure, Genito femoral nerve.
• Leydig cells produce testosterone, which stimulates differentiation of the wolffian (mesonephric) duct into epididymis, vas deferens, seminal vesicle and ejaculatory duct.
• Pathologic changes in testis can be demonstrated at 6-12 months.
• Risk of malignancy is 4-10 times higher.

• Peak age of tumor is 15-45 years; Most common seminoma (65%).
• Orchiopexy does not change the risk of developing malignancy.
Complications: Infertility, malignancy, injury, associated hernia, torsion etc.
Treatment: Orchiopexy should be done at 9-15 months.
• If testis is non-palpable, go for diagnostic laparoscopy.
• Hormonal treatment is used infrequently: HCG (human chorionic gonadotropins, LHRH analog (Buserelin).

Hyperparathyroidism

• Primary hyperparathyroidism in children is almost always due to single benign adenoma.
• Secondary hyperparathyroidism is due to decrease serum calcium e.g. Rickets, Malabsorption, chronic renal failure (CRF).
•Teritiary hyperparathyroidism: Parathyroids continue to be hyperactive even after the removal of the primary cause.
Clinical features: Muscular weakness, Calcium may be deposited in the renal parenchyma leading is *nephrocalcinosis*.
• Bone changes: pain, deformity, Short stature, fracture.
• Anorexia, irritability, lethargy, Constipation, polyuria, polydipsia.
• As part of *MEN-I*: It includes *Hyperparathyroidism, Hyperpituitarism*
Hyperplasia of pancreas
• As part of *MEN-II A*: It includes *Hyperparathyroidism, medullary thyroid carcinoma and pheochromocytoma*.
Diagnosis: S. Calcium > 12 mg%, S. phosphate level low (3 mg% or low), decrease S. magnesium.
• ↑ Serum Alkaline phosphatase (with skeletal involvement).
• ↑S. PTH (parathyroid hormone and calcitonin level is normal.
X-ray shows: *Resorption of subperiosteal bone* (phalanges)
• Skull: trabeculation and granular appearance
• Generalized rarefaction leading to fracture, cysts, and tumors.
• Rickets in 10% of cases.
Treatment: surgical exploration in all cases.

Cushing's syndrome

Cushing disease: indicates B/L adrenal hyperplasia secondary to excessive pituitary ACTH, often from a basophilic pituitary adenoma leading to increased cortisol and glucocorticoids.
• *Microadenoma* is present in about 80% cases.
Cushing syndrome: Can be by ectopic production of ACTH or Exogenous administration of glucocorticoids (most common cause).
Clinical features: Characteristics obesity, moon shaped facies (Round face, prominent cheek, Flushed appearance)
• Buffalo hump, thin extremities, purplish striae, HT (Hypertension), hyperglycemia, Hypertrichosis, growth impairment.
Diagnosis: Diurnal rhythm is abolished (Normally Cortisol levels ↑ at 8 am and ↓ to < 50% by midnight). Increased Cortisol level.
• Urinary free cortisol and 17-OH steroids are all elevated.
• Adrenal androgens are normal (DHEA, and DHEAS).
• Abnormal GTT (glucose tolerance test) despite elevated levels of insulin.

Dexamethasone suppression test: single dose 25-30 ug/kg given at 11 pm, this results in a plasma cortisol level < 5 ug% at 8 Am in individuals. It is not seen in Cushing syndrome.
Large doses of dexamethasone suppress cortisol level in pituitary adenoma/ pituitary Cushing syndrome, But not in patients with ACTH independent Cushing syndrome (i.e ectopic ACTH secreting tumors).
Treatment: Trans-sphenoidal pituitary microsurgery
• Adrenalectomy.

CENTRAL NERVOUS SYSTEM

• Partial seizures are most common in seizure in childhood (60%).

Febrile Convulsions

• Commonest cause of seizures during early childhood.
• Age of presentation is 6 months-5 years, incidence is 3-4%, and recurrence rate is 30-40%.
• It is not related to the degree of temperature rise.

Types:
1. Simple/Typical: Occurs with in 24 hrs onset of fever.
• lasts < 10 min • usually single per febrile episode
• generalized tonic clinic seizure • No post-ictal neurological deficit
• EEG few days later is normal • Family H/O febrile seizures
2. Complex/Atypical: lasts > 15 minutes, focal seizures activity or focal findings are present.

Factors that ↑ risk of febrile episodes and subsequent Epilepsy: • Family H/o epilepsy • Female sex • Neurodevelopmental delay
• Atypical episodes • Initial seizure < 9 month of age.
Diagnosis: It is clinical.
• No role of EEG and neuroimaging in febrile seizure.

Indications of Lumber Puncture:
1. 1st episode of febrile seizure
2. Infants < 1 year of age
3. Presence of meningeal signs

Treatment: Antipyletics: PCM 10-15mg/kg/dose
• *Diazepam*: 0.2-0.3 mg/kg/dose. Alternative is phenobarbitone
Prophylaxis:
1. Intermittent: It is for 3 days
• Diagram or Benzodiazepines: can be given as 1/V, rectal or oral
Other drugs effective are midazalam and clonazam.
2. Continuous: Indications are
a. Failure of intermittent therapy **b**. recurrent atypical seizure **c**. Family H/o epilepsy **d**. Parental concern.
• Drugs used are Na valproate (10-20 mg/kg/day) and Phenobartitone (3-5 mg/kg/day).
• Given for1-2 years or till 5 year of age.
• Phenytoin and carbamazipine are ineffective for prophylaxis.
• Future Risk of epilepsy *if no risk factors are present* is 1-2%.
• Future Risk of epilepsy *if risk factors are present* is 9%.
• Drug prophylaxis may not reduce the subsequent risk of developing epilepsy but reduces risk of subsequent partial complex seizures.

Absence attacks/ Petit mal seizures

• Peak age is 6-8 years (uncommon < 5 years). Common in females.
Typical attack: Is not preceded by an aura.
• Brief abrupt lapse of awareness or consciousness
• Sudden discontinuation of the activity being performed with staring spells, Eye fluttering, Rhythmic movements etc. Last < 30 sec
• No loss of posture, (or tone but head may fall slightly) or bladder/bowel involvement. *No post-ictal drowsiness and confusion*.
• Seizure is precipitated by *Hyperventilation for 3 minutes*.
• May occur in multiple episode/day.
EEG has characteristic 3/sec spike and slow wave pattern and shorter duration of about 10 sec (< 30 sec).

Different from Complex partial seizure by:
1. Absence of aura.
2. Shorter duration (10 sec).
3. Abrupt return of full consciousness.
Treatment: *Ethosuximde in drug of choice*. Others are clonazepam, Na valproate, pamotrigine.

Treatment of choice for seizures

• Partial tonic-clonic or generalized seizures: Carbamazepine
• Complex partial seizure: Carbamazepine
• Myoclonic and akinetic: ACTH
• In West's syndrome: Prednisolone.
• Tuberous sclerosis (infantile spasms): Vigabatrin or valproic acid.
• During Ist year of life: Phenoparbitone

Juvenile myoclonic epilepsy (JANZ syndrome)

• Begins at age 12-16 years.
• Patients have frequent myoclonic jerks on awakening, making hair combing and tooth brushing difficult. Few years later, early morning generalized tonic-clonic seizures develop.
• EEG shows 4-6/sec irregular spike and wave pattern, which is enhanced by photic stimulation.
• Neurological exam is normal.
Treatment: *Valproate is given for life long*. The majority *respond dramatically* to valproate. Discontinuation of the drug causes a *high rate of recurrence* of seizures.

Acute bacterial meningitis

• It is usually hematogenous spread.
Causes: **In neonatal period**: Gm-ve infections. Streptococcus pneumoniae (Gr B Streptococcus: *Streptococcus Agalactiae* and Gr D Streptococcus: Entercocci and non enterococci), E coli, Salmonella, Pseudomonas, Staphylococcus.
3 months to 2-3yrs: Hemophilus influenzae, Streptococcus pneumoniae, Meningococci (N. meningitides), Staphylococcus.
> 3 year to 5 yrs: Streptococcus pneumoniae, Neisseria meningitides.
• Those with immune defect or anatomic defect: Pseudomonas, Staphylococcus, Coagulase negative Staphylococcus, Fungal infection.
Clinical features: As acute febrile illness, Headache, vomiting, bulging fontanel, Seizure etc.
• Brisk DTR, B/L plantar ↑, neck rigidity, Kernig's sign (extension of knee < 135°) positive, Brudzinski sign (on neck flexion, knee get flexed) positive , are present.

Gr.B Streptococcus (GBS) or streptococcus agalactiae meningitis: β hemolytic organism. *Most common cause in neonates*.
• Causes Neonatal sepsis, meningitis, Puerperal infection, UTI.
Treatment: Penicillin.
Meningococcal meningitis: Common serotype is A. Presents as:
• *Petechial hemorrhages on skin or mucosa*.
• May present as adrenal insufficiency, shock, coma called *waterhouse freiderichsen syndrome* (due to adrenal glands hemorrhage and Necrosis).
Treatment: Penicillin or cephalosporin.

Hemophilus influenzae type B: Present at 3-12 months of age.
• Subdural effusion is common.
• I.V. dexamethasone 6 hrly × 2 days, in treatment of children > 6 weeks, reduces auditory nerve damage (give 1-2 hr before antibiotic).
Treatment: Most strains are susceptible to Ampicillin or amoxycillin.
• 1/3rd produce β-lactamase, in these cases chloramphenicol is effective. *If there is resistant to chloramphenicol*, give 3rd generation cephalosporins or quinolones.

Tubercular Meningitis (TBM)

• It is common between 6-24 months.
• Meningeal surface is covered with yellow grayish exudates and tubercles: Most severe at base, Temporal lobes and along the course of middle cerebral Artery.
• Usually presents as Communicating hydrocephalus, Infarction, hemorrhage in CNS.
Clinical features: There stages:
1. Prodromal stage: In this there is decrease Sleep, Irritability, photophobia, Vomiting, headache.
2. Stage of meningitis: Sign's of meningitis, Seizures, neurological defect are present.
3. Stage of coma: Loss of consciousness, opthalmoplagia, irregular breathing, Posturing (decerebrate/decorticate).
Diagnosis: CSF examination: Cells: 100-500/mm3. In early stage Polymorphonuclear cells, later is replaced by *lymphocytes.*
• Raised CSF pressure. Protein is raised very high. Sugar is low or normal. Staining and culture may show AFB.
• If spinal block is present, *Xanthochromia* will be present. On standing CSF, *cobweb coagulum* is formed.

CT scan: Will show basal exudates, communicating hydrocephalous
Infarction, and Inflammatory granulomas.
Sequelae: Mental retardation, seizures, Motor/cranial nerve deficits, optic atrophy, hydrocephalus.
Treatment: HRZE + steroid.
HRZE: Isoniazid, Rifampicin, Pyrazinamide, Ethambutol.

Brain tumors

• It is 2nd most common group of neoplasm in children after leukemia.
• 2/3rd of brain tumors are *infratentorial*. 1/2 to 1/3rd are medulloblastoma and 1/3rd are astrocytomas of cerebellum.
• Common supratentorial tumors are Astrocytomas, Ependymomas and Craniopharyngioma.
• Ataxia telengiectasia and neurocutaneous syndrome are associated with higher incidence of brain tumors.
0-1 year: Supratentorial tumors are common (Choroid plexus complex and teratomas).
1-10 years: Infratentorial tumors are common (Juvenile pilocytic astrocytoma and medulloblastoma).
> 10 years: Supratentorial tumors (diffuse astrocytomas).
• Infratentorial or midline tumors presents with *classical triad* of headache, vomiting and papilledema. Disorder and gait, equilibrium and coordination. Blurred vision, diplopic and nystagmus.
• Supratentorial tumors presents with focal disorder.
• Brain stem region tumor presents with Cranial Nerve palsies, Gage palsy, and upper motor neuron defect e.g. hemiparesis.

1. **Medulloblastoma**: It is midline cerebellar tumor, fast growing, malignant.
Clinical features: Truncal ataxia, papilledema, broad base gait, raised intracranial pressure, 4th ventricular obstruction, hydrocephalus
Treatment: Surgery is cornerstone of treatment.

2. **Astrocytomas**: It is most common pediatric brain tumor (40%).
Types: a. Low grade astrocytomas: Juvenile pilocytic astrocytoma.
b. Malignant: Anaplastic astrocytoma (grade III) and Glioblastoma multiforme (grade IV).
• These are common in cerebellar hemisphere.
Clinical features: Ataxia, incoordination, more on side of lesion. Areflexia, hypotonia etc.
Treatment: Surgery, Chemotherapy, Radiation.

3. **Brain stem tumors**: Signs and symptoms of raised intracranial pressure are minimal. Hemiparesis, cranial nerve palsies and personality changes are common.
• Brain stem glioma *carry worst prognosis*.

4. **Craniopharyngioma**: It arises from squamous epithelial cell rests of the *embryonic Rathke's pouch*.
Clinical features: Growth failure, *Bitemporal hemianopsia*, *visual field defects*, signs and symptoms of raised intracranial pressure.
• Diabetes insipidus and delayed puberty.
X ray: May show calcification.
Treatment: Surgery, radiotherapy

5. **Meningioma**: It is derived from mesoderm, is usually benign and attached to the duramater. Most often occur along the sagittal sinus.
Clinical features: Focal seizure, slowly progressive neurologic deficit or symptoms of raised intracranial pressure.
CT/MRI: *Dural-based, extraaxial mass* with dense, uniform contrast enhancement is diagnostic.
• May have *"dural tail",* a streak of dural enhancement flanking the main tumor mass.

Hereditary syndromes associated with brain tumors

• Neurofibromatosis type I (Von Reckling hausen's disease) and Neurofibromatosis type II.
• Tuberous sclerosis: Astrocytoma

• Von hippel-Lindau syndrome: Hemangioblastoma of retina, cerebellum and spinal cord.
• Li-fraumeni syndrome: Malignant glioma.
• Retinoblastoma: Pineoblastoma, malignant glioma.
• Turcot syndrome: Medulloblastoma, malignant glioma.
• Gorlin syndrome: Medulloblastoma, malignant glioma.
• Multiple endocrine neoplasia I (Werner syndrome): Pituitary adenoma.

Hydrocephalous

• CSF is secreted by choroids plexus with in ventricles.
Pathway: lateral ventricles → 3rd ventricle → 4th ventricle → Basal cisterns →Cerebral and spinal subarachnoid spaces.
• CSF is absorbed via arachnoid villi.
Types:
1. Communicating
2. Non-communicating (obstructive): Block is at any level in the ventricular system e.g. aqueduct, foramina of luschka and megendie
Causes: Intrauterine infection, bacterial infection (meningitis), Intracranial bleed, Intraventricular hemorrhage, Congenital malformation, malignancy, TBM, aneurysm etc.
Treatment: Carbonic anhydrase inhibitor (acetazolamide)
• Shunt surgery: Most commonly Ventriculo-peritonial.
• Treatment of cause.

Pseudo tumor cerebri (Benign intracranial hypertension)

• It is benign self-limiting disorder with generally a favourable outcome. Intracranial pressure is elevated. Papilledema is present.
• Ventricular system in normal.
• *No vision loss.* Visual field shows enlargement of blind spot.
• More common in young, female and in obese.
Causes: Drugs: Outdated tetracyclines, Hypervitaminosis A, Quinolones. • Lateral sinus thrombosis • Super vena cava syndrome
• Withdrawal of corticosteroid therapy • Addison's disease
• Hypoparathyroidism • SLE
CT/MRI: Normal.
Treatment: Carbonic anhydrase inhibitors (Acetazolamide).

Neural tube defects (NTD)

• Due to failure of closure of neural tube at 3-4 weeks of gestation.
• **It involves**: Spina bifida occulta, dermal sinus, meningocele, myelomeningocele, encephalocele, anencephaly, tethered cord, syringomyelia, diastematomyelia and lipoma involving the conus medullaris.
• Most common site is lumbosacral region.
• Myelomeningocele in the most severe form of dysraphism.

Etiology: Multifactorial: Genetic predisposition, Nutritional folic acid deficiency, Environmental factors e.g. radiation exposure
Risk factors: Radiation, Drugs, Malnutrition, Chemicals, Genetic determinants (mutation in folate responsive or folate dependent pathway).
• Drugs: That antagonise folic acid: Trimethoprim, Anti epileptic drugs (Carbamazine, phenytoin, Phenobarbitone, primidone, Valproic acid),
Pyrimethamine, methotrexate, pentamidine.
Clinical features: Myelomeningocele: At sacral region: Bladder and bowel incontinence, Perianal anesthesia. No motor impairment.

Mid lumbar: Bladder and bowel incontinence. Lower motor neuron signs: Flaccid paralysis of lower limb, Sensory loss, absent DTR.
Lower thoracic: Increasing neurologic deficit.
Upper thoracic and cervical: very minimal neurologic deficit.
• Hydrocephalus is associated with type II Chiari defect (develops in 80% of patients with myelomeningocele).
Diagnosis: In antenatal period: Excretion of fetal substances *α-feto protein* and *acetylcholinesterase* into amniotic fluid (biochemical markers of Neural tube defects).
• Amniocentesis is done at 16-18 weeks.
• Maternal serum α-feto protein increases in NTD.
Prevention: Prevented by folic acid.
Dose: For primary prevention 0.4 mg/day.
• For secondary prevention 4 mg/day.
• Given in *periconceptional period*: 1 month prior to 3 months after conception.
• 75% of NTD are folic acid preventable.
Risk of recurrence: 5% if Ist baby is affected.
• 10% if 2nd baby is also affected.

Treatment: Surgery:
a. if child has no neurological deficit and CSF leak is present immediate surgery is to be done.
b. If intact sac/skin can delay surgery.
c. Child with neurological deficit, gross hydrocephalus, gross congenital Malformations, parents counseling is needed.

Landau Guillain Barre Syndrome (LGBS)

• In this autoimmune process to *protein component of myelin* causes demyelization. There is history of preceding viral infection 2-3 weeks prior to illness in2/3rd cases.
• It may follow viral infections: Infection mononucleosis (EBV), Mumps, Measles, Echo, Coxsackie, Influenza etc.
• Can follow rabies infection, neural vaccine of rabies, Campylobacter infection.
Clinical features: Symmetrical, ascending weakness, absent/ decreased reflexes. Predominantly motor involvement.
• More marked in proximal muscle groups, hypotonia.
• Cranial nerve involvement, most common is facial nerve.
• Autonomic nervous system (bladder/bowel) involvement is late.
Diagnosis: CSF examination: *Albumino-cytological dissociation* (increased protein but normal cell number).
Treatment: IV Immunoglobulin: Response is best if given within 3-4 days of illness. • Plasmaparesis • Physiotherapy.

Acute flaccid paralysis (AFP)

• It is acute onset (< 4 weeks) flaccid paralysis in < 15 years of age.
• When no obvious cause found e.g. trauma, injection etc.
• **AFP surveillance**: It is carried out for all AFP cases.
Efficacy: for good efficacy at least 1 case of non-polio AFP for every 1, 00,000 population in < 15 years per year.
• 2 stool specimens should be sent with in 14 days of paralysis.
• Follow up is done for 60 days.
• 2 adequate stored sample (adequate volume: 8-10 gm or thumb size) at least 24 hrs apart should be sent.
• Samples are to transported with in 72 hrs of collection at 4-8° c or frozen at –20°C (as reverse cold chain).

Ataxia telengiectasia

• It is autosomal recessive disorder.

• Progressive cerebellar ataxia is seen at 1-3 yr of age. And later telangiectasia is observed over conjunctiva (first on bulbar conjunctiva) and skin by 2-7 yrs of age.
• Serum IgA, IgG, IgE levels are usually reduced (AGE ↓). Impaired cellular immunity, frequent sino-pulmonary infections, and increase chances of lympho-reticular malignancies, Defect in DNA repair (excessive chromosomal breakage).
• Elevated of α-feto protein levels.
• Increased incidence of abnormal movements (choreoathetosis), vitiligo and abnormal GTT is observed.

Cerebral palsy

• It is Non-progressive encephalopathy and is due to multiple risk factors, prematurely and small birth weight is important risk factors. There is predominantly motor development delay.
• Most common form is spastic quadriplegia.
• There is Persistent of neonatal reflexes.

Mental retardation (MR)

• It is sub average general intelligence. Prevalence is 1-3%.
• It can be: Mild: IQ of 51-70. They are educable.
Mod: IQ of 36-50. They are trainable.
Severe: IQ of 21-35. They are custodian.
Profound: IQ of ≤ 20. They are custodian.
Borderline: 71-90
***** Intelligence quotient (IQ) = Mental age/ Chronological age × 100
Etiology: It includes prenatal factors (hypothyroidism etc), Natal (birth asphyxia etc), Post natal factors (vitamin deficiency, infection etc).
Recurrence: For Down syndrome (discussed earlier).
• Risk of MR for other siblings is 50% for autosomal dominant conditions, 25% of autosomal recessive conditions and < 5% of idiopathic MR.

NEUROMUSCULAR DISORDER
DUCHENNE MUSCULAR DYSTROPHY (DMD)

• It is genetically determined, *progressive*, severe muscle wasting, primary disorders of muscle. It is *X-linked recessive* disorder.
• Gene responsible for DMD and BMD is on short arm of the X chromosome. 60% have deletion of one or more axons.
• *Dystrophin*, cytoskeletal protein is a part of dystrophin-glycoprotein complex that span the muscle *sarcolemma*. This is expressed in *skeletal muscle, Smooth muscle, Brain, Peripheral N and several other tissues.*

Clinical features: Perinatal history is normal.
• It manifest in 2nd year with clumsy walking or fall on walking, wadding gait, positive family history.
• *Pseudohypertrophy* of calf muscles at *4-5 years*. It is also seen in glutei, deltoid, serrati anterior, Brachio-radialis and tongue muscles.

• Contractures develop at the ankles and hips.
• Wheel chair dependency by 12 years of age.
• *Death is by pulmonary insufficiency* by 20 years of age.
• *Gower's sign positive.* 1/3rd have IQ < 75.
• Cardiac involvement is after 10 years. They may have Cardiomyopathy- fibrosis, Cardiac failure, cardiac arrhythmia.
• Intestinal pseudo-obstruction is also seen.

Becker muscular dystrophy (BMD): less severe form than DMD.
• Majority of patients survive 4-5th decades.
• Ambulate beyond age of 15 years.

Diagnosis: In ANP period: By Chorionic villous biopsy.
In childhood: Increased serum Creatine Phosphokinase (CPK) level, usually in thousands (15,000-20,000 U/L).
• EMG is rarely necessary. It shows ↓ AMP and duration of major unit potential and ↑ frequency of polyphasic potentials.
Histology: Muscle fibers shows-*diffuse changes of degeneration and regeneration.* Muscle in replaced by fat and degenerative changes.
Treatment: Encourage ambulation.
• Cardiorespiratory care: treatment of infection, treatment of CCF and Respiratory exercises.
• Supportive care: Braces, wheel chair etc.
• Drugs: Prednisolone. Deflazacort: it is synthetic derivative of prednsolone.

Myotonic dystrophy

• It is autosomal dominant disorder. It has Multi organ involvement.

Clinical features: facial wasting and hypotonia.
• Myotonia is very slow relaxation of muscle after contraction.
• *Hatchet-faced appearance*: Inverted v-shaped upper lip, thin cheeks, scalloped, concave temporalis muscle, High arched palate.
• Muscles are wasted and atrophied. Other features are:
Cataract, **D**iabetes, **E**sophageal and colonic motility is decreased, **F**rontal baldness, **G**onadal atrophy, **H**ypersomnia, **I**ntellectual impairment.
• *More of distal muscle involvement*: thenar, hypothenar, Interossei.
(*This is exception to the general ruling that: myopathies having proximal* and neuropathies having distal distribution patterns)
Diagnosis: EMG: will show myotonia evidence. CPK is normal.
• CTG trinucleotide repeats sequence.

Myasthenia gravis

Types:
1. Neonatal transient Myasthenia gravis:
• It is due to maternal transfer of antibodies against acetylcholine receptor.
Clinical features: Hypotonia, weak suck, cry, ptosis, generalized weakness, decreased movement, and respiratory distress.
• Usually it resolves in 4 weeks to few months.
• Reflexes are preserved.
2. Juvenile Myasthenia gravis: Childhood onset, Autoimmune. Present as ocular or Generalised adult Myasthenia gravis.
***** Edrophonium (Tensilon test): 0.2 mg/kg is given to look response.
***** EMG: Repetitive stimulation show decremental response.
Treatment: Transient form is self resolving.

• Severe causes: Oral *pyridostigmine* is given. If can't swallow then can be administered I/M. Alternative is *neostigmine*.
• Immuno-suppressive therapy: steroids
• Others therapy include Plasmapheresis and I/V Immunoglobulins for refractory cases. In older children thymectomy can be done.

Floppy infant

• Infant with marked hypotonic of all muscle: Decreased movements, Unusual posture- *frog legged*, Excessive range of joint mobility.

Causes

1. CNS: Birth asphyxia, neonatal encephalopathy, Cerebral palsy, Intraventricular hemorrhage, kernicterus, Down syndrome, inborn error of metabolism (Mucopolysaccharidosis, Cerebral lipidosis, Aminociduria) etc.
2. Spinal cord: Poliomyelitis (anterior horn cell disease), SMA (*Werdnig Hoffman disease*).
3. Peripheral nerves: Acute polyneuropathy, congenital sensory neuropathy.
4. Neuromuscular Junction: Myasthenia gravis, Botulism.
5. Muscles: Muscular dystrophies (DMD, BMD), Congenital myotonic dystrophies, Congenital Myopathies (central core disease, nemaline myopathy), Polymyositis, Glycogen storage Disease (2, 5, 7)-*Pompe's disease*.
6. Others: *Hypothyroidism*, Protein energy malnutrition, Rickets, *Prader-Willi syndrome*, Malabsorption syndrome, Ehler Danlos syndrome.

Spinal muscular atrophy (SMA)

• It is autosomal recessive disorder but can be inherited as, X-Linked or sporadic. Degeneration of motor neurons occurs in the spinal cord and brain stems nucleic. This is *important cause of floppy infant*.
• There is loss of anterior horn cells (*unregulated apoptosis*). Genes implicated are *SMN (survival motor neuron*) and *NAIP (neuronal apoptosis inhibitory protein)* on chromosome 5. These genes arrest apoptosis.
Clinical features: In Antenatal period: ↓ *fetal movements* and hydramnios.
• After birth: *Generalized symmetrical weakness* (hypotonic), poor feeding, poor cry but *child is Alert and intelligence is normal*.
• *Tongue fasciculation, DTR absent, Delayed motor mile stones*.
• History of affected siblings in the family may be present.
Investigation: CPK is normal, On EMG: Fasciculation.
Muscle biopsy: Neurogenic type of atrophy.
Types: **Type I:** Werdnig-Hoffman disease. Present with in six months. Child can never able to sit. Die by 2 yrs of age.
Type II: Present in 1st year of life (late infantile form). Child can sit but walking is not achieved.
Type III (Juvenile form): Present later in life, walking is present.
Treatment: No effective treatment. Rehabitilation.

HEMATOLOGY ANEMIA

• WHO define anemia as HB < 11 gm % at 6 months-6 years.
• HB < 12 gm % at 6-12 years and < 13 gm% adult males.
• Normal MCV is 86-98 µm³ in adults and 80-95 µm³ in children. *Microcytosis* is MCV < 80 µm³ and *Macrocytosis* is MCV > 100 µm³.
• Normal MCH is 28-32 pg/cell in adults and 24-34 in children.
• Normal MCHC is 32-36 % Hb /cell in adults and children.

Hematopoiesis

• There are three anatomic stages of hematopoiesis:
1. Mesoblastic hematopoiesis: Begins in extraembryonic structures *(yolk sac)* by 10-14 days of gestation. By 10-12 weeks of gestation extraembryonic hematopoiesis is ceased.
2. *Liver* (6 weeks to continue till birth) replaces yolk sac by 6-8 week of gestation. In liver hematopoiesis occurs throughout gestation.

***** Hepatic production decreases during second trimester and inactive soon after birth.
3. *Bone marrow* hematopoiesis (starts at 12 weeks) increases in second trimester. At birth, Bone marrow through out the skeleton is hematopoietically active till puberty.
***** By 18 years only vertebrae, ribs, sternum, skull, pelvis and proximal epiphyseal regions of the humerus and femur retain red marrow hematopoietically active.
***** Extramedullary hematopoiesis can reappear in liver, spleen and lymph node e.g. in hemolytic anemia and so hepatosplenomegaly.

Hemoglobulins

Fetal HB (Hb F): Fetal Hb is α2 γ2. It is resistance to denaturation by strong alkali (basis of *Kleihauer-betke test* for detecting fetal RBC in maternal circulation).
• After 8 weeks of gestation: Hb F predominates. *Before Hb F, embryonic Hb -Gover-1, Gover-2 and Portland Hb predominates*.
• At 24 weeks of gestation it is 90% of total Hb. In 3rd trimester it gradually declines. At birth it is 70% of total Hb.
• Post natally it decreases rapidly and at 6-12 months traces is presents (< 2.0% of total Hb).
Adult Hb (Hb A): Adult Hb is α2 β2. It is detectable as early as in Embryo. *Amniocentesis at 16-20 weeks, prenatal diagnosis of β- thalassemia major is possible.*
• At 24 weeks of gestation it is 5-10% total Hb. At birth it is 30%.
• At 6-12 months normal Hb pattern appears.
***** *Switch to Adult Hb begins at 16-20 weeks* and nearly exclusive synthesis of Hb A occurs at 38 weeks.
Hb A2: It is α2 δ2. It is minor component of Hb A.
• At birth it is < 1%. At 12 months it is 2.0-3.4% (normal).
• Ratio of Hb A/ Hb A2 is 30%.

Iron deficiency anemia

• It is most common cause of nutritional anemia.
• Ferrous salt is better absorbed than ferric salt. Substances that inhibit iron absorption are: Phosphates, phytates, Calcium salts, milk and eggs, Tannic acid in tea and coffee.
• Substances that enhance iron absorption are: Lactose, ascorbic acid, fruit juices, Amino acids-cystine, lysine and histidine, gastric acid.
• Iron is absorbed from *duodenum* and upper jejunum.
• In Gut mucosa: ferrous + Apoferritin → ferritin.
• In plasma: Iron + transferrin.
• Serum ferritin is best indicator of iron status. Serum ferritin < 10ng/ml is indicative of iron deficiency.
Clinical features: Pallor, failure to thrive, frequent infection, mild splenomegaly, tongue papillae are atrophied, ↓ activity and attention span.
• Koilonychia: Spoon shaped and concave.

Diagnosis: Serum Ferritin < 10 ng/ml.
• Serum Iron < 30 µg% (normal is 50-150).
• Total iron binding capacity (TIBC) > 350 µg% (normal is 250-350).
• Saturation of transferrin < 15% (normal is 25-50%).

Treatment:
1. Treatment of cause.
2. Deworming of patient.
3. Diet rich in iron.
4. Oral iron therapy: Dose of elemental iron is 3-6 mg/kg/day. (Rise in Hb will be 0.4gm% per day).
Elemental iron content:
• Anhydrous ferrous sulphate: 37%
• Ferrous fumarate: 33%
• Ferrous gluconate: 12%

***** Iron therapy is to be continued for at least 6-8 weeks after the Hb has reached normal level to repleting iron stores.
Sequence of improvement:
12 to 24 hrs: Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite.
36 to 48 hrs: Initial bone marrow response; erythroid hyperplasia.
48 to 72 hrs: Reticulocytosis; peaking at 5-7 days.
4 to 30 days: Increased in Hb level.
1 to 3 months: Repletion of stores.
5. Blood transfusion: If Hb < 4 gm%. If in child in CCF, do partial exchange transfusion.

Megaloblastic anemia

Risk factors: Exclusively breast feed by anemic or malnourished mother with vitamin B12 deficiency, Delayed weaning.
• Chronic diarrhea, malabsorption or recurrent infections.
• Drugs: All drugs which antagonize folic acid.
Clinical features: Pale, sick, irritable, Failure to thrive.
• Increased pigmentation in the back of hands, fingers (knuckle hyperpigmentation) and nose.
• Tremors and developmental regression: Infantile tremor syndrome.
LAB: Macrocytic, normochromic anemia, Polymorphonuclear leukocytes-*enlarged and hyper segmented*.
Bone marrow: Erythroid hyperplasia.
Treatment: Vitamin B12 100 µg/week× 8 weeks. FA 1-5 mg/day.

Aplastic Anemia

Types:
1. Congenital: Fanconi's anemia.
2. Acquired: Dyskeratosis congenita, Shwachman-Diamond syndrome, Amegakaryocytic thrombocytopenia.
Other syndromes: Down syndrome, Dubowitz syndrome.
Fanconi's Anemia: It is autosomal recessive disorder.
• Physical abnormalities include: *Hand and arm anomalies* (absent/hypoplastic thumb), Hyperpigmentation, café-au-lait spots, Short stature, Genitourinary tract anomalies.
• Facial features include Micropthalmia, depressed and wide nasal bridge, epicanthic folds, micrognathia.
• *Leukemia in12%*, liver disease in 4%, Cancers in 5%.
• *Chromosomal breaks increase with clastogens* (occur in most pts).
• *Increase in Hb F*.
Diagnosis: Characteristic skeletal and cutaneous abnormalities with short stature should suggest diagnosis of congenital pancytopenia.
Treatment: Steroids, Androgens-oxymethalone, nandrolone and bone marrow transplantation.
Prenatal diagnosis: It is by chromosomal breaks, noted in most pts.
Dyskeratosis congenita: It can be XL, AR, and AD disorder.
Clinical features: It includes Physical abnormalities, ↑ Hb F, ↑ Chances of leukemia and cancers.
• Bleomycin sensitive, Chromosomal breaks only in 10% patients.
Treatment: Androgen and bone marrow transplantation.

Thalassemia

• Thalassemia is reduced hemoglobin synthesis (ineffective erythropoiesis). There is Hemolysis, hypochromic anemia.
• In *α-thalassemia*, synthesis of α chains is suppressed therefore all three Hb (HbA, HbA2 and HbF) is reduced.
• In *β thalassemia*, synthesis of β chains is suppressed. There is ↓ HbA, very high HbF and HbA2 is normal.
• In *Delta beta thalassemia*, there is suppression of both β and δ chains synthesis. HbF is ↑.
• In *β thalassemia trait,* elevated HA2, variable elevation of HbF.

• β thalassemia gene is β thal, are on *short arm of chromosome 11*.
• In *Hereditary persistence of fetal Hb*, Hb F is 100% (Homozygotes).
• α thalassemia with 4 gene deletion is *hydrops fetalis*. Newborn will have 90% Bart's with Gower 1 and 2 and portland Hb.
(Excess of γ chains in fetal life γ4 called Bart's Hb. after birth excess of β chains leads to Hb H ie 4 β chains).

NESTROF (naked eye single tube red cell osmotic fragility) test: • This is simple and cheap screening test to detect carriers of β thalassemia. Antenatal women should be screened with this test in high risk group.
• 2 ml each of freshly prepared (0.36%) buffered saline and distilled water (control) are taken in two test tubes → Add 20 µl of maternal blood to each tube → Well mix and keep for 5 minutes→ note hemolysis in both tubes by holding them against black.
→ If hemolysis is present, black line can be seen → so normal person. → if hemolysis is not present, then black line cannot be seen→ so thalassemia trait. *Thalassemia trait Individuals will resist hemolysis.*
β-thalassemia: Synthesis of β chains is suppressed and there is excess of α chains so produces and α tetramers. These get precipitated in RBC leading to hemolysis with in bone marrow.
• Severity depends on type of mutation affecting the β chain synthesis, Presence of α chain mutation, effect on gamma chain synthesis and presence of other hemoglobinopathies.
• Increased erythropoiesis, which is ineffective →expansion of the medullary cavity of various bones.
• Extramedullary hematopoiesis →Hepatosplenomegaly.
• Increased hemolysis →hemosiderosis (iron deposition in various organs).

Clinical features: Born normally then *progressive anemia* during infancy. *Not responding to iron*. Hepatosplenomegaly, *Hemolytic facies*, Growth retardation.
Diagnosis*: Hb electrophoresis*: ↓ HbA, ↑ HbF and ↑ or normal HbA2.
• ↓ RBC counts, ↓Hb, ↓ MCV, MCH or MCHC.
• ↑ Reticulocytes, *hypochromic-microcytic anemia*
• Bone marrow is hypercellular with erythroid hyperplasia with increased stippled erythroblasts and sideroblasts.
• *Osmotic fragility is decreased*.
X-rays: small bones have rectangular appearance. There can be rarefaction, fractures. *Skull has hair on end appearance.*
α-thalassemia: The deletion of 1 α globulin gene produce *silent trait.*
• The deletion of 2 α globulin gene results in *α thalassemia trait*.
• The deletion of 3 α globulin gene results in *Hb H disease*.
• The deletion of 4 α globulin gene results in *Bart Hb*.
• Bart Hb results in *Hydrops fetalis* (*severe form γ4 chains*). *Bart Hb has high oxygen affinity and therefore hydropic infant have very little useful Hb.*

Treatment of thalassemia:
1. **Blood transfusion** (keep Hb 10-12 gm %). Child should be vaccinated with Hepatitis B vaccine before starting transfusion.
2. **Chelation therapy**:
a. Desferrioxamine: Parenteral form, given as subcutaneous infusion (25-50 mg/kg/day). Start by 10-15th transfusion. Serum ferritin level is kept 1,000-2000 ng/ml.
Side effects: Growth retardation, visual and auditory toxicity.
b. Deferiprone (kelfer): 75-100 mg/kg/day. It is oral chelating agent.
Side affects: *Arthropathy (most common*), Agranulocytosis.
c. Pyridoxine hydrazine.
d. Deferrothiocine.
3. **Splenectomy**: Should be delayed beyond 6 yrs. Child should be immunized for pneumococcal, H. influenzae and Meningococcal vaccine. Life long penicillin prophylaxis is needed.

Immune/ Idiopathic thrombocytopenic purpura (ITP)

• There is increased destruction of antibody coated platelets by reticuloendothelial system in the spleen.
• Antiplatelet antibodies are usually of *IgG class.*

Pathophysiology: Antibody coated or immune complex bound platelets are formed →FC portion of the antibody binds with Fc receptor of the reticuloendothelial cell → Phagocytosis of the platelets.

• Spleen is major site of destruction.

Classification:	Acute ITP	Chronic ITP
Duration:	4-6 weeks	> 6 months
Onset:	Acute	Insidious
Peak age:	2-6 yrs	Adolescence
Sex:	None	F: M is 3:1
Antecedent Infection (viral):	Common	Unusual
Hemorrhagic bullae (mucosal):	Common in severe causes	Rare
Eosinophilia/lymphocytosis:	Common	Rare
Associated immunological Abnormalities:	None	20%
Spontaneous remission:	80%	Uncommon

***** Children with SLE, Rheumatoid arthritis and collagen disease are at higher risk of having chronic ITP.

Clinical features: *Petechiae, purpurae, ecchymoses, mucosal bleed*,

• Malena, Hematemesis and joint bleeding is unusual.
• Anemia is proportional to degree of bleeding.
• Spleen is *not palpable or just tip is palpable* (5-15%).

LAB: Isolated thrombocytopenia (< 1 lakh), Capillary fragility test (Tourniquet test) is positive. Mean platelet volume is increased.

• Bleeding time is prolonged. PT and PTTK are normal.
• Bone marrow show *increased megakaryocytes*.

Treatment: treat patient, not the platelet count.

1. Supportive care: Bed rest, avoid NSAIDS, Platelet transfusion is of no use but may be given in life threatening situations or prior to surgery.
2. Corticosteroids: Prednisolone for 2-3 weeks, then taper over next 1-2 weeks. I/V methylprednisolone.
3. I/V immunoglobulin: Acts by blocking Fc receptor and protect the platelet from antibodies.
4. Anti-Rh (D) therapy: Acts by blockage of Fc receptor by the antibody coated RBC in place of antibody coated platelet
5. Splenectomy: In chronic ITP, uncontrolled bleeding, or those not responding to steroids or 1V Ig therapy.

Factor XIII deficiency

• Factor XIII is responsible for the cross linking of fibrin or stabilization of fibrin clot. There is an increased solubility of clot because of the failure of cross linking. t 1/2 of factor XIII is 5-7 days.

Clinical features: Mild bruising, Poor wound healing. In woman it causes recurrent spontaneous absorptions.

• Symptoms of delayed hemorrhage are secondary to instability of the clot (have history of trauma one day prior to bleeding).
• There may be delayed separation of umbilical stump (> 4 week).

Investigations: *Usual screening tests for hemostasis are normal* (BT, PT and PTTK).

• Normally clot remains insoluble in the presence of 5 M urea but in factor XIII deficiency, clot formed dissolves (*clot solubility test).*

Treatment: Fresh frozen plasma/cryoprecipitate.

RESPIRATORY SYSTEM PNEUMONIA

Etiology:

Viral: RSV, influenza, para-influenza or adenovirus. These are the predominant cause of lower tract respiratory tract infection (LRTI) in infants and children younger than 5 yrs.

Bacterial: In < 2 months: gm + ve organisms are pneumococcal and staphylococcal. Gm-ve organisms are klebsiella, E. coli.
3 months-3years: Pneumococcal, H. influenzae, Staphylococcus
> 3 years: Pneumococcal, Staphylococcus
Atypical pneumonia is caused by Chlamydia, Mycoplasma.
In Immunocompromised: pneumocystis carinii.
In cystic fibrosis: Pseudomonas.

Pneumococal pneumonia: Thick rusty sputum, lobar consolidation. Treatment is penicillin.

Staphylococcal pneumonia: may be a complication of measles, influenza and cystic fibrosis.
• There can be pneumatoceles, pneumothorax, and empyema. May have pyodermas, purulent pericarditis etc.
• Pneumatoceles are also seen in klebsiella pneumonia. Risk factors: Malnutrition, Diabetes mellitus, Macrophage dysfunction.
• Treatment is penicillin, cloxacillin. For empyema/pneumothorax → intercostals tube drainage.
H. influenzae pneumonia: Mimicks acute bronchiolitis. Treatment is ampicillin.

Acute bronchiolitis

• Age of presentation is 2months- 1year (till 2 years).
• *Most common cause is respiratory syncytial virus (RSV*). Others are para-influenza virus, Influenza and Adeno virus.
• High secretary Ig A antibodies to RSV are present in colostrums. So breast feeding decreases acute bronchiolitis.
• It presents as first wheezing episode with respiratory distress, Hypoxemia. Lungs are hyper inflated.
• It occurs in winter and spring. It is Self-limiting illness of 3-7 days.

Treatment: Humidified oxygen, IV fluids,
• Epinephrine / bronchodilator.
• Ribavirin: In infants with underlying congenital heart disease, chronic lung disease and immunodeficiency.
• Plavizumab: Monoclonal antibodies may be given.

Bronchial asthma

Clinical features: Poor respiratory efforts, Cyanosis, silent chest,
Altered sensorium, PEFR < 30% of predicted, Spo2 < 90%.

Treatment: O2, S/C terbutaline or adrenaline, B2 agonist, anticholinergics, 1/v hydrocortisone, MgSo4 or Aminophylline drip and Ventilation depending on severity.

GENERAL PEDIATRICS

Cheery red spot

It is seen in:
• Central retinal artery occlusion (not vein).Berlin's edema (trauma).
• Taysach's disease, Sandhoff's disease (GM1 and GM2 Gangliosidoses).
• Niemann-pick disease, Sialidosis I and II.

Intraosseous Cannulation

• The medullary cavity of marrow is composed of a spongy network of venous sinusoids. It functions as rigid vein. Do not collapse in presence of hypovolumia.
• Done in < 6 yrs of age. After 6-8 yrs red mallow is replaced by yellow marrow, which is less vascular.
Site: Proximal tibia is optimal site, 1-3 cm below the tibia tuberosity, in the middle of antero-medial surface of tibia.

• Alternate sites are distal femur and tibia.
Entry into marrow space is confirmed by:
• Aspiration of marrow • Needle standing up right with out support.
• Sudden decrease in resistance • Ease with which fluid can be given.

Lead poisoning

• Usual sources of exposure leading to toxicity are lead from paints, from wall either directly (PICA) or indirectly by ingestion of lead-contaminated house dust, food and water stored in load containers.
Acute toxicity: Abdominal colic, constipation, fatigue, Anemia, peripheral neuropathy, seizure, coma, renal failure.
Subclinical toxicity: Anemia, Slowed nerve conduction, foot drop etc. There is altered excretion of uric acid.
• Harmful effects start at 10 μg% (serum level)
• Chronic poisoning is called *Plumbism***.**
• Facial pallor is one of the earliest and most consistent sign.
• Lead line, called *Burtonian line* is seen on gums in 50-70% cases.
• In RBC: Basophilic stippling or punctate basophilia.
***** Three organ systems are mainly affected:
1. CNS: Central and peripheral **2**. Erythrocytes **3**. Renal.
Treatment: Removal of source of lead exposure.
• Chelation therapy:
1. **BAL** as 1/M use every 4 hrly.
2. **EDTA** as 1/V infusion (renal excretion) or I/M.
3. **d-penicillamine**: Oral chelating agent, *Used only when unacceptable reactions have occurred* with BAL or EDTA.
• Supportive therapy: Gastric lavage, whole bowel irrigation.

Kerosene poisoning

• Incidence is 30-60%
• *Commonest poisoning in pediatrics* (Most Common Hydrocarbon poisoning)
Clinical Features:
• Respiratory: Chemical pneumonitis →Breathlessness, Cough, fever, cyanosis, hypoxia
• CNS: Seizures, coma
• GIT: Vomiting, nausea, pain abdomen, diarrhea
Treatment: No role of antibiotics and steroids.
• No emesis, no gastric lavage (***** these are contraindicated)
•Supportive therapy: O2, ventilation care, B2 agonists for bronchospasm.
• Detoxification: All source of kerosene must be removed from patient contact.