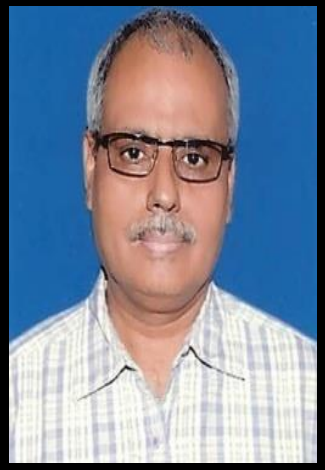
NEONATAL JAUNDICE



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Objectives

- Definition of neonatal jaundice
- Metabolism of bilirubin
- Physiological v/s Pathological jaundice
- Causes of neonatal jaundice
- Approach to neonatal jaundice
- Management of neonatal jaundice
- Dangers of Hyperbilirubinemia

Neonatal hyperbilirubinemia

Jaundice is the yellowish discolororation of skin and sclera caused by deposition of bilirubin(total bilirubin >95th percentile on the hour specific Bhutani nomogram).

Visible when total serum bilirubin

Adult > 2mg /dl ,

Newborn > 5 to 7 mg /dl

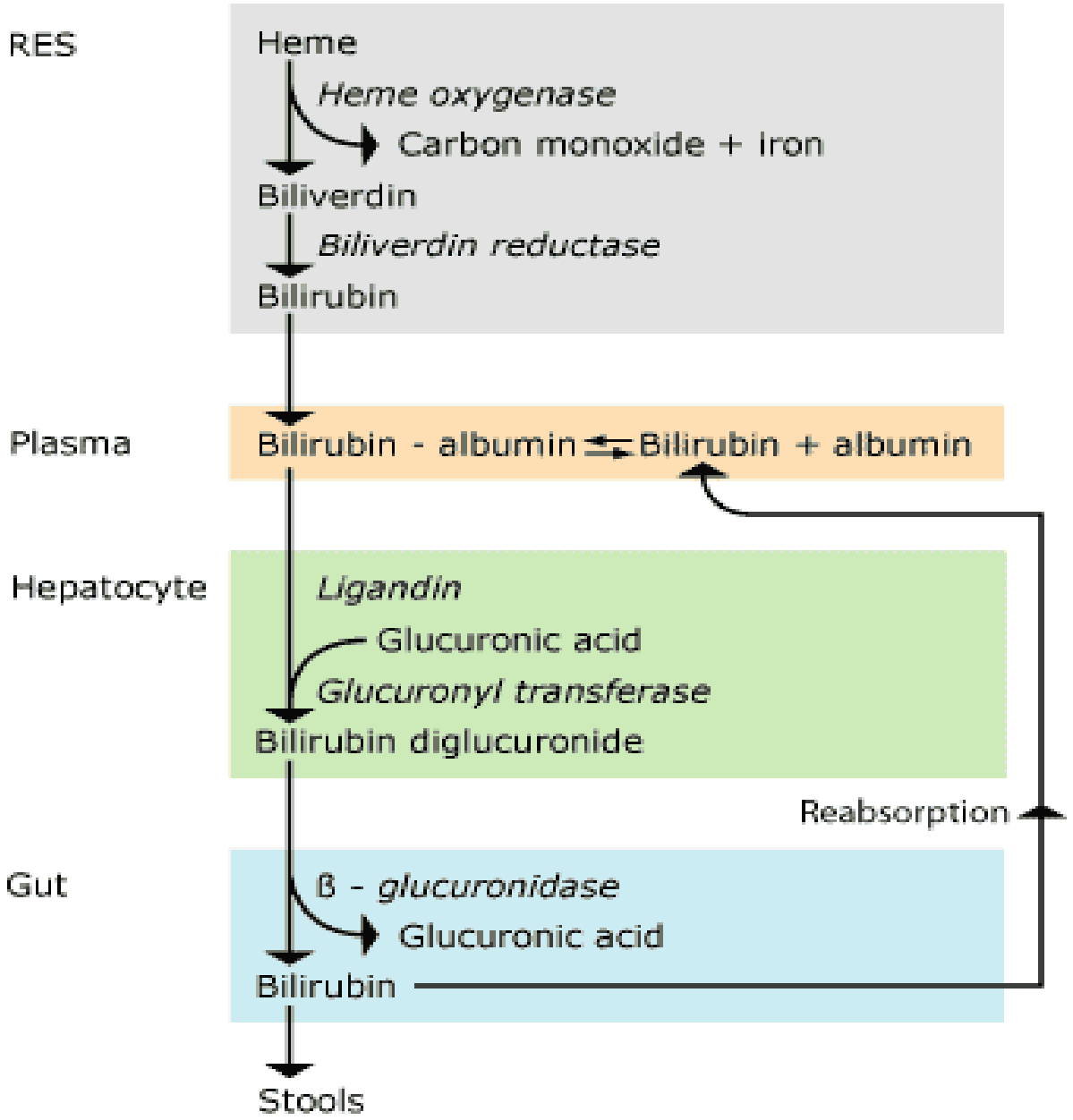
Incidence of Neonatal jaundice

Term : Occurs in 60% of term neonates.

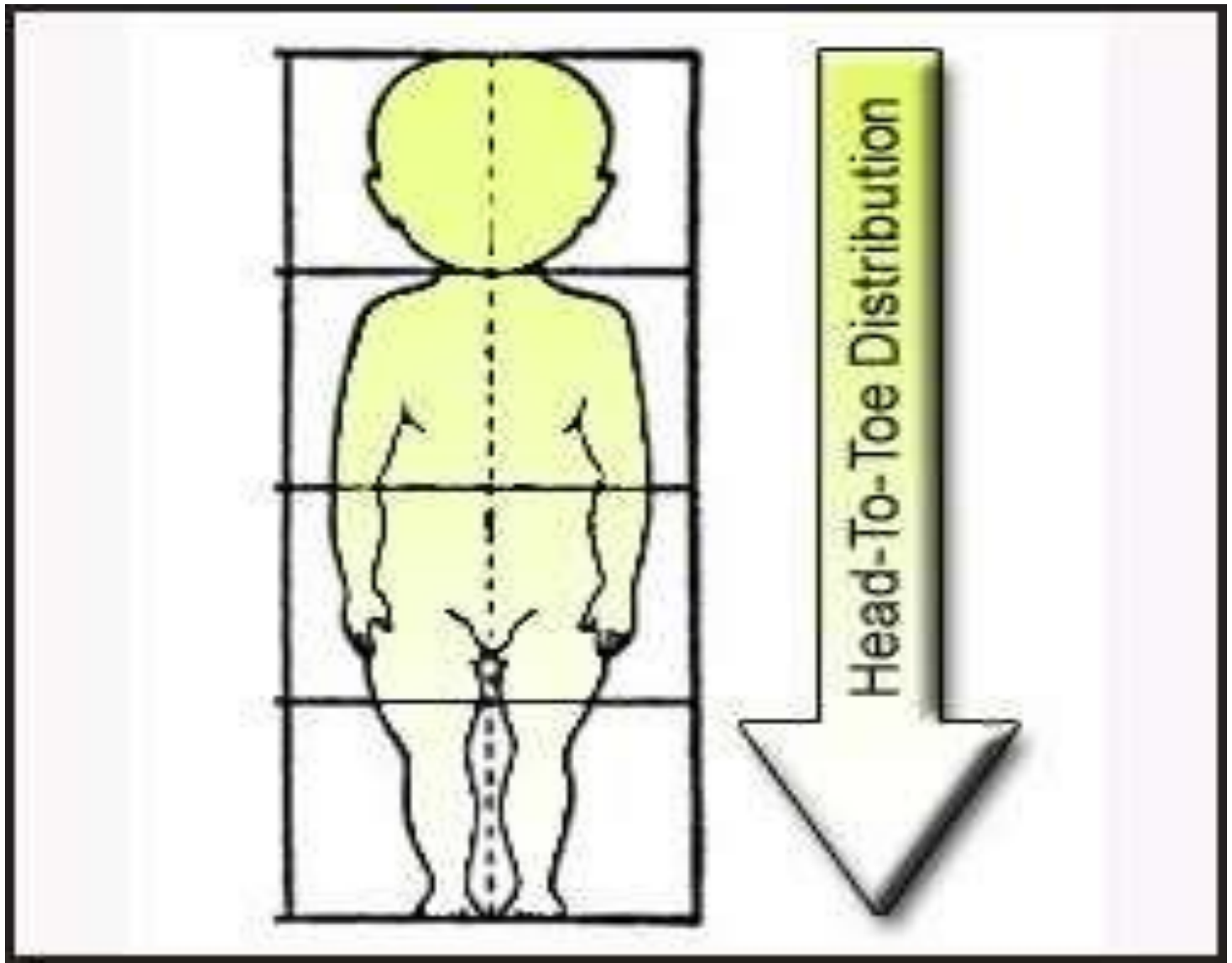
Preterm : 80% of preterm neonates.

Jaundice is the most common condition that requires medical attention in newborn.

BILIRUBIN METABOLISM

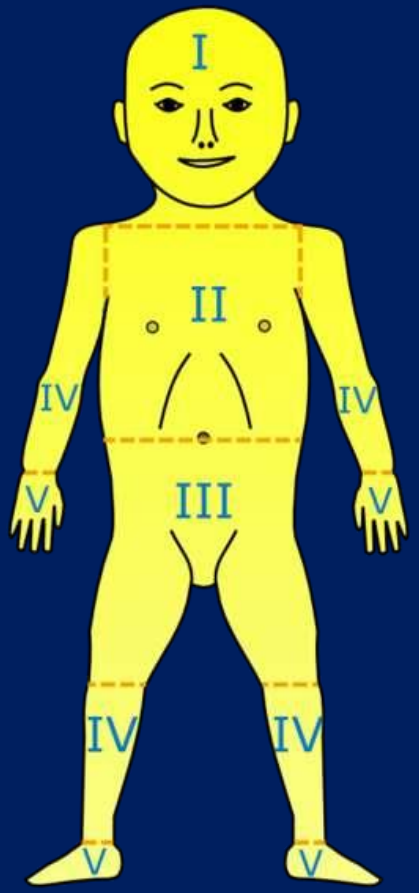


CEPHALOCAUDAL PROGRESSION



Clinical assessment of jaundice (KRAMER'S RULE)

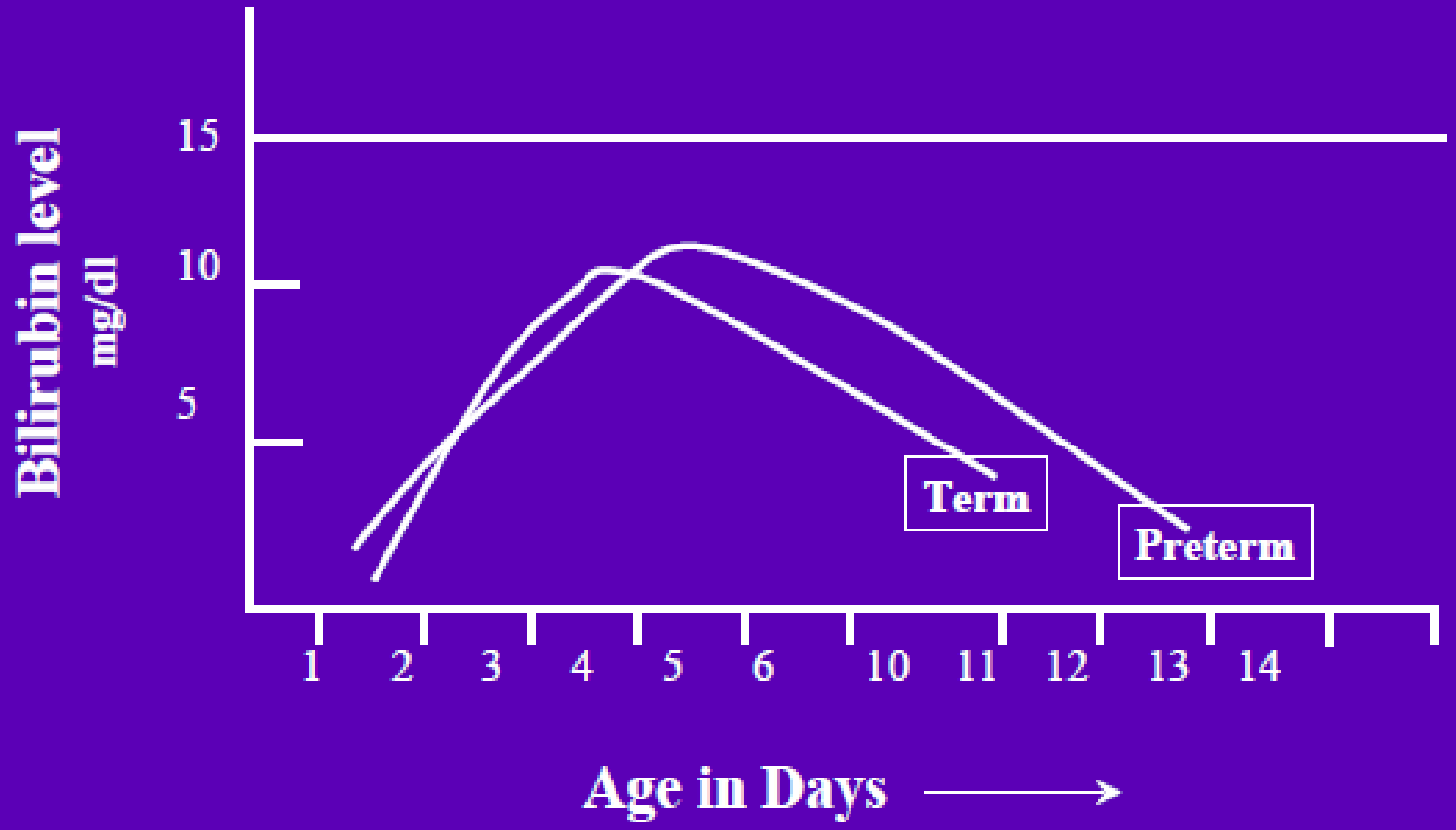
Area of body	Bilirubin levels(mg/dl)
• Face and neck	4-6
• Upper trunk	6-8
• Lower trunk & thighs	8-12
• Arms and lower legs	12-14
• Palms & soles	> 15



Physiological Jaundice

- Appears between 24 to 72 hours of age.
- Total bilirubin rises by less than 5 mg/dl per day.
- Maximum intensity by 4^{th} -5^{th} day in term & 5^{th}- 6^{th} day in preterm.
- Serum level is less than 15 mg / dl.
- Clinically not detectable after 14 days.

Course of physiological jaundice



WHY DOES PHYSIOLOGICAL JAUNDICE DEVELOPS?

1. Increased bilirubin production-decreased RBC survival(90 days), increased RBC vol /kg and polycythemia of newborn.

2. Poor hepatic uptake due to decreased ligandin or Y-protein.

3. Poor conjugation due to enzyme deficiency-
   UGT1A1 activity.

4. Increased enterohepatic circulation due to
    - High level of intestinal beta-glucoronidase
    - delayed colonization by bacteria
    -Decreased gut motility

5.Decreased hepatic excretion of bilirubin

Pathological jaundice

1. Visible jaundice within 24 hours of age.
2. Increase of bilirubin > 5 mg / dl / day or 0.2 mg/dl/hr or >95th centile as per age specific nomogram.
3. Presence of jaundice on arms and legs on day 2.
4. Yellow palms and soles anytime.
5. Clinical Jaundice persisting after 2 weeks in term and 3 weeks in preterm
6. Direct bilirubin > 2 mg / dl at any time
7. Signs of acute bilirubin encephalopathy or Kernicterus.

Etiology Of Jaundice

CAUSES OF JAUNDICE ON THE BASIS OF AGE OF ONSET -

within 24 hours of age

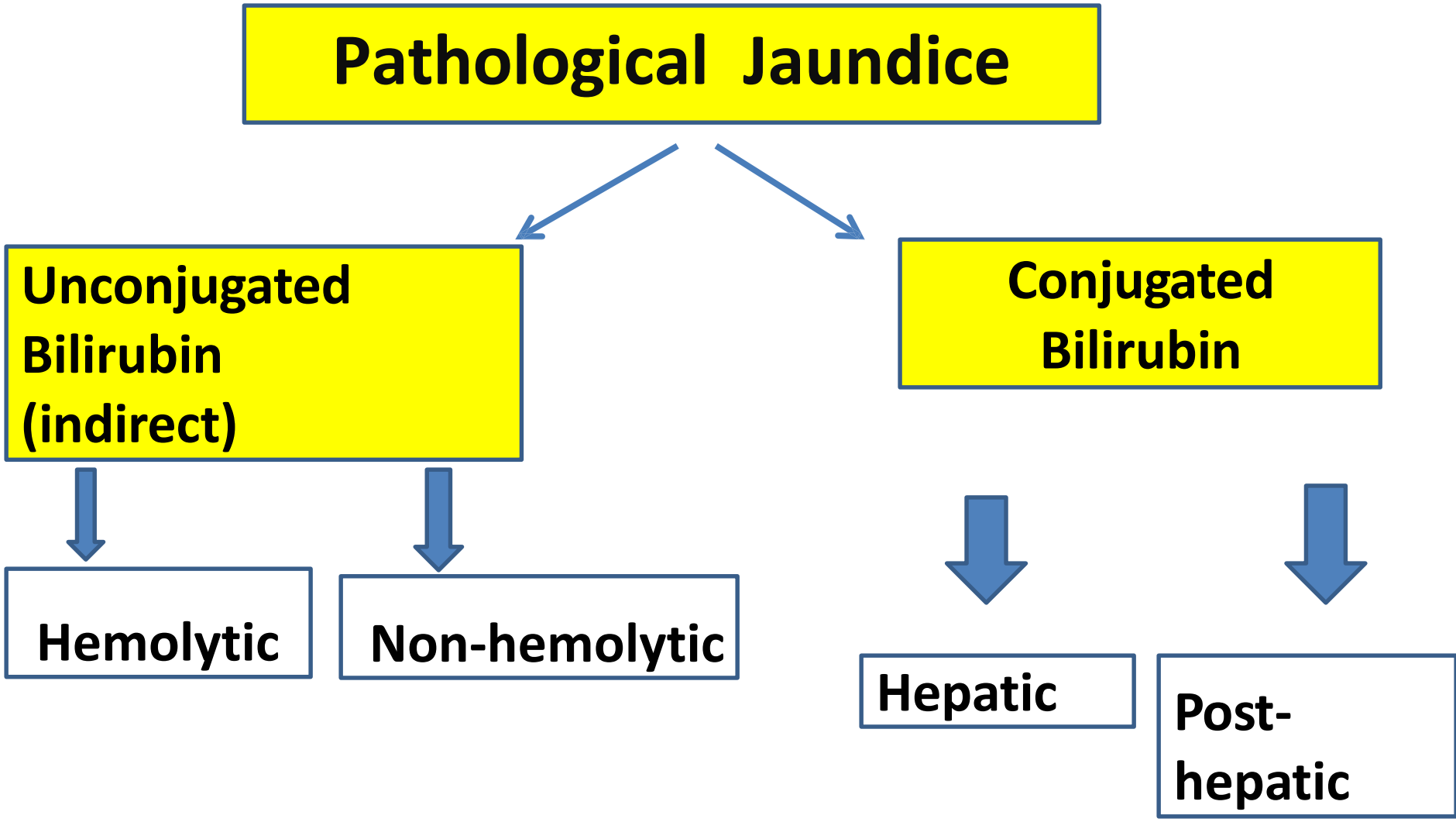
- Hemolytic disease of Newborn : Rh, ABO incompatibility
- Infections: TORCH, malaria, bacterial
- Red cell enzymes defects like G6PD deficiency, pyruvate kinase deficiency
- Administration of large amount of certain drugs like Vit K, sulfonamides.
- Hereditary spherocytosis.
- Crigler-najjar syndrome, Homozygous alpha thalassemia

between 24-72 hours of life

- Physiological
- Sepsis
- Polycythemia
- Concealed hemorrhages- Cephalhematoma, Subarachnoid bleed, IVH.

After 72 hours of age

- Sepsis
- Cephalhaematoma
- Neonatal hepatitis
- Extra-hepatic biliary atresia
- Breast milk jaundice
- Metabolic disorders such as galactosemia, tyrosinemia, cystic fibrosis, gilbert syndrome.


Pathological Jaundice
Unconjugated Bilirubin (indirect)
Conjugated Bilirubin
Hemolytic
Non-hemolytic
Hepatic
Post-hepatic

Unconjugated (Indirect) hyperbilirubinemia

1. Hemolysis

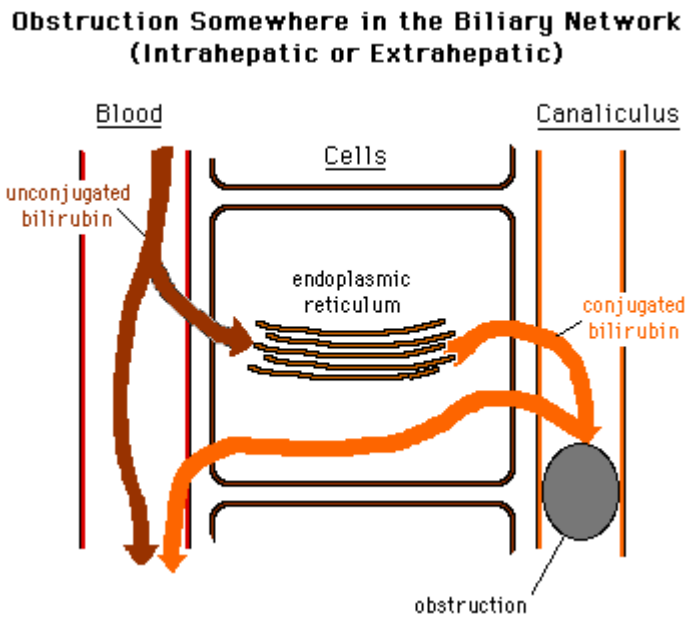
- Rh , ABO and other blood group incompatibilities
- H.spherocytosis, H.elliptocytosis,Alpha thalassemia
- Sepsis ,DIC
- Hematomas
- Polycythemia

2. Non hemolytic

- Breast milk jaundice
- Crigler-Najjar syndrome, types I and II
- Gilbert syndrome

Conjugated hyperbilirubinemia

1. Hepatic
   - Idiopathic neonatal hepatitis
   - Infections - TORCH, sepsis
   - Inborn errors of metabolism
     - Galactosemia
     - Tyrosinemia



2. Post hepatic
   - Biliary atresia, choledochal cyst

Common causes of jaundice

- Physiological
- Blood group incompatibility
- Breast milk jaundice
- G6PD deficiency
- Cephalhaematoma
- Infections

Breast feeding/ Breast failure jaundice

Infants who are breastfed have higher bilirubin levels on day 3 of age compared to formula-fed infants.

It typically occurs with lactation failure during the first postnatal week

This leads to insufficient intake causing slow bilirubin elimination and increased enterohepatic circulation with weight loss and sometimes hypernatremia.

Breast milk jaundice

In 2.4 % of Exclusively Breast Feed babies.

S.Bilirubin>10mg/dl beyond 3rd-4th week of life.

Due to presence of beta glucoronidase in human milk that deconjugates intestinal bilirubin and promotes its absorption.

T/t: Some babies may require Phototherapy ,Continue breast feeding.

Usually declines over a period of time.

Hemolytic disease of the newborn due to ABO incompatibility

- Mothers with type O blood may have circulating antibodies of IgG class to other red cell antigens that can cross the placenta and cause hemolytic disease in a baby with a different blood type, such as blood type A or B. (ABO incompatibility)

- The baby develops jaundice on the 1st day of life.

DRUGS AND NEONATAL JAUNDICE

Aggravate Hemolysis –
Vitamin K in large doses and drugs causing hemolysis in G6PD deficient infants.

Blocking Y-acceptor protein-
Vitamin K and Kanamycin

Competing with glucoronyl transferase for hepatic conjugation – Novobiocin, Moxalactam, Gentamycin, Kanamycin and Chloramphenicol.

Blocks Bilirubin binding sites in albumin –
Salicylates, Sulfonamides, caffeine, furosemide, indomethacin, fusidic acid .

Differential Diagnosis of Hereditary Jaundice with Normal Liver Chemistries & No Signs or Symptoms of Liver Disease

Unconjugated Hyperbilirubinemia			
		Crigler-Najjar Syndrome	
	Gilbert's	Type I	Type II
Usual clinical features	Appear in early adulthood; often 1st re-cognized w/ fasting	Jaundice, kernicterus in infants, young adults	Asymptomatic jaundice, kernicterus rare
Liver biopsy	Normal	Normal	Normal
Treatment	Not needed	Liver transplant	Phenobarbital

RISK FACTORS FOR HYPERBILIRUBINEMIA TOXICITY

Isoimmune hemolytic disease
G6PD Deficiency
Asphyxia
Sepsis
Acidosis
Albumin< 3mg/dl
Significant lethargy
Temperature instability

APPROACH TO NEONATAL JAUNDICE

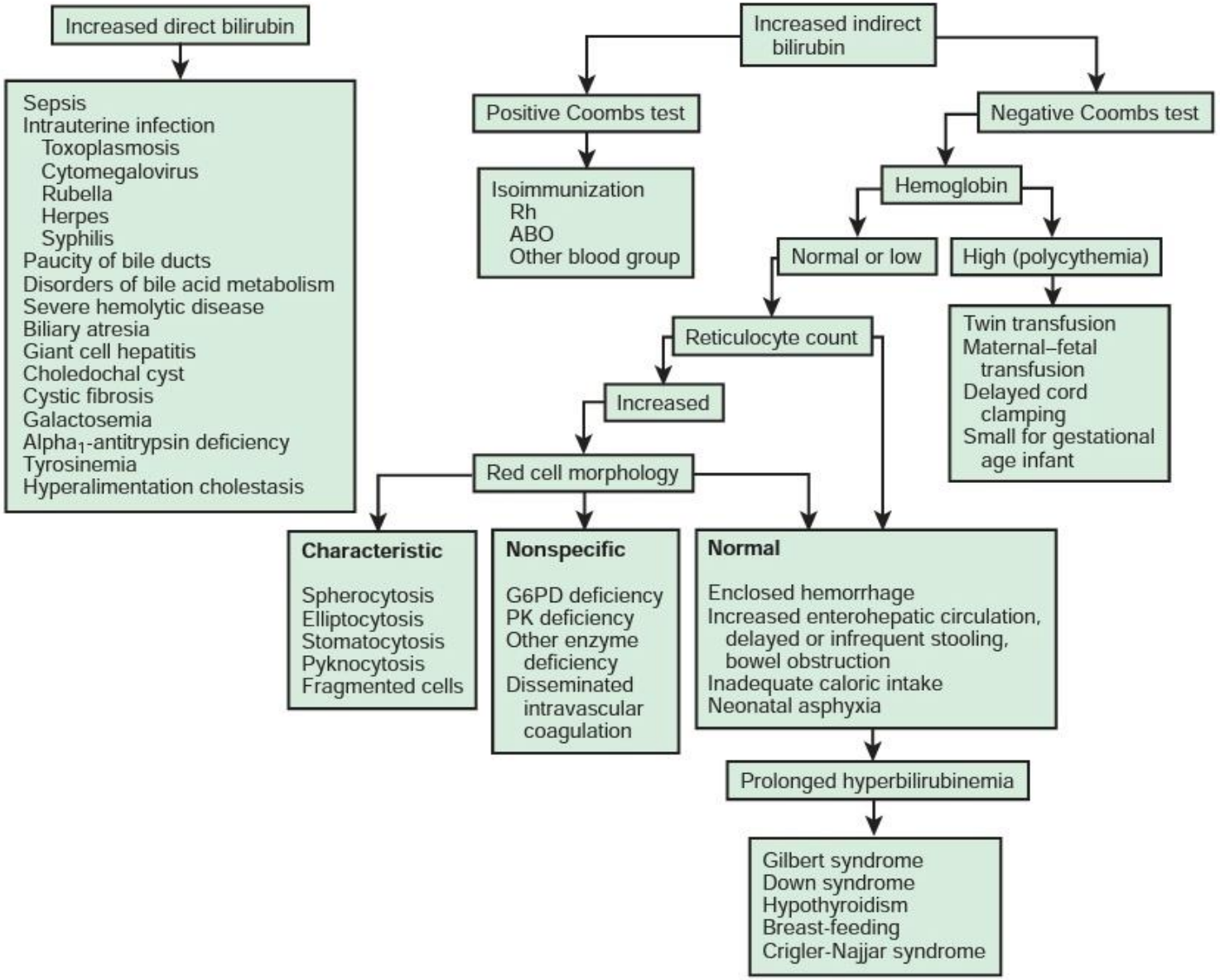
History –

Family history
Pregnancy history
Labor and delivery history
Infant history

Physical examination-

Visual inspection
Lower gestational age
Small for gestational age
Extravascular blood
Pallor, pretechiae, omphalitis or other sign of infection
Hepatosplenomegaly , choriretinitis,

Laboratory tests


Increased direct bilirubin
Sepsis
Intrauterine infection
Toxoplasmosis
Cytomegalovirus
Rubella
Herpes
Syphilis
Paucity of bile ducts
Disorders of bile acid metabolism
Severe hemolytic disease
Biliary atresia
Giant cell hepatitis
Choledochal cyst
Cystic fibrosis
Galactosemia
Alpha1-antitrypsin deficiency
Tyrosinemia
Hyperalimentation cholestasis
Increased indirect bilirubin
Positive Coombs test
Isoimmunization
Rh
ABO
Other blood group
Negative Coombs test
Hemoglobin
Normal or low
High (polycythemia)
Twin transfusion
Maternal–fetal transfusion
Delayed cord clamping
Small for gestational age infant
Reticulocyte count
Increased
Red cell morphology
Characteristic
Spherocytosis
Elliptocytosis
Stomatocytosis
Pyknocytosis
Fragmented cells
Nonspecific
G6PD deficiency
PK deficiency
Other enzyme deficiency
Disseminated intravascular coagulation
Normal
Enclosed hemorrhage
Increased enterohepatic circulation, delayed or infrequent stooling, bowel obstruction
Inadequate caloric intake
Neonatal asphyxia
Prolonged hyperbilirubinemia
Gilbert syndrome
Down syndrome
Hypothyroidism
Breast-feeding
Crigler-Najjar syndrome

Laboratory tests

- Total & direct bilirubin*
- Blood group and Rh for mother and baby*
- Hematocrit, reticulocyte count and peripheral smear*
- G6PD assay
- Coomb's test
- Sepsis screen
- Liver and thyroid function
- TORCH titre
- Liver scan when conjugated hyperbilirubinemia
- Ultrasonography of the liver and bile duct in cholestatsis

(must in all)*

Measurement of serum bilirubin

(a)Transcutaneous bilirubinometry

(b) Bilimeter

(c) Van der bergh's test(diazo test)

(d)High performance liquid chromatography(HPLC)

(e)Measurement of carboxyHb ,pulmonary excretion rate of CO or EtCO breath level

Measurement of bilirubin by Transcutaneous bilirubinometer ⟶

Laboratory Diagnosis

Laboratory Features Of Hemolytic Disease

Laboratory Features	Rh	ABO
Blood type of Mother	Rh negative	O
Blood type of Infant	Rh positive	A or B
Anemia	Marked	Minimal
Direct Coomb's test	Positive	Negative
Indirect Coomb's test	Positive	Usually positive

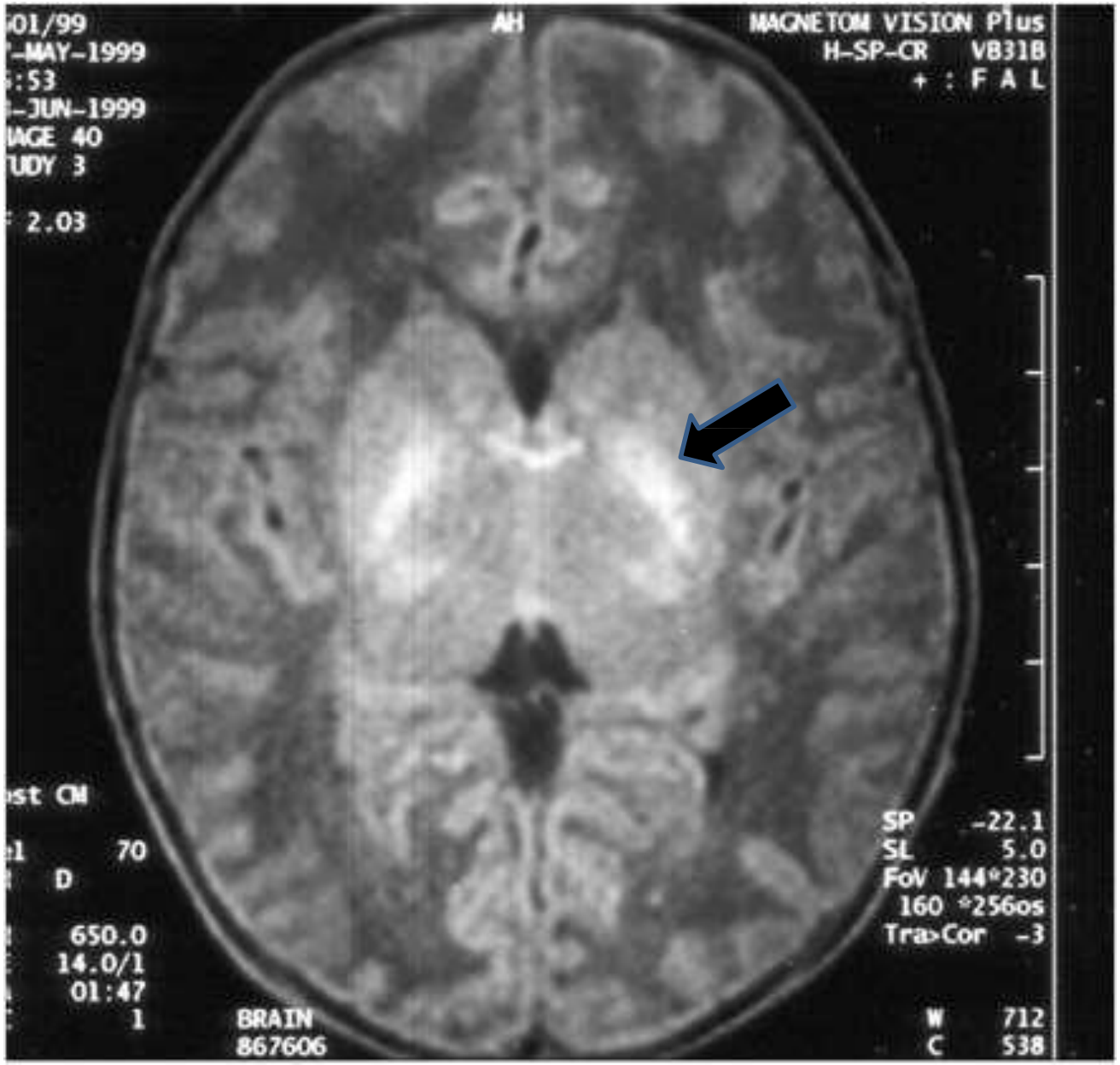
Other Tests -

- **Reticulocyte** count (>7%) can indicate the presence of an ongoing hemolytic process in neonates.

- **Direct hyperbilirubinemia** in the neonate is defined as a direct fraction more than **2 mg/dL** or more than **15%** of the total bilirubin concentration . It is always pathological.

- **Hearing tests (Brainstem auditory-evoked potentials)** should be done after 3 months in severe neonatal jaundice to exclude sensorineural hearing loss.

- MRI in kernicterus.



bilateral basal ganglia hyperintensity

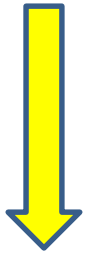
Management

1. Phototherapy
2. Exchange transfusion
3. Intravenous immune globulin (IVIG)
4. Drugs

Principle of phototherapy

Bilirubin (**water Insoluble**)

460-490nm of light



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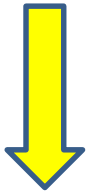
Lumirubin (**water soluble**)



Bile and Urine

Conversion of insoluble Bilirubin into soluble Bilirubin -

1.Photo-isomerization-conversion of Z4Z,15Z bilirubin isomer to less toxic 4Z,15E form soluble
form , but the process is reversible and clearence is slow.

2.Structural isomerization - conversion to lumirubin - rapidly excreted in bile and urine(main mechanism).

3. Photo-oxidation- slow process, least important mechanism.

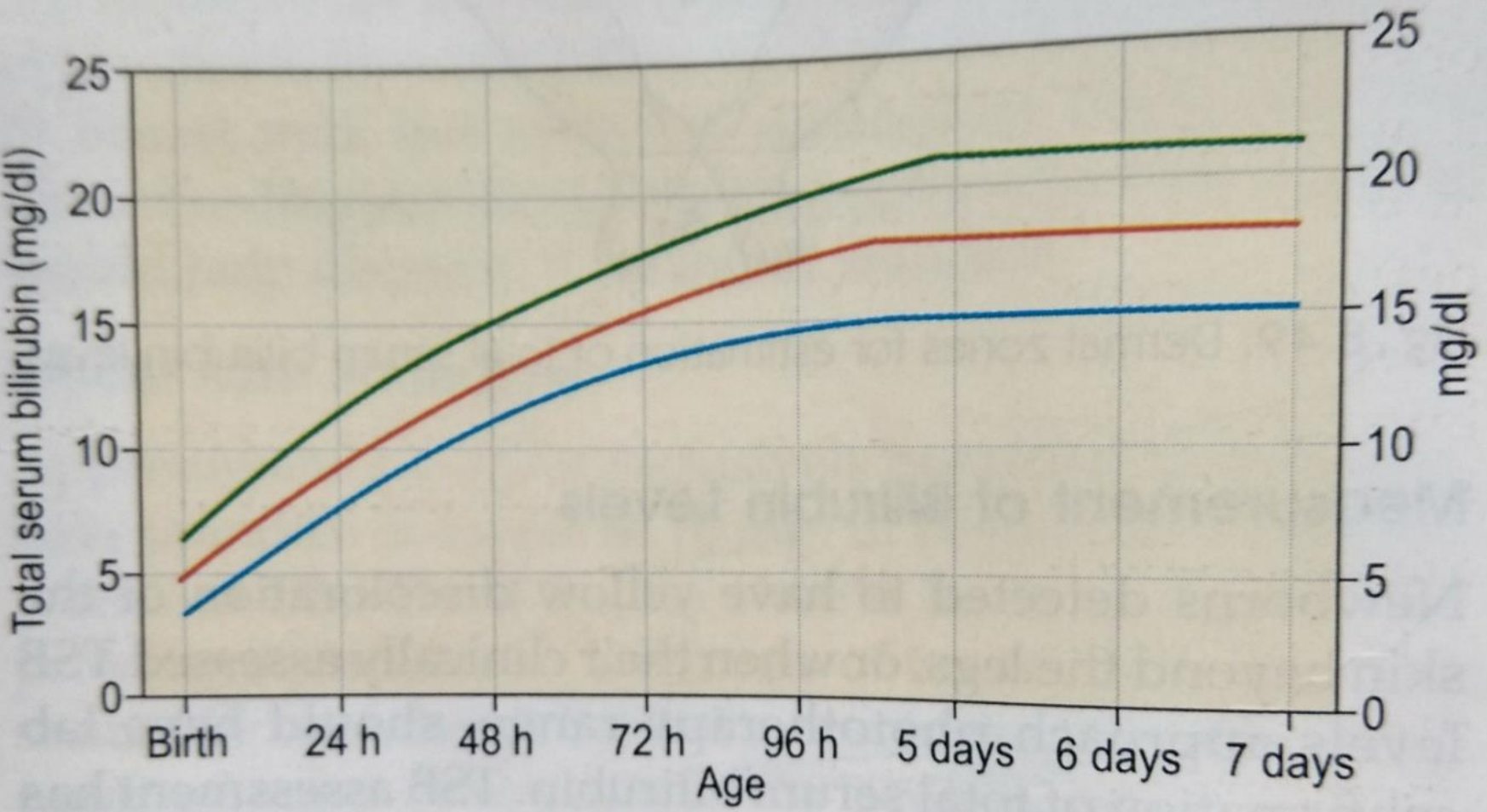
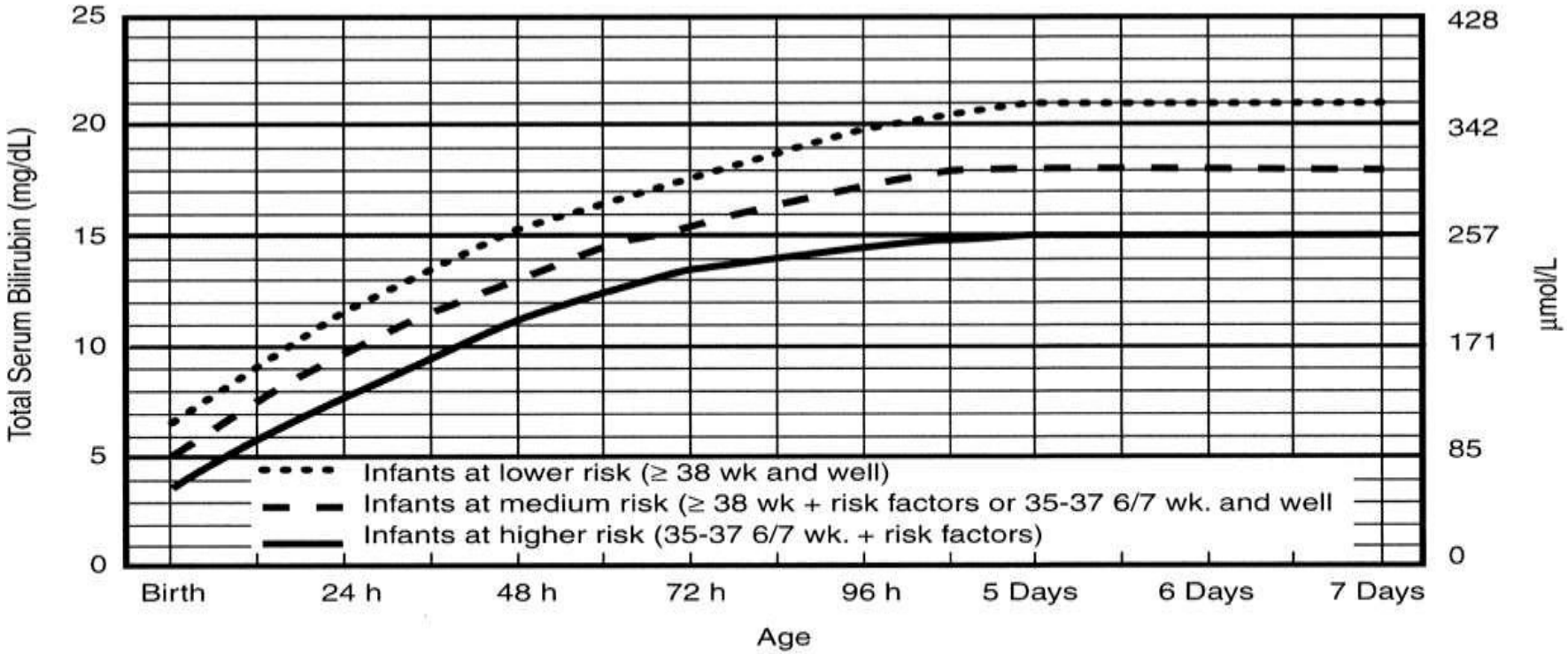


Fig. 8.51: Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation. — Infants at lower risk (>38 week and well) — Infants at medium risk (>38 week + risk factors or 35–37 6/7 week and well) — Infants at higher risk (35–37 6/7 week + risk factors)

Table 8.25: Suggested TSB cut-offs for phototherapy and exchange transfusion in preterm infants <35 weeks

Gestation (completed weeks)	*Phototherapy*	*Exchange transfusion*
<28	5–6	11–14
28 to 29	6–8	12–14
30 to 31	8–10	13–16
32 to 33	10–12	15–18
34	12–14	17–19

Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

µmol X0.055 = mg/dl

American Academy of Pediatrics

Phototherapy Technique

- Perform hand wash and Place baby naked in cradle or incubator.
- Fix eye shades.
- Keep baby at least 15-20 cm from lights.
- Start phototherapy.
- Ensure optimum breastfeeding.
- Temperature record 2 to 4 hourly.
- Weight record- daily.
- Monitor urine frequency.
- Monitor bilirubin level 12-24 hourly.
- Irradiance of lights should be periodically measured , minimum level of 30 microwatt/cm2/nm in wavelength range of 460-490 nm must be ensured.

- Lamps should be changed if lamps are flickering or ends are blackened, or irradiance falls below the specific level.

TYPES OF PHOTOTHERAPY LIGHTS

1. Blue compact florescent(CFL)
2. High Intensity Light Emitting Diodes(LED)
3. Halogen white lights
4. Fibroptic blakets or pads (Biliblanket)

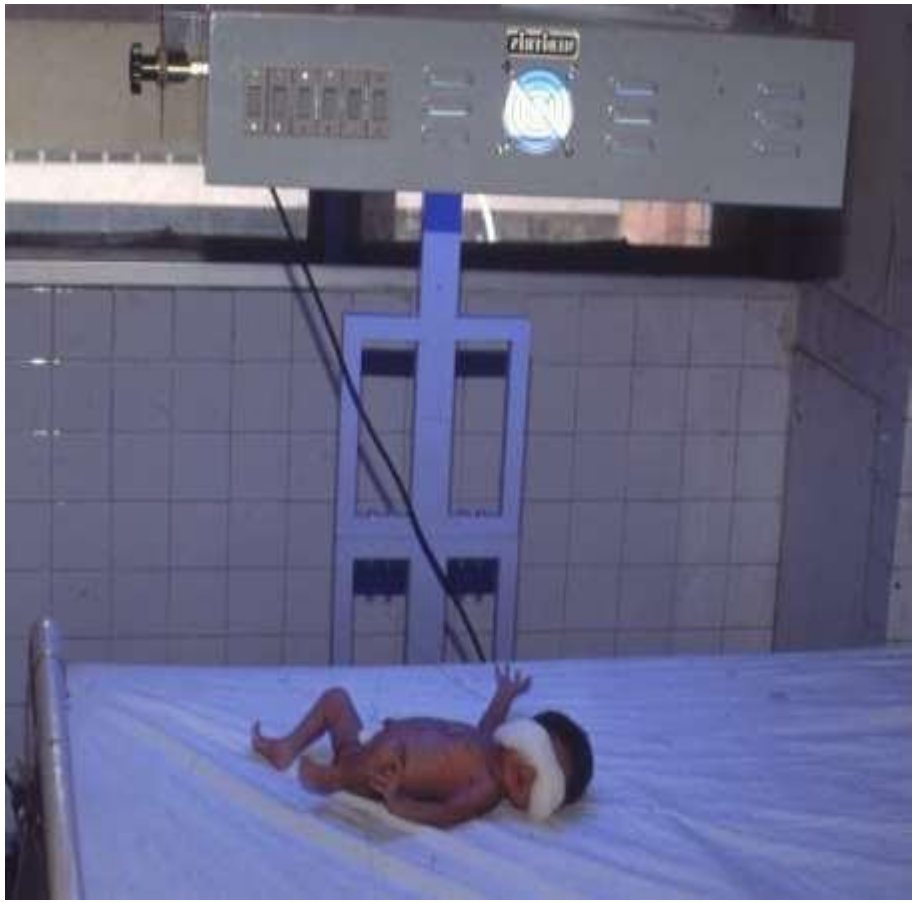
Blue LED Advantages-

-long half life (upto 50,000 hours)

- capable of delivering higher irradiance than CFL Lamps.

Biliblanket

They can be placed directly under the infant, generate little heat and provide high irradiance than fluorescent lights. Typically used together with overhead lights.



Baby under conventional phototherapy

Baby under triple unit intense phototherapy

Side effects of phototherapy

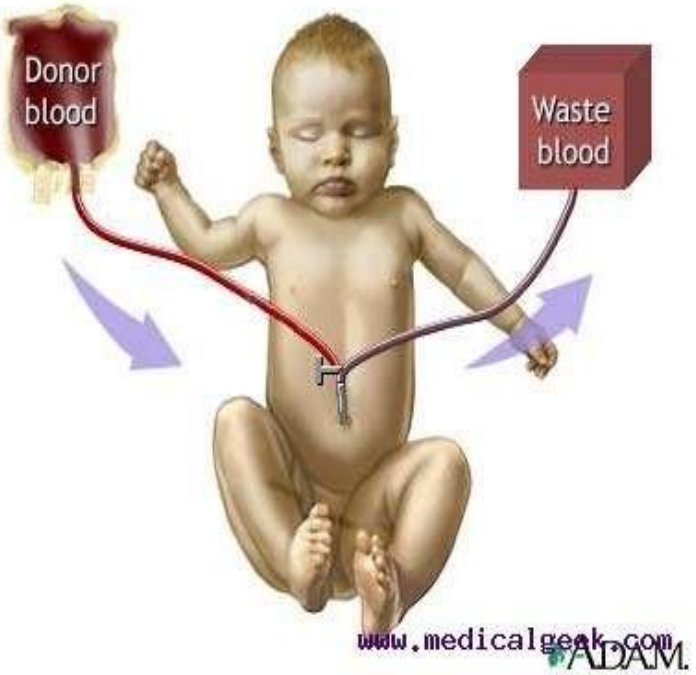
- Increased insensible water loss
- Loose stools
- Skin rash
- Bronze baby syndrome
- Hyperthermia
- May result in hypocalcemia

Exchange transfusion

Most effective method for rapid removal of bilirubun.

Exchange transfusion is indicated for avoiding bilirubin neurotoxicity when other therapeutic modalities have failed or are not sufficient.

Double volume exchange transfusion (DVET) should be performed if the TSB level reach to age specific cut-off for exchange transfusion or infant showing sign of kernicterus.



Indications for DVET in infants with Rh isoimmunization include –

1. Cord bilirubin is 5mg/dl or more
2. Cord Hb is 10 gm/dl or less.

At birth if a baby shows sign of hydrops or cardiac decompensation in presence of low PCV(<35%), partial ET with 50 ml/kg of packed cells should be done.

The Exchange transfusion should be performed by pull and push technique using umbilicus venous route.

Immediately after DVET(160-180 ml/kg), TB are typically half the value prior to the procedure. After 30-60 minutes, TB level returns to approximately 85% of the circulating RBC.

Albumin infused 1 to 2 hours prior to exchange transfusion promotes removal of more bilirubin because more extravascular bilirubin is drawn into the circulation.

Intensive phototherapy should be resumed after exchange transfusion and TB should be monitored at 2, 4 , 6 hours after transfusion and then atleast 12-24 hours.

Type and Volume of Blood for Exchange Transfusion

CONDITIONS	TYPE OF BLOOD
Rh isoimmunisation	*O –ve or that of baby suspended in AB plasma,cross matched with baby's & mother's blood.*
ABO incompatibility	*Rh compatible & O group(not that of baby) suspended in AB plasma, cross matched with baby's & mother's blood.*
Other conditions(G6PD deficiency,non-hemolytic,other isoimmune hemolytic jundice)	*Baby's group & Rh type,cross matched with baby's and mother's blood.*

COMPLICATIONS

Common-

Throbocytopenia and coagulation abnormalities

Hyperglycemia

Hyperkalemia

Hypocalcemia

Acid-base abnormalities

Less common -

NEC

Portal vein thrombosis

Cardiac arrythmias

Infection

IV HYDRATION

Infants with severe hyperbilirubinemia and evidence of dehydration(eg. Excessive weight loss) should be given IV hydration.

An extra fluid of 50 ml/kg of N/3 saline over 8 hours decreases the need for exchange transfusion.

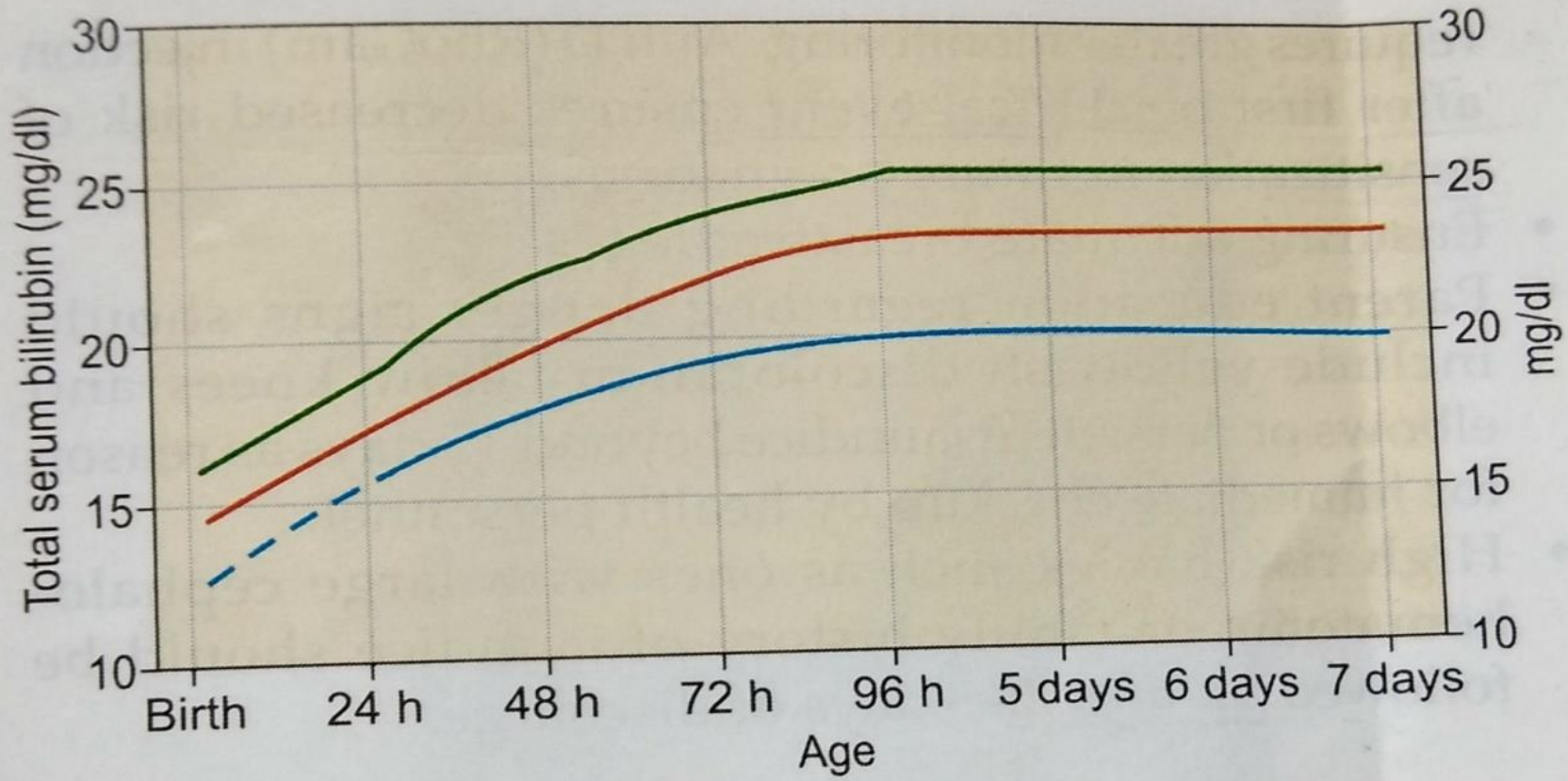


Fig. 8.52: Guidelines for exchange transfusion in infants 35 or more weeks' gestation. — Infants at lower risk (> 38 week and well) — Infants at medium risk (> 38 week + risk factors or 35–37 6/7 week and well) — Infants at higher risk (35–37 6/7 week + risk factors) (Adapted from AAP 2004)

FOLLOW UP

Babies with TSB >20 mg/dl and those who require ET should be kept under followup in the high risk clinic for neuro developmental outcome.

BERA should be done at 3 months of age.

With prompt t/t even TSB 25-29 mg/dl are not likely to result in longterm adverse effects on neurodevelopment.

Intravenous immune globulin

- IVIG has been used in infants with Rh or ABO incompatibility .
- It can significantly reduce the need for exchange transfusion, acts by occupying the Fc receptors on macrophages, decreasing removal of antibody coated red cells from the circulation.
- 0.5 to 1 gm/kg/dose IV over 2 hours and repeat the dose in 12 hours if needed.
- Subsequent studies did not prove the efficacy and its use.

DRUGS

- There is no proven benefit of drugs like Phenobarbitone, Clofibrate, or Steroids to prevent or treat neonatal hyperbilirubinemia.

Prolonged unconjugated hyperbilirubinemia

- Breast milk jaundice
- Immaturity
- Hemolytic disease of newborn
- Hypothyroidism
- Pyloric stenosis
- Crigler Najjar syndrome
- Gilbert syndrome
- Concealed hemorrhage

Conjugated hyperbilirubinemia

Suspect when

- High colored urine
- White or clay colored stool

Caution

- Always perform investigations so that biliary atresia or metabolic disorders can be diagnosed and managed early.

Danger of hyperbilirubinemia

•Jaundice in a neonate is a medical emergency as unconjugated hyperbilirubinemia may cause bilirubin encephalopathy or kernicterus.

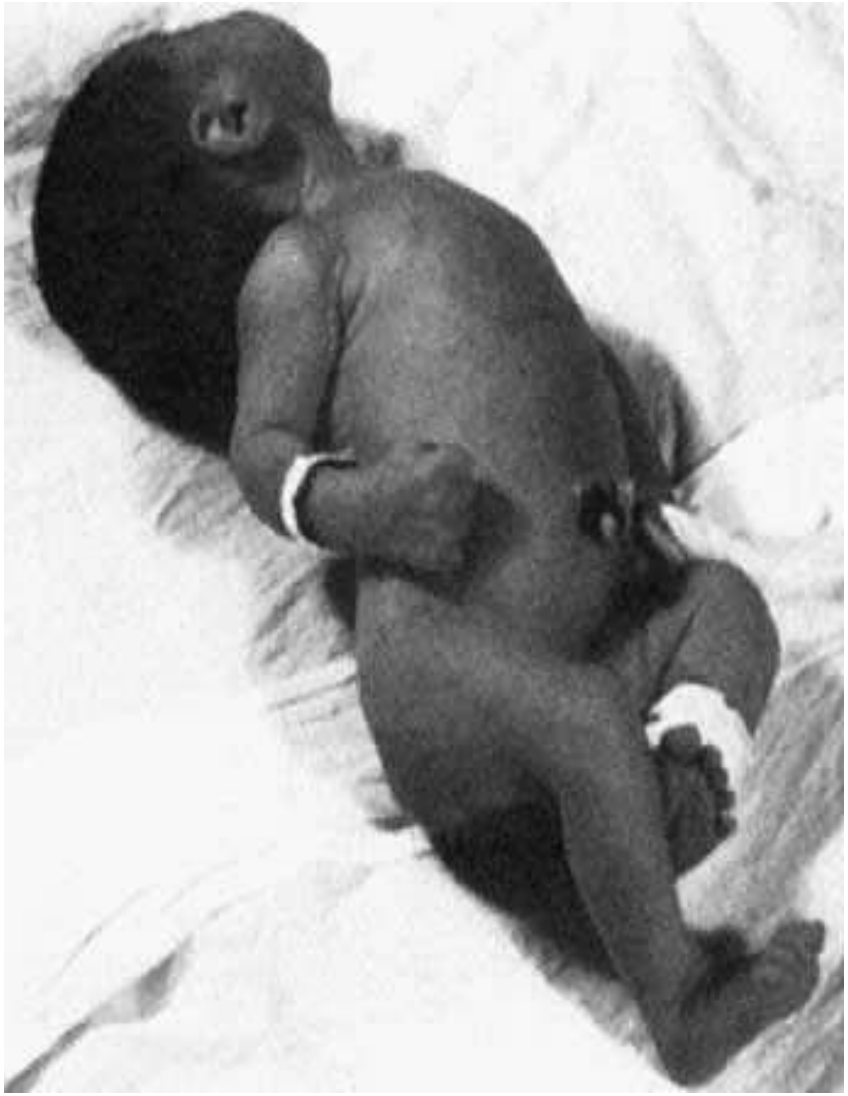
•KERNICTERUS: results from deposition of Unconjugated Bilirubin in the basal ganglia &brainstem nuclei resulting in neuronal necrosis.

•It occurs usually in an infant with a bilirubin > 20 mg/dl but may occur at lower level in presence of risk factors e.g. prematurity, hypoxia , acidosis ,sepsis.

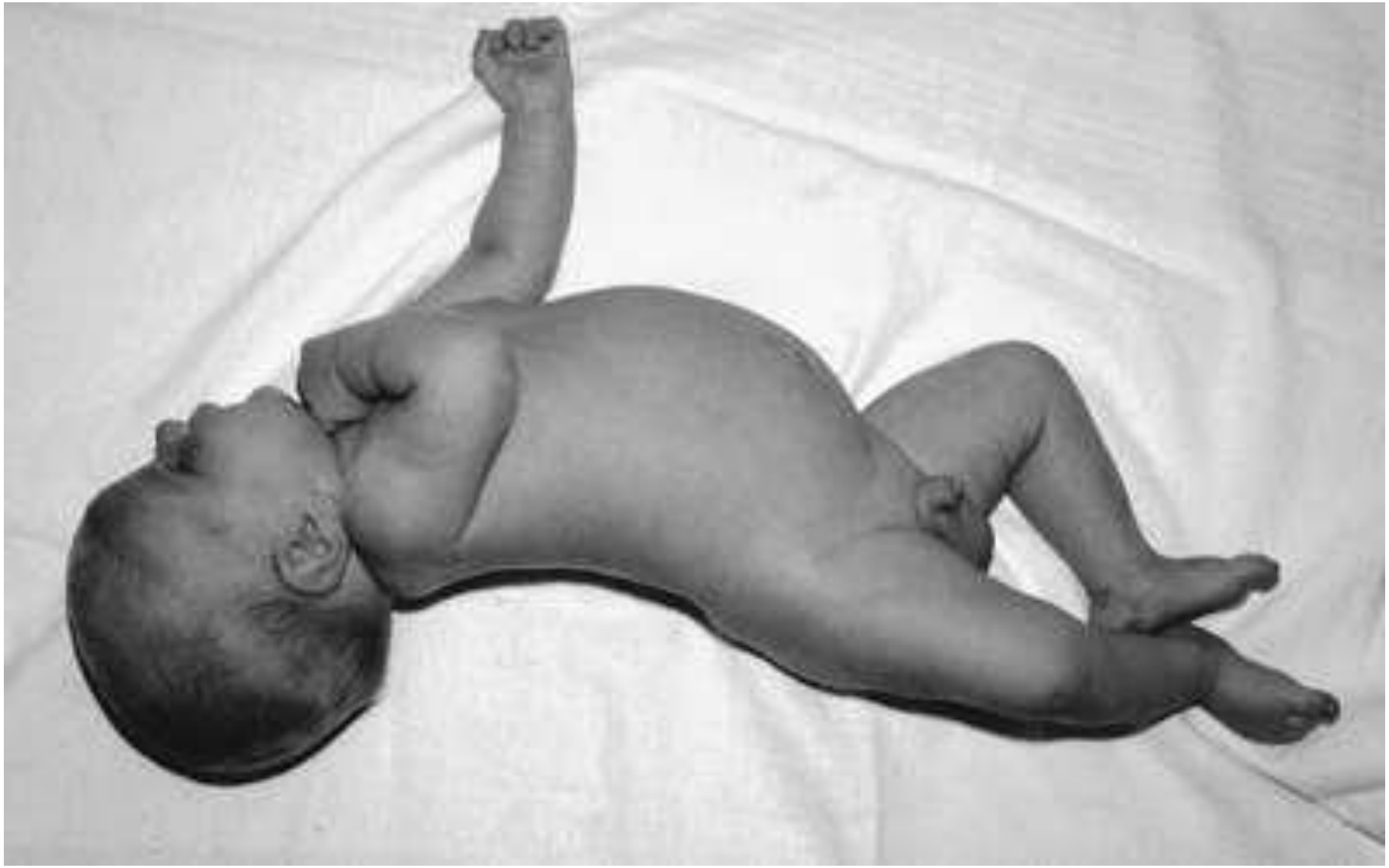
Major Clinical Features of Acute Bilirubin Encephalopathy

- Lethargy
- poor sucking
- Abnormal moro's reflex
- Retrocollis,opisthotonos

  Convulsions



Retrocollis (backward arching of the neck)
Opisthotonus (backward arching of the back)

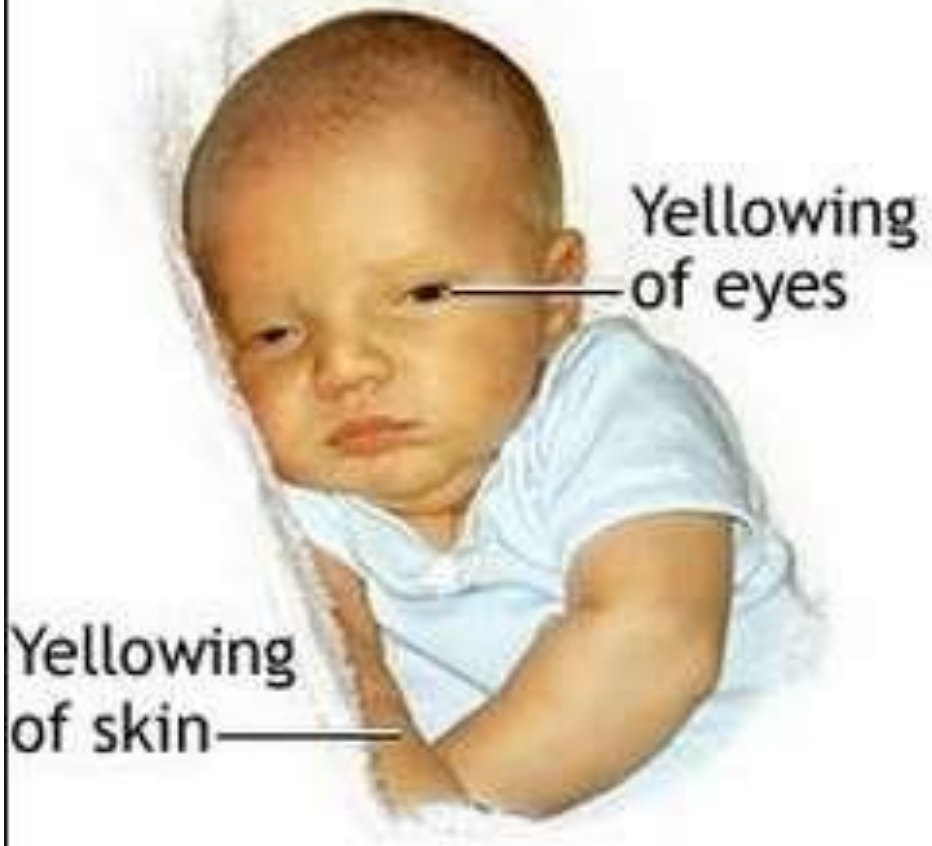


This infant presented at age 30 days with a serum bilirubin level of 30 mg/dL (513 µmol/L) secondary to the **Crigler-Najjar syndrome** type I. He demonstrates retrocollis and opisthotonos, signs of the intermediate to advanced stage of acute bilirubin encephalopathy.

Major clinical features of chronic bilirubin encephalopathy

- Choreoathetoid cerebral palsy
- Limitation of upward gaze
- Sensorineural hearing loss
- Intellectual deficits
- Dental enamel dysplasia

Jaundice



Excess bilirubin in blood

Kernicterus

Bilirubin moves from bloodstream into brain tissue

TAKE HOME MESSAGE

Jaundice is the most frequent cause of admission after early discharge from nursery.

In most cases jaundice is benign & no intervention is required but we should always have a high index of suspicion and in slightest doubt we should go for investigation.

It is not physiological if: appears in first 24 hrs, increases by > 0.5 mg/dL/hr , evidence of hemolysis, abnormal examination, direct bilirubin is > 15% of total, or persists > 2 wks.

Early interventions give excellent result and also prevent life long disability like CP due to bilirubin encephalopathy.


THANKYOU
THE WALK TO CURE DIABETES
JDRF 2005
We're on Track For a Cure