

Neonatal Jaundice Hyperbilirubinemia

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100 \$ questions on Neonatal Jaundice (NJ)

1. What is the commonest cause of neonatal J ?
2. What is the frequently used therapy for neonatal J ?
3. Why do we need to study Neonatal J ?

Introduction



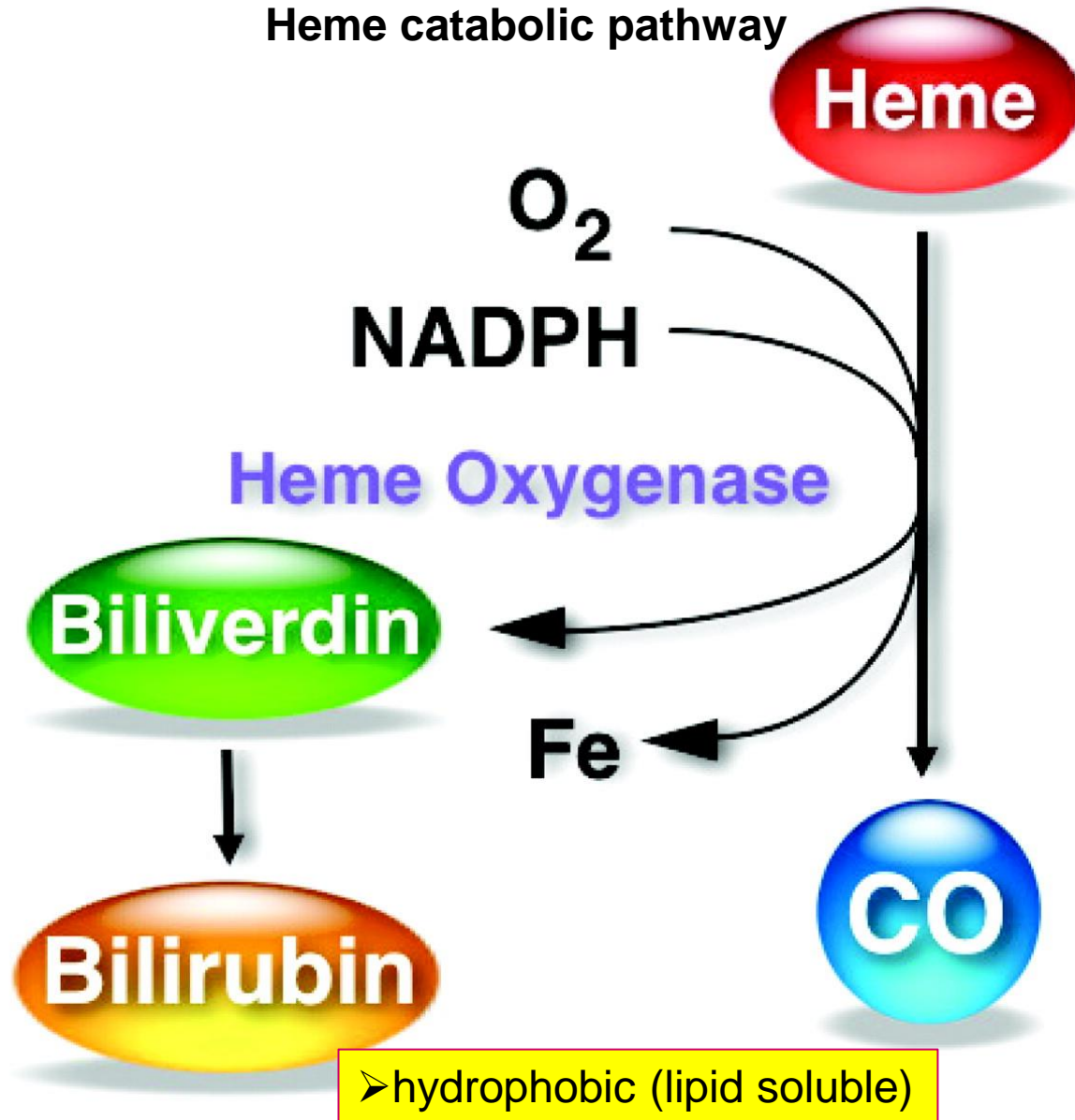
- Yellow-orange pigment Icterus –ikteros - bilirubin in the skin and sclerae
- It is one of the most common clinical phenomena encountered in newborns (How common is it?)
- It may be a sign of another illness
- It may lead to catastrophic complication (**kernicterus**)

Clinical Physiology

1- Bilirubin Production

- *What is (are) the source(s) of Bilirubin ?*
- Degrading heme from hemoglobin-containing RBCs (80%)
- 20% from ineffective erythropoiesis
- Turnover of other hemoproteins (e.g., myoglobin, catalase, nitric oxide synthase, peroxidases, and cytochromes).

Heme catabolic pathway



2- Bilirubin Transport

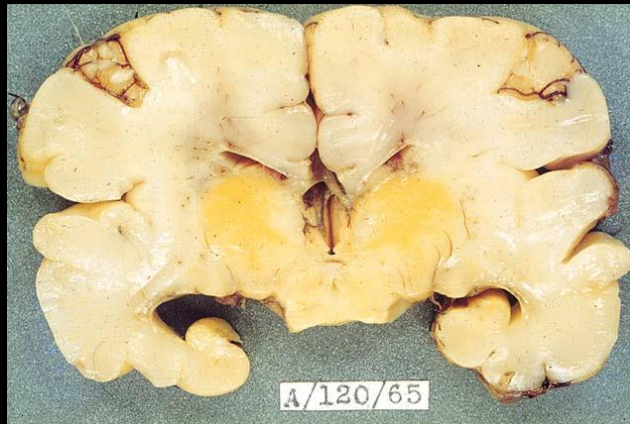
- It binds reversibly to albumin
(bilirubin:albumin)
(about 0.8 - 7 mg of bilirubin per gram of albumin)
- Low Albumin level and affinity binding sites
- Free" bilirubin is hydrophobic (lipid soluble)
- The movement of bilirubin from the circulation into tissue cross blood brain brayer

basal ganglia

hippocampus

Kernicterus

geniculate bodies



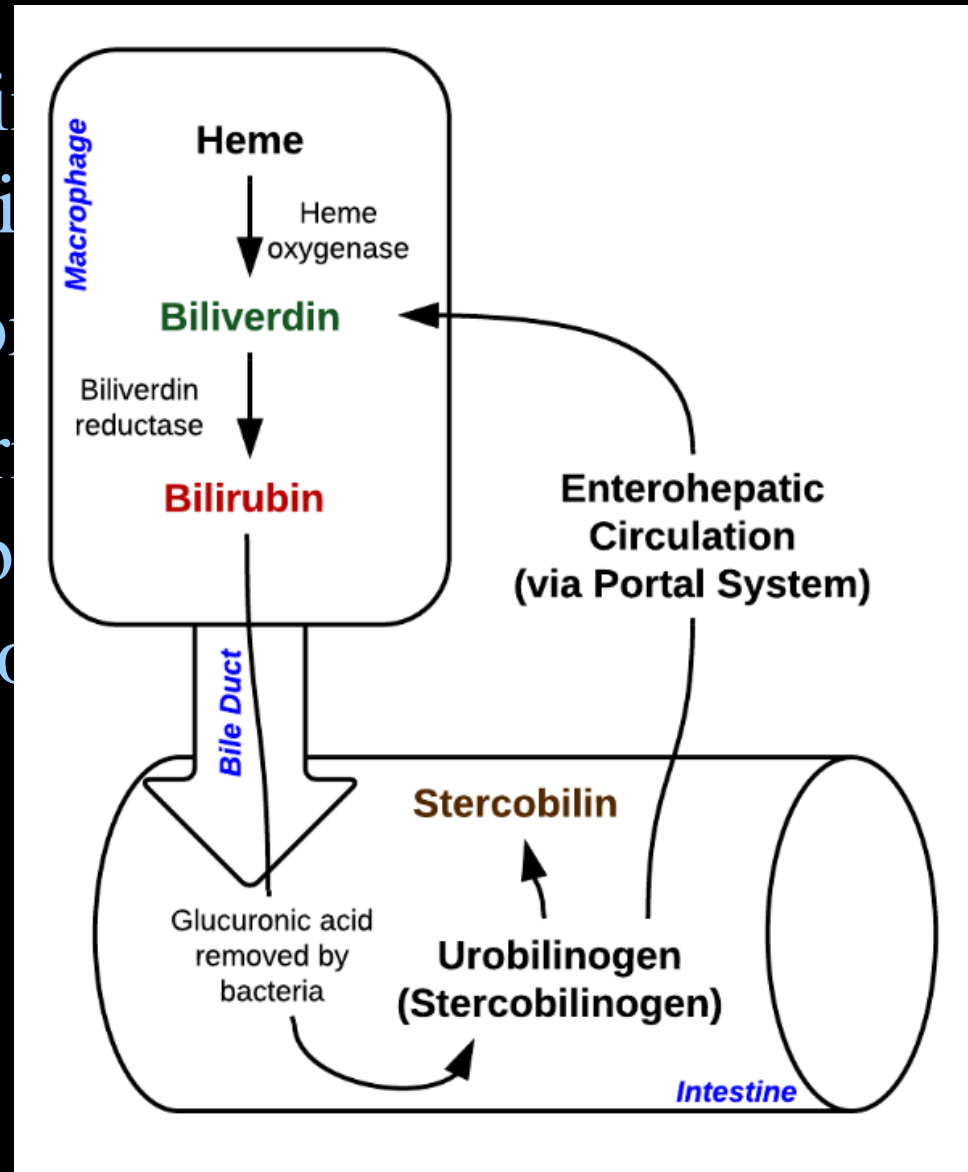
cranial nerve nuclei

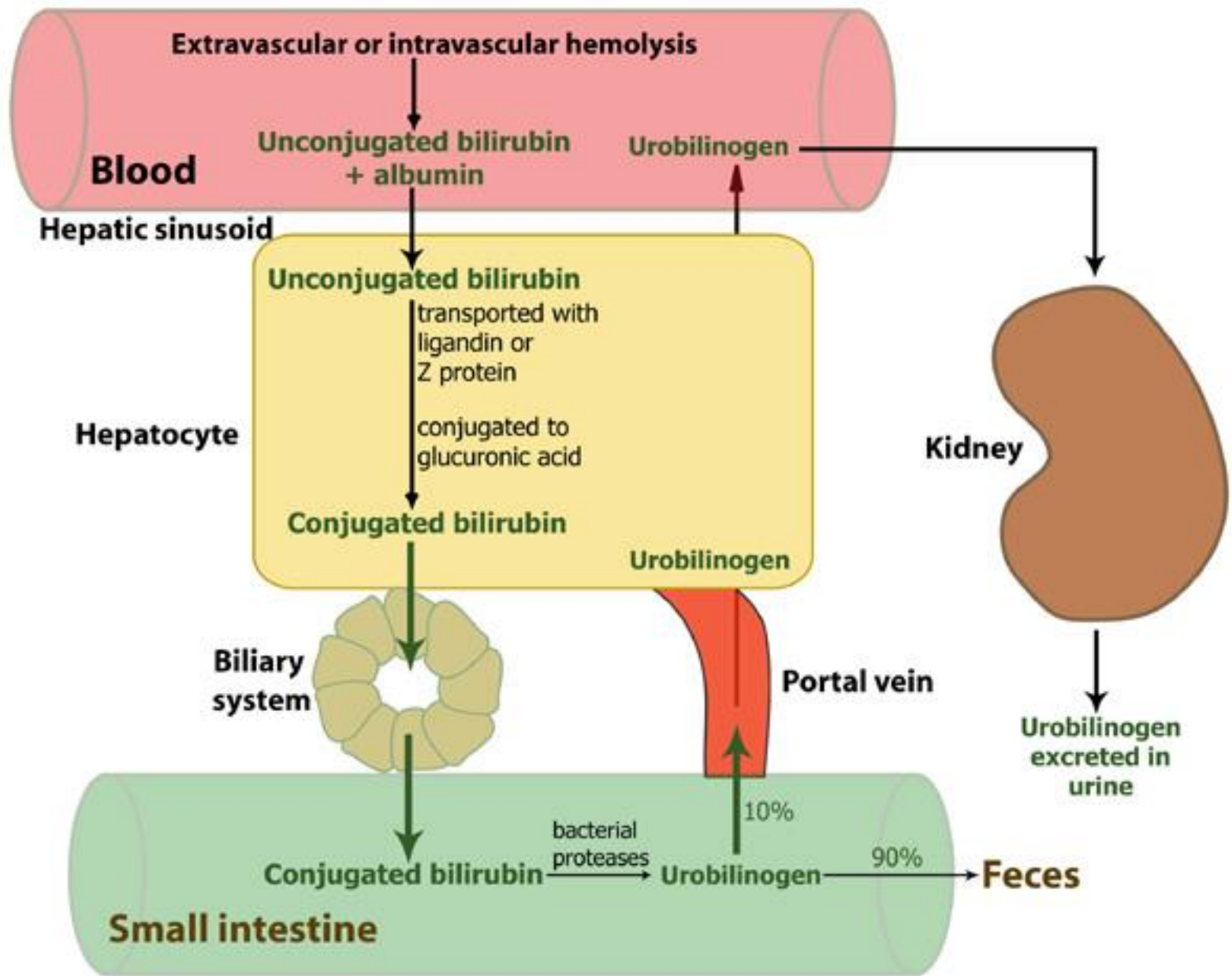
3- Conjugation

- Conjugation of bilirubin with glucuronic acid (water-soluble, non-neurotoxic bilirubin)
- *Uridine diphospho- **Glucuronosyl Transferase** (UGT)*
- *Why does the neonates developed jaundice?*
 1. *Slower rate of hepatic uptake of free bilirubin from the blood*
 2. *Decreased concentrations and activity of (UGT) ?*

4- Bilirubin Excretion

- Conjugated bilirubin is excreted with the bile
- Mono or Diglucuronides
- In the colon, bacteria hydrogenate bilirubin to urobilins, and stercobilins





Etiological Classification

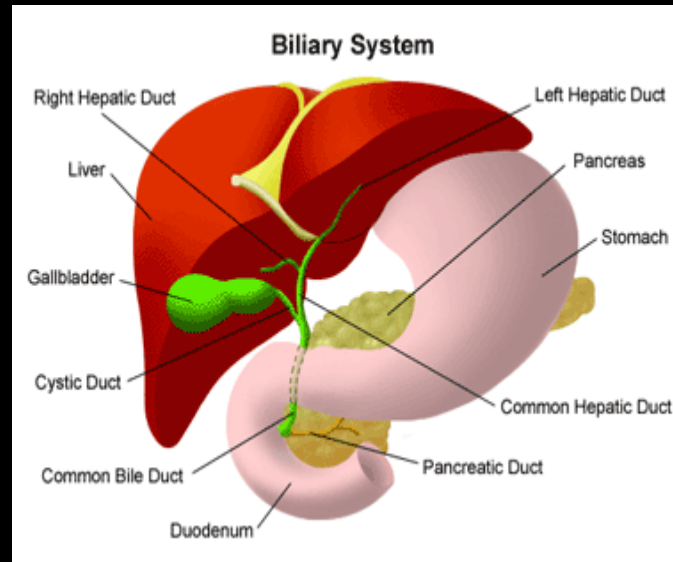
Bilirubin
production

Binding

Transportation

Entero-hepatic
conjugation

Hour-specific
Bilirubin load



Bilirubin
Elimination

What are the risk factors?

Risk Factors for Neonatal Hyperbilirubinemia

JAUNDICE

- ◉ **J**aundice visible on the 1st day of life
- ◉ **A**sibling with neonatal jaundice or anemia
- ◉ **U**nrecognized hemolysis (ABO, Rh incompatibility); **U**DP-glucoronyl transferase deficiency (Crigler-Najjar, Gilbert disease)
- ◉ **N**onoptimal feeding (formula or breast-feeding)
- ◉ **D**eficiency of G6PD
- ◉ **I**nfection, **I**nfant of diabetic mother, **I**mmaturity (prematurity)
- ◉ **C**ephalhematoma or bruising, **C**entral hematocrit >65% (polycythemia)
- ◉ **E**ast Asian, Mediterranean, Native American heritage

Etiological Classification

□ Increased bilirubin load

1. Haemolytic causes

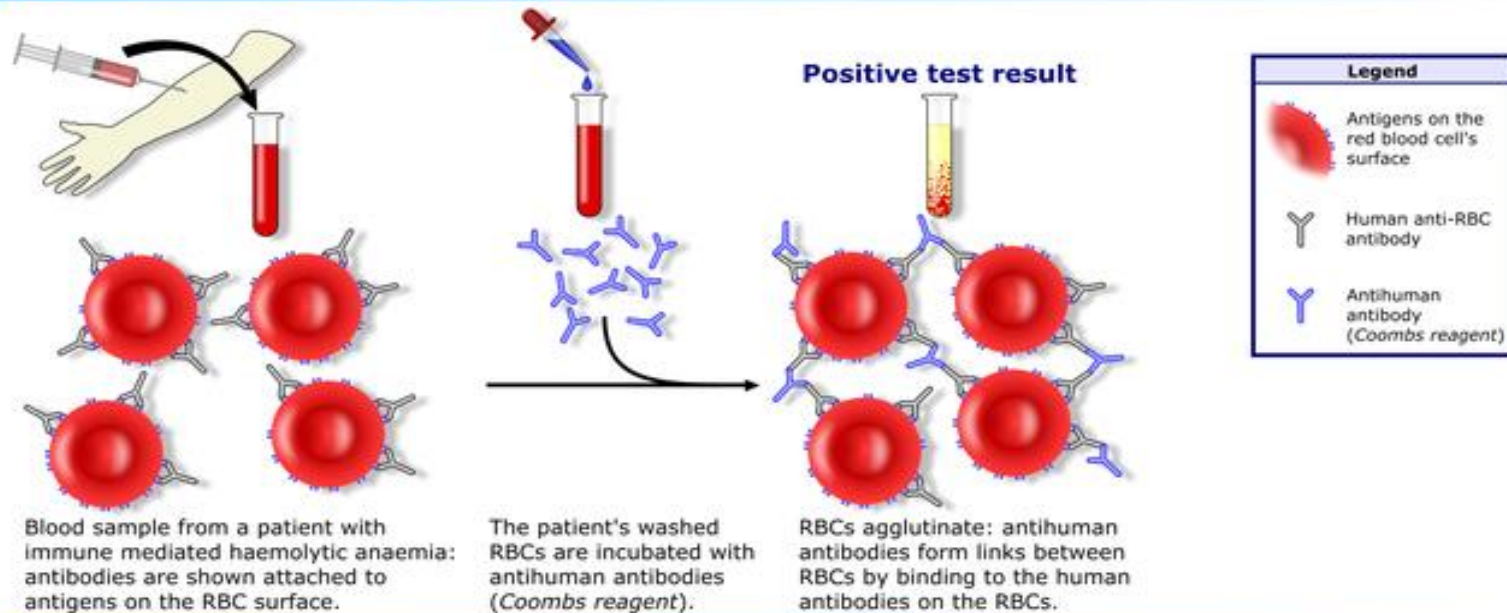
➤ Coombs' test positive: Examples ?

➤ Coombs' test negative: Examples ?

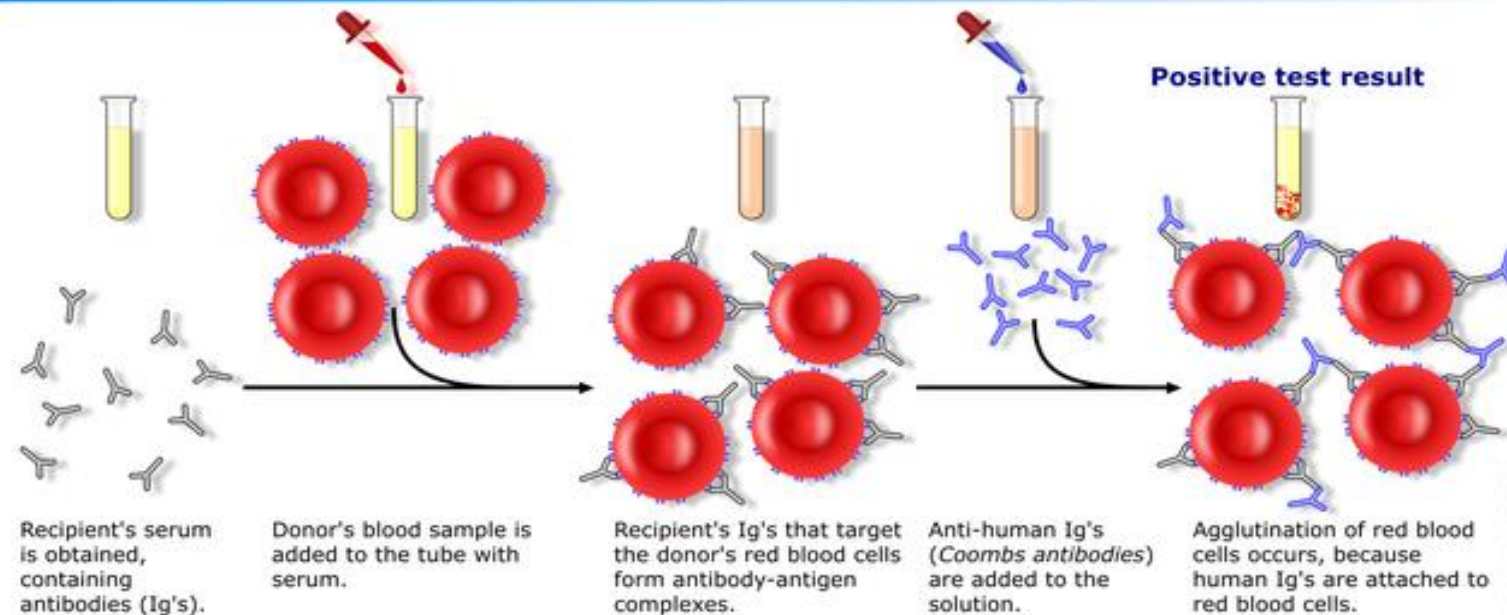
(red blood cell membrane defects (spherocytosis, elliptocytosis),
red blood cell enzyme defects (G6PD deficiency, pyruvate
kinase deficiency)

■ Why we do not include thalassemia or SCD ?

Direct Coombs test / Direct antiglobulin test



Indirect Coombs test / Indirect antiglobulin test



1. Haemolytic Disease

- Jaundice in the first 24 hours of age
- Blood group incompatibility (ABO, Rhesus
Less common Kell and Duffy)
- Red cell enzyme deficiency
- Red blood cell membrane defect
- + ve family history
- Sepsis (... *poor intake reduce hepatic function and an increase EHC*)

2. Non-hemolytic N jaundice

- Increased un-conjugated bilirubin level, absent of hemolytic Markers **what are these ?**
 1. Physiologic jaundice
 2. Extra vascular sources
 3. Polycythemia
 4. Exaggerated Entero - hepatic circulation (EHC)

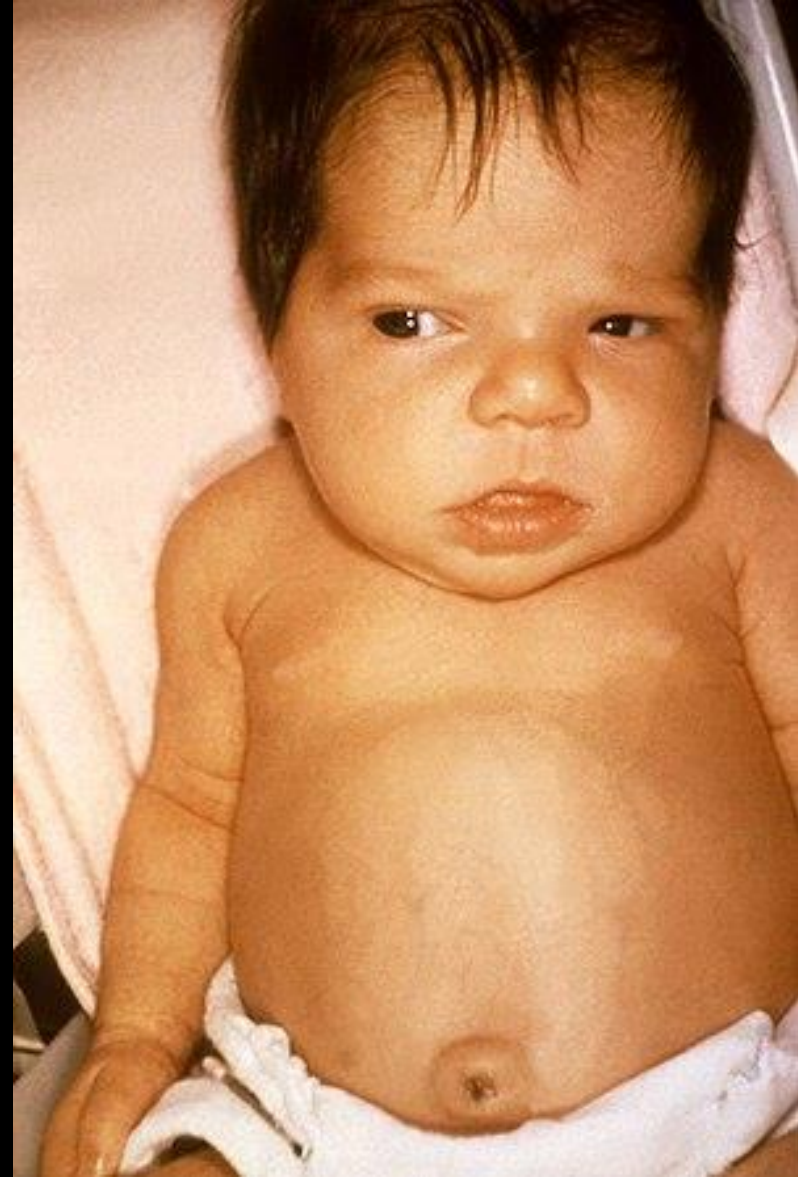
3- Decreased bilirubin conjugation

1. Physiologic jaundice
2. Crigler-Najjar syndrome
3. Gilbert syndrome
4. Hypothyroidism
5. Breast milk jaundice

more than 3wk



6week male infant with prolonged N.J
What is your diagnosis?
How do you manage ?



5- Impaired bilirubin excretion
Direct hyperbilirubinemia
Obstructive J

- Conjugated bilirubin level of >2 mg /dL ($34 \mu\text{mol/L}$) or $>20\%$ of total serum bilirubin level
- Baby passing dark urine and pale stools
 1. Biliary atresia or obstruction (*need early promptly DX*)
 2. Infection (Hepatitis)
 3. Metabolic disorder
 4. Chromosomal abnormality

Case scenario

Term male newborn, presented on the second day of life with jaundice

- What farther questions do you want to obtain?
- Clinical signs you want to elicit?
- How do you manage such neonate ?

Infants with multiple risk factors may develop an exaggerated form of physiologic jaundice in which the total serum bilirubin level may rise as high as 17 mg per dL (291 μ mol per L)

What is the commonest cause
of non hemolytic
hyperbilirubineamia?

Criteria for Physiological Jaundice

1. Onset
2. Rate of TSB increment (*5mg/dl/day*)
3. Level of TSB
4. Type of Bili
5. Duration (*Less than 2wks in term and 3wks in preterm Neonates*)

JAUNDICE AND BREAST FEEDING

- Early-Onset Breast feeding associated Jaundice or Breast feeding failure.
- Breast milk jaundice occurs later in the newborn period usually peaking in the sixth to 14th days of life. Why?

PATHOLOGIC JAUNDICE

All etiologies of jaundice beyond

- 1) Physiologic
- 2) breastfeeding or
- 3) breast milk jaundice

are considered pathologic.

Classification of neonatal jaundice

Physiologic jaundice

- Appears after 24 hours
- Maximum intensity by 4th-5th day in term & 7th day in preterm
- TSB levels within normal centiles for age in hours based on normogram.
- Clinically not detectable after 14 days
- Disappears without any treatment.

Pathologic jaundice

- Appears within 24 hours of age
- Increase of bilirubin $> 5 \text{ mg / dl / day}$ or at a rate of $>0.2 \text{ mg/dl/hr}$
- Serum bilirubin >95 percentile for age in hours based on normogram.
- Jaundice persisting after 14 days in fullterm babies.
- Stool clay / white colored and urine staining clothes yellow
- Direct bilirubin $> 2 \text{ mg / dl}$ or $>20\%$ of TSB.

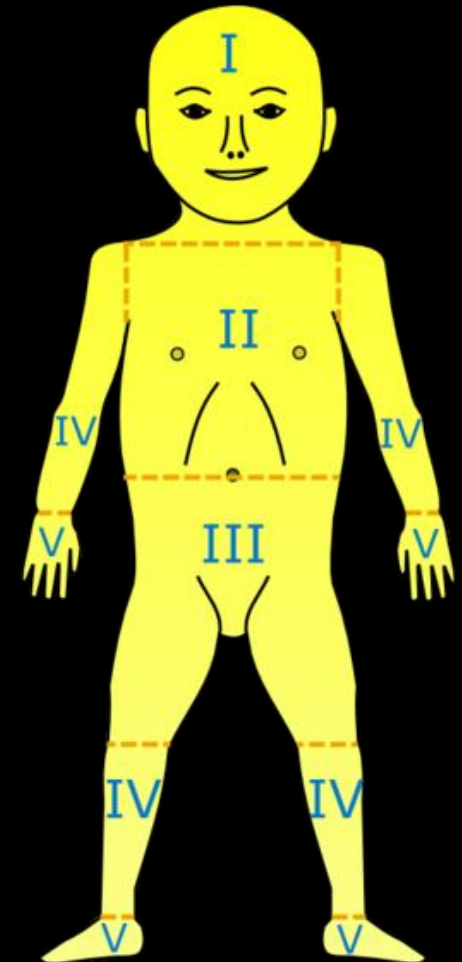






ABO Incompatibility

- ABO Incompatibility is the most common cause of hemolytic jaundice (10-20%)
- Most ABO antibodies are IgM (some have IgG)
- Commonly Anti A haemolysin occasionally group B
- Coombs positive ABO is more likely to cause hemolysis but less severe than Rhesus
- Hb. is usually normal or slightly reduced
- No hepato-splenomegaly

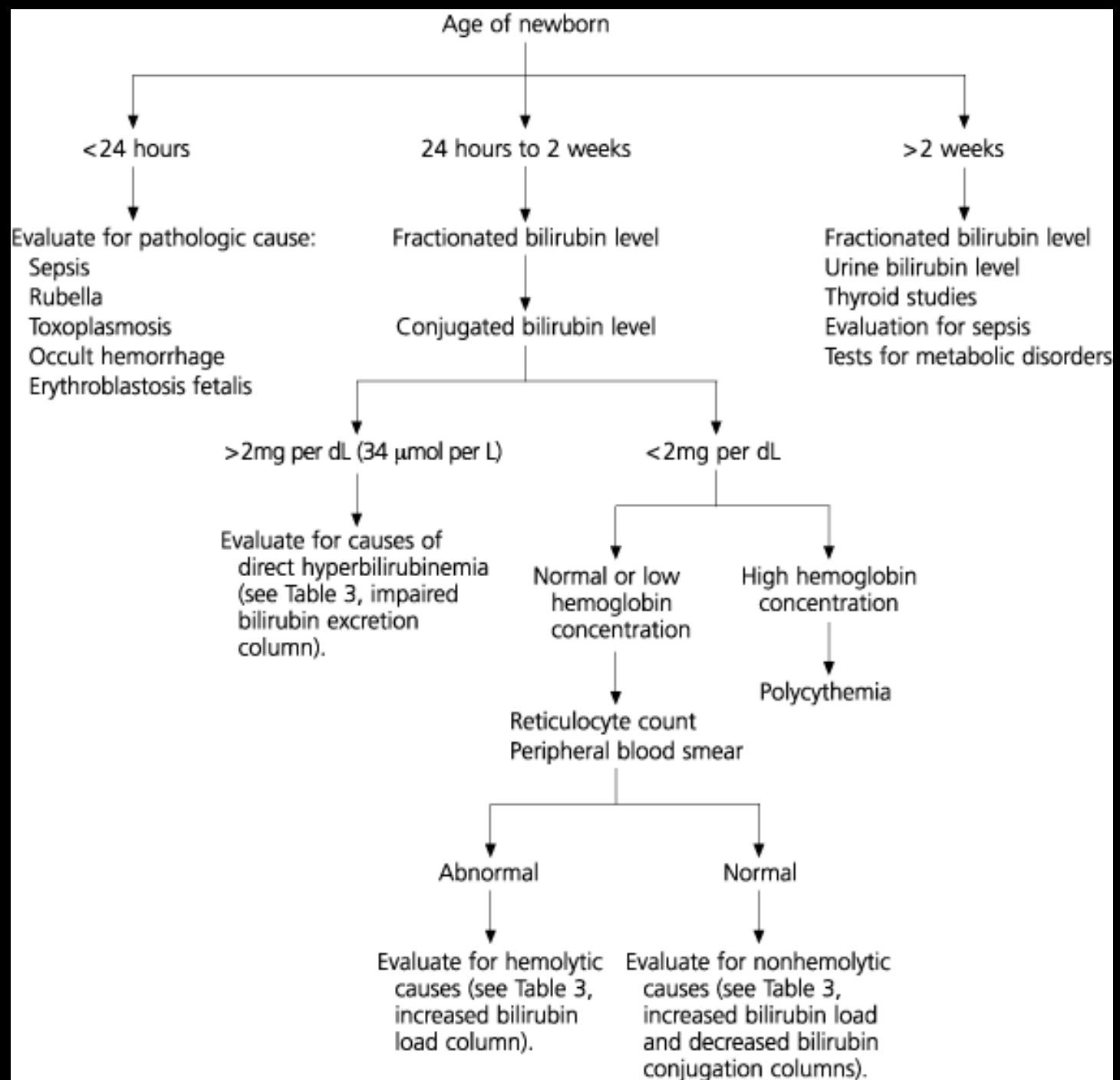
Diagnosis

- History
- Physical Examination
- Investigation



	Zone 1	Zone 1 = Face Bilirubin \cong 100 μ mol/L (6 mg/dL)
	Zone 2	Zone 2 = Upper body segment up to umbilicus Bilirubin \cong 150 μ mol/L (9 mg/dL)
	Zone 3	Zone 3 = Lower abdomen up to knee Bilirubin \cong 200 μ mol/L (12 mg/dL)
	Zone 4	Zone 4 = Lower leg up to ankle Bilirubin \cong 250 μ mol/L (15 mg/dL)
	Zone 5	Zone 5 = Involvement of sole and palm Bilirubin > 250 μ mol/L (>15 mg/dL)

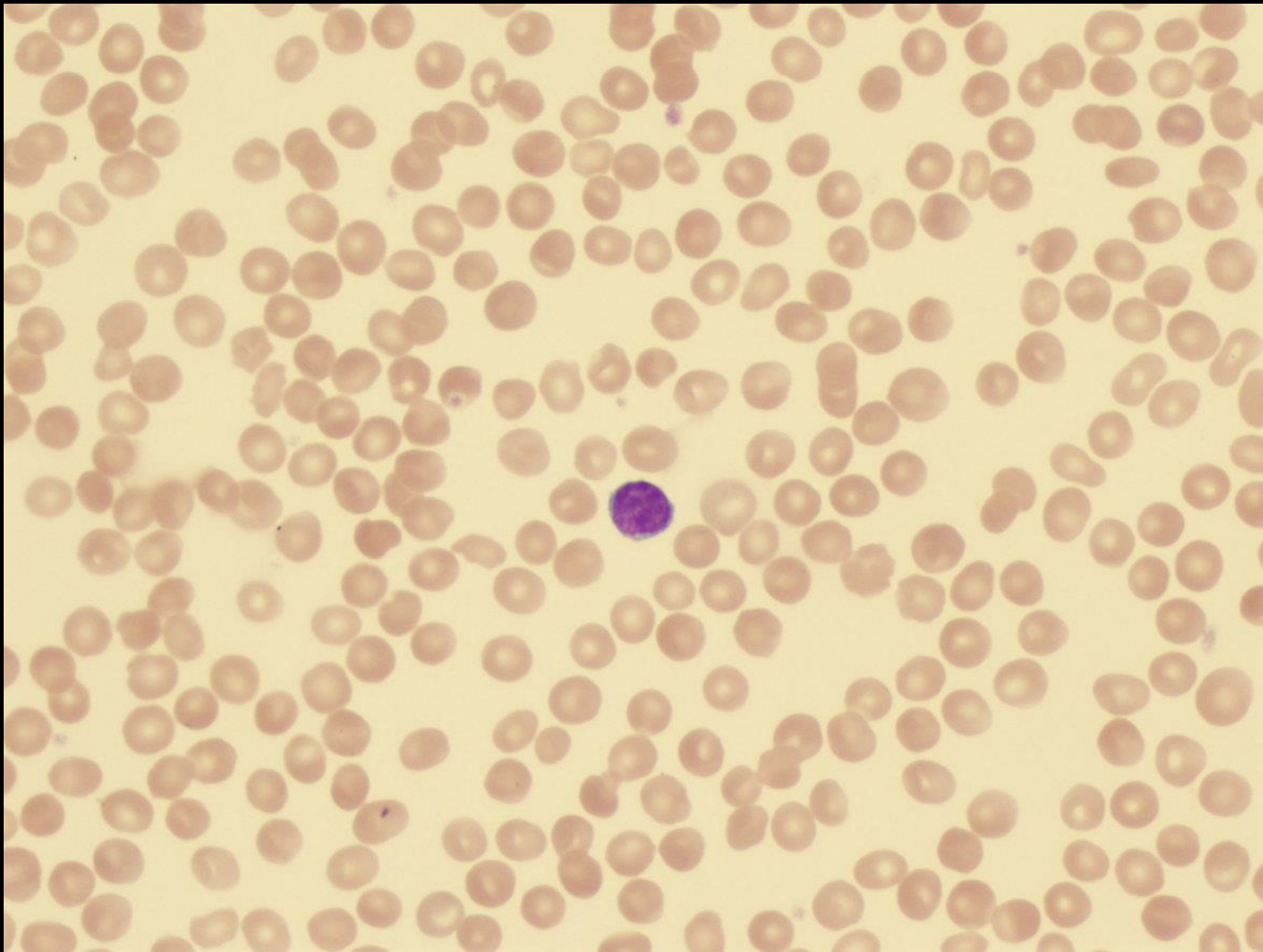
Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*:
www.accesspediatrics.com

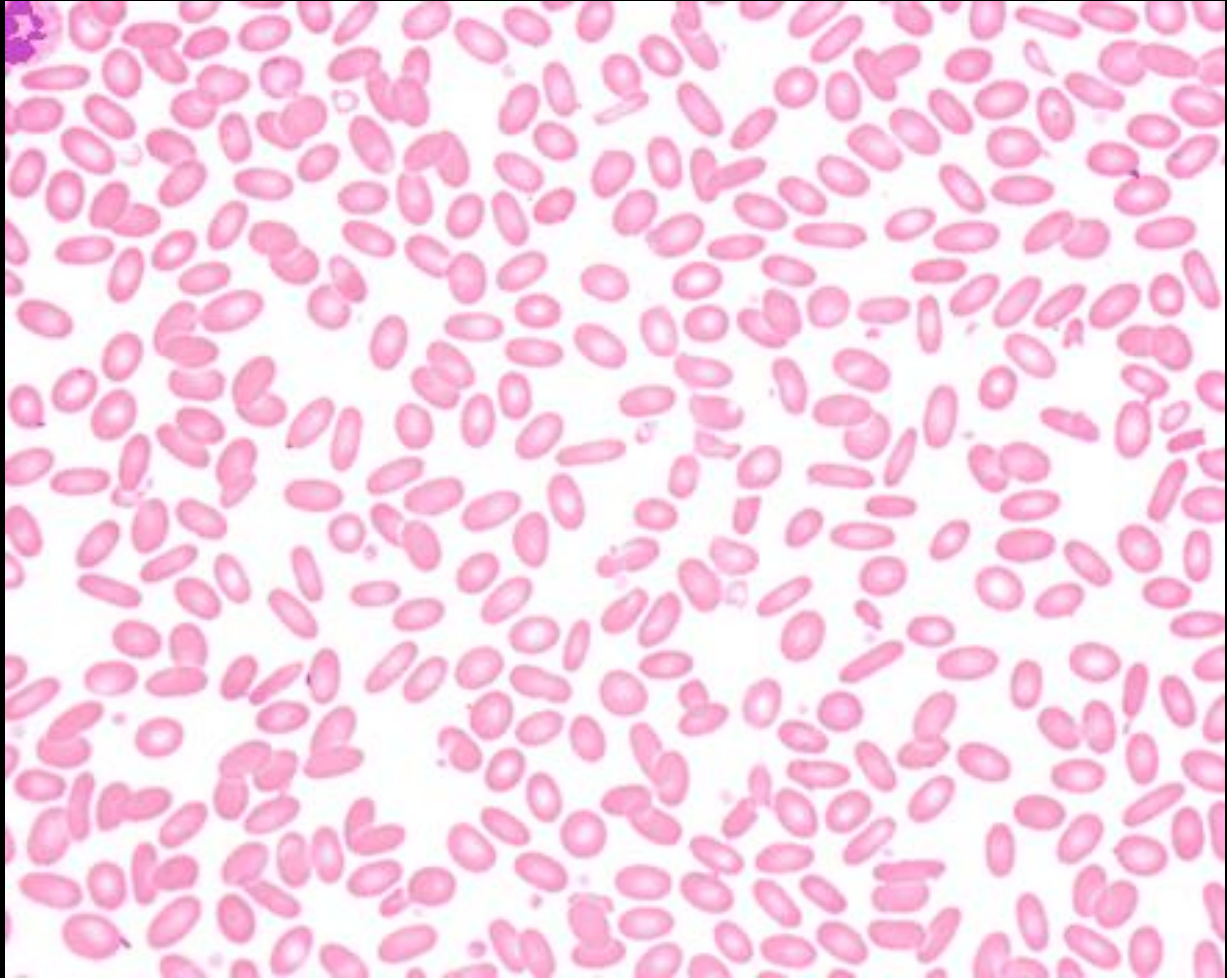


Laboratory Evaluation of Term Newborn with Jaundice

- TOTAL SERUM BILIRUBINE (TSB)
- Bilirubin fraction (conjugated OR non conj.)
- Blood group and comb's test
- CBC. Diff. Reticulocytes
- G6PD level
- Peripheral blood smear
- Blood and urine culture **IF** suspected
- Thyroid function & LFT



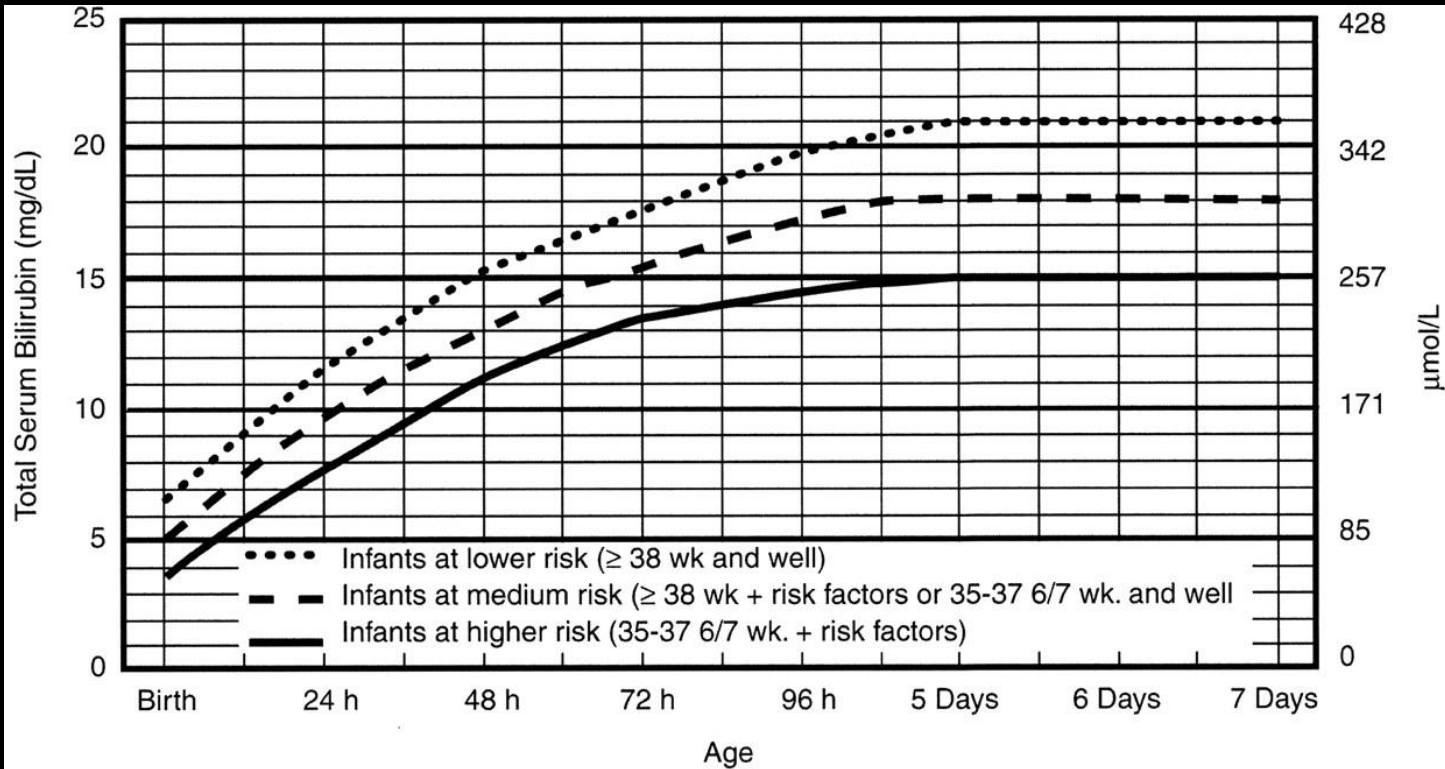




Management

- An increased incidence of kernicterus was found to be associated with total serum bilirubin levels above 20 mg per dL in the presence of hemolysis
- ✓ Hydration And Supportive measures
- ✓ Management guidelines now focus primarily on phototherapy as initial treatment.
- ✓ Aggressive guidelines recommending the use of exchange transfusion in all infants with significant hyperbilirubinemia

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



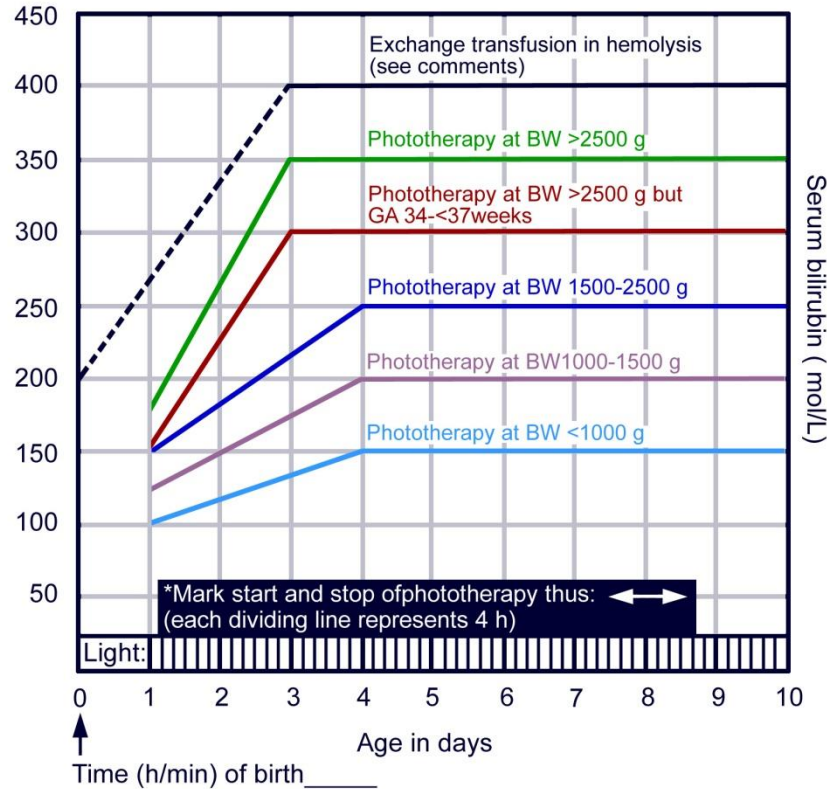
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin $< 3.0\text{g/dL}$ (if measured)
- For well infants 35-37 6/7 wk can adjust 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.

Guidelines for management

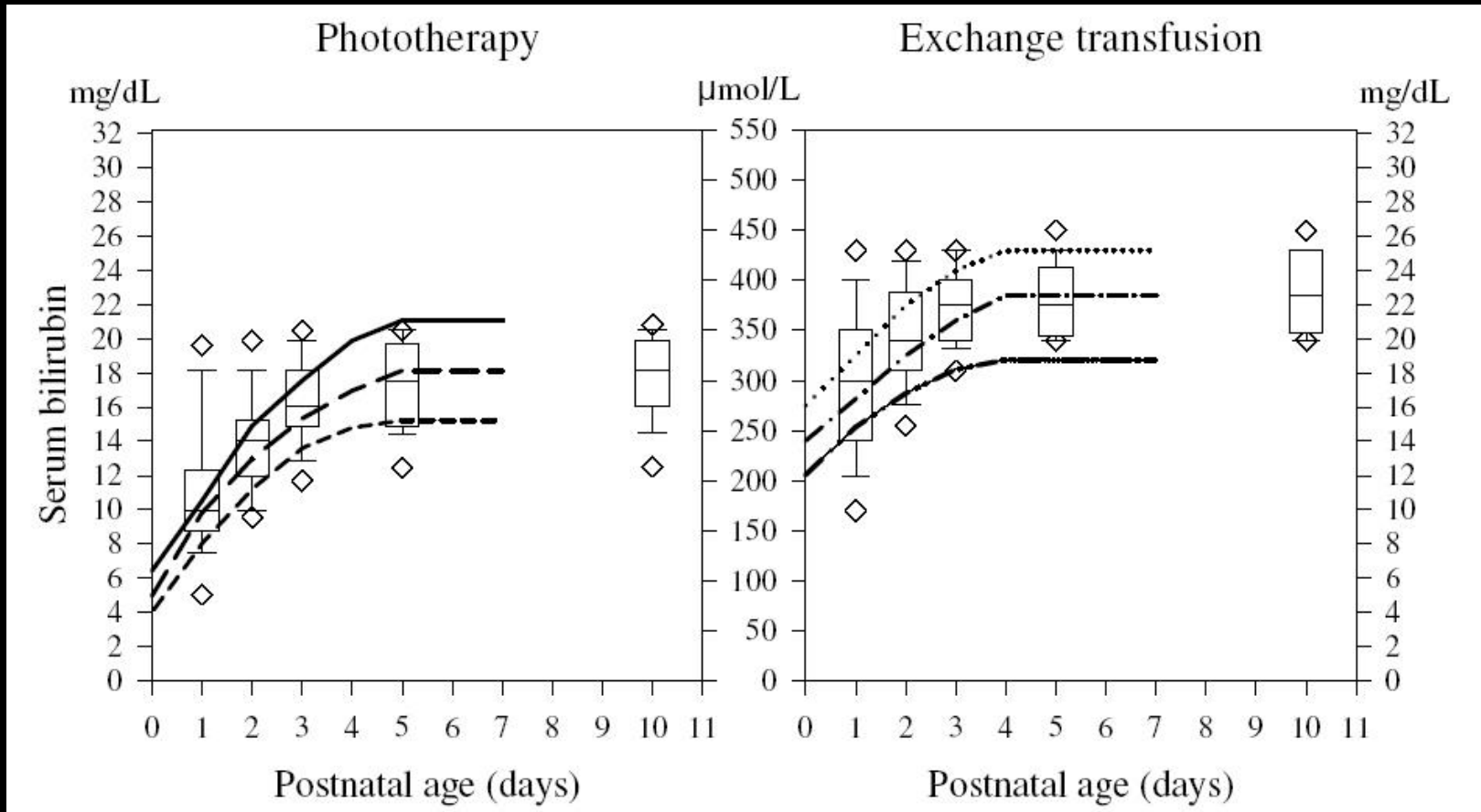
Norwegian guidelines for management of neonatal jaundice

Date and time (h/min) of birth ____/____ - ____ h ____ min ____
 Birthweight ____ g Maternal blood group ____
 Infant's blood group ____ DAT (Coombs) ____
 Gestational age (weeks) ____

Exchange transfusion in term infants without risk factors



AAP recommendations



PHOTOTHERAPY

light at blue or blue-green wavelengths converts the bilirubin molecule into a form that is either easier to excrete or is less toxic to the neonate

The effective spectrum for this process has been identified *in vitro* to peak at around 450nm (blue light)



PHOTOTHERAPY



Conjugated hyperbilirubinemia is never physiologic, and it may indicate the presence of a potentially serious underlying disorder

HOWEVER

ELEVATED CONJUGATED BILIRUBIN LEVELS ARE NOT DIRECTLY TOXIC TO BRAIN CELLS IN THE NEONATE.

The therapeutic effect of phototherapy depends on

1. the light energy emitted in the effective range of wavelengths
2. the distance between the lights and the infant
3. the surface area of exposed skin,
4. the rate of hemolysis

During phototherapy :

1. Cover the eyes and Genitals
2. Supplemental hydration
3. monitoring for side effects
4. Monitoring of bilirubin level

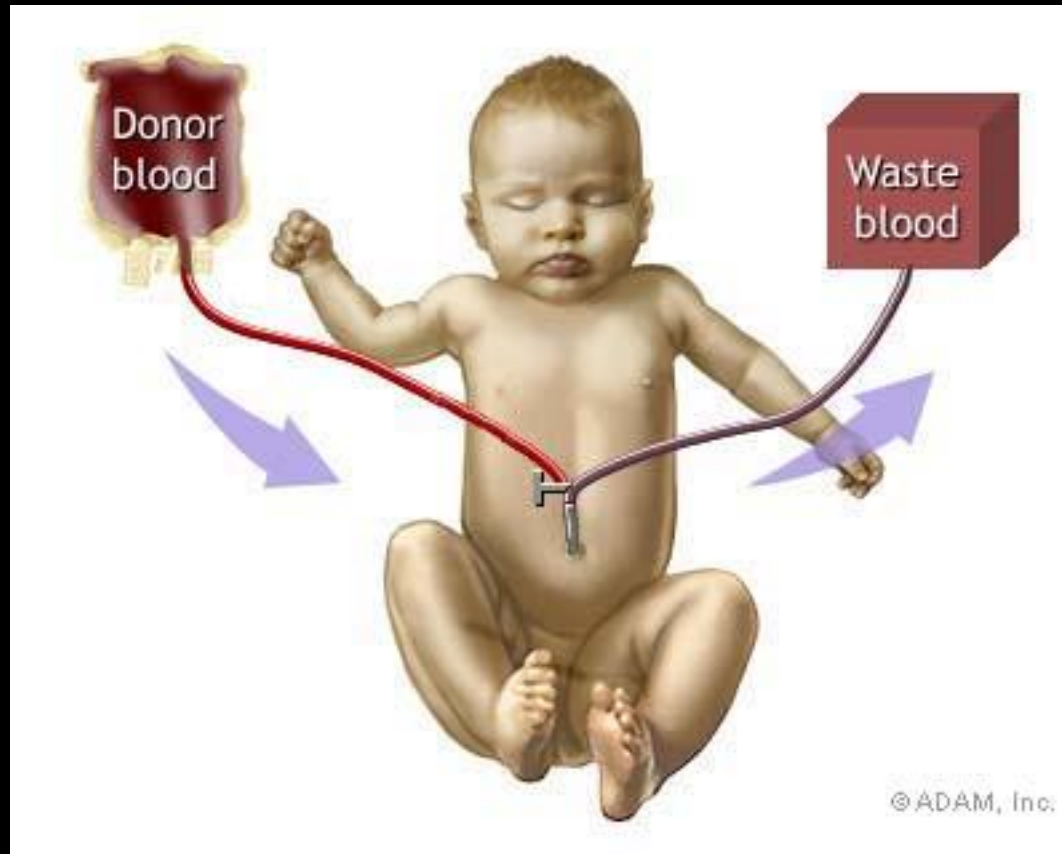
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Side effects of phototherapy

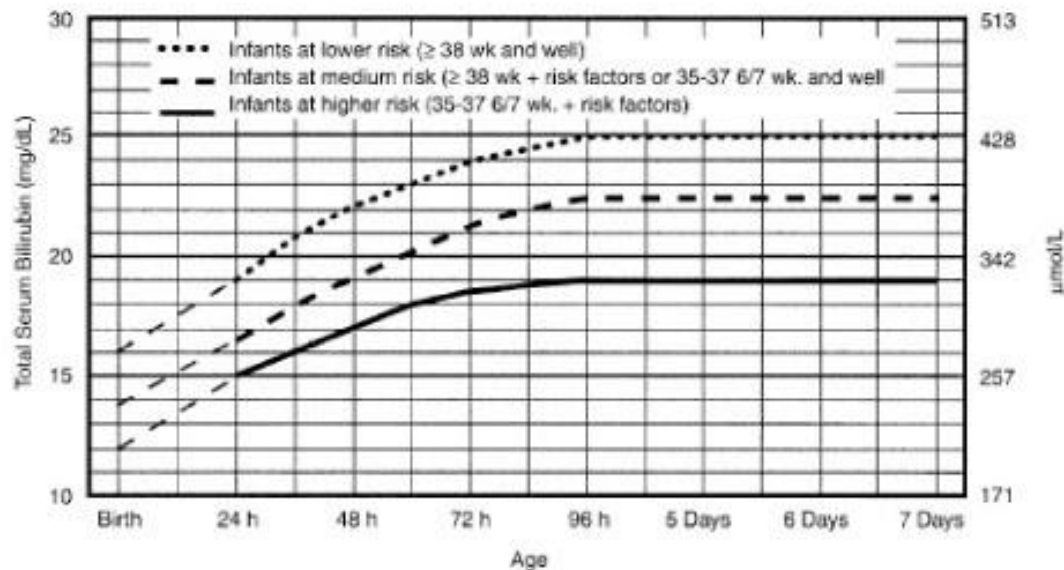
- **Increased insensible water loss:** Frequent Breast feeding.
- **Loose green stools:** weigh often and compensate with breast milk.
- **Skin rashes:** Harmless, no need to discontinue phototherapy.
- **Bronze baby syndrome:** occurs if baby has conjugated hyperbilirubinemia. If so, discontinue phototherapy.
- **Hypo or hyperthermia:** monitor temperature frequently.

EXCHANGE TRANSFUSION



<https://youtu.be/ywFFyzjqbJQ>
https://youtu.be/0aRHSgBF_Is

EXCHANGE TRANSFUSION

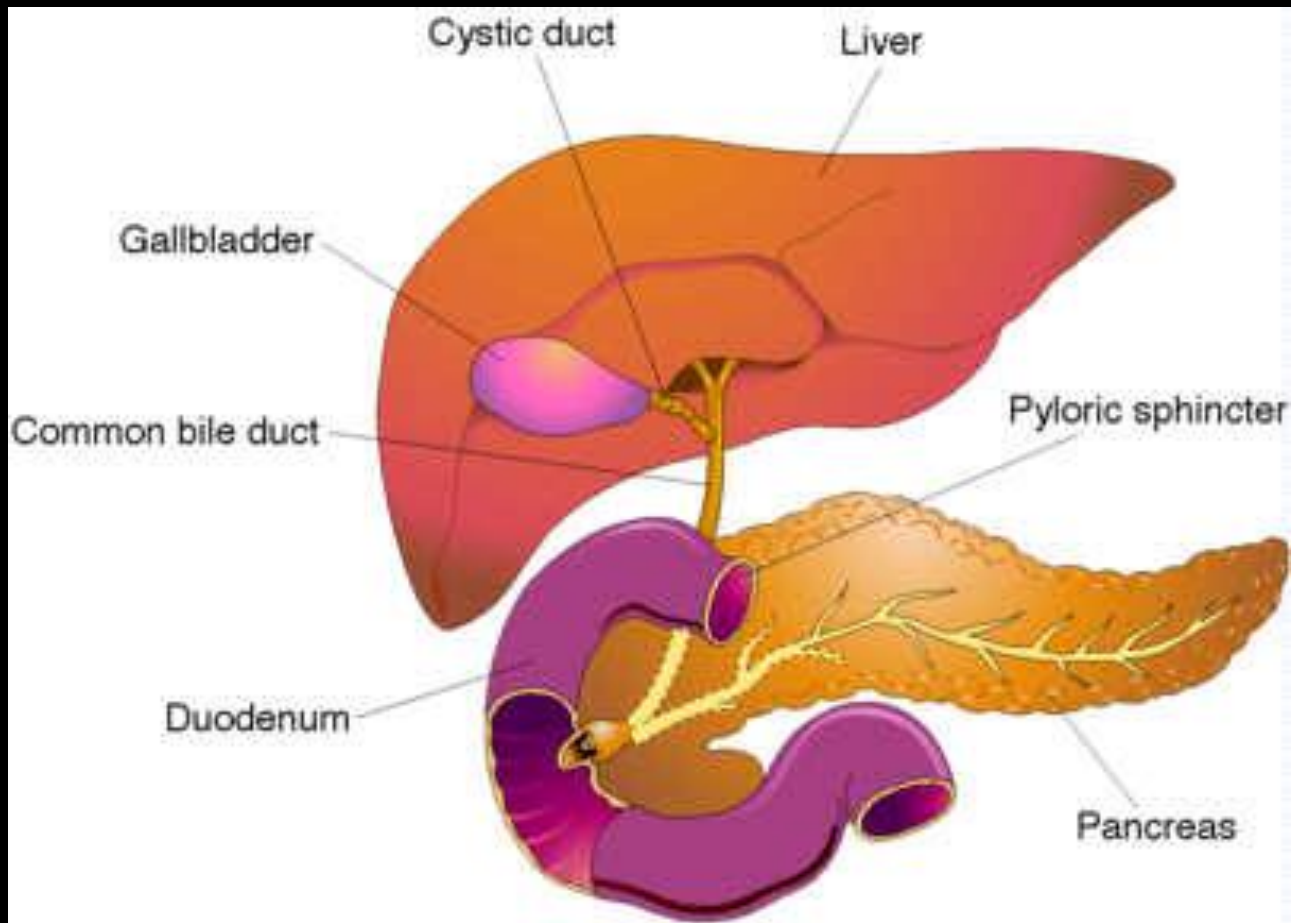


- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is $\geq 5\text{mg/dL}$ ($85\ \mu\text{mol/L}$) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis
- Measure serum albumin and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

OTHER

- Immunoglobulin
- Albumin transfusion
- Antibiotics
- Fluid and Electrolytes
- D5% water sun exposure NO
- Phenobarbital ?
- Mesoporphyrin Still under investigation

Conjugated Hyperbili





basal ganglia

hippocampus

Kernicterus

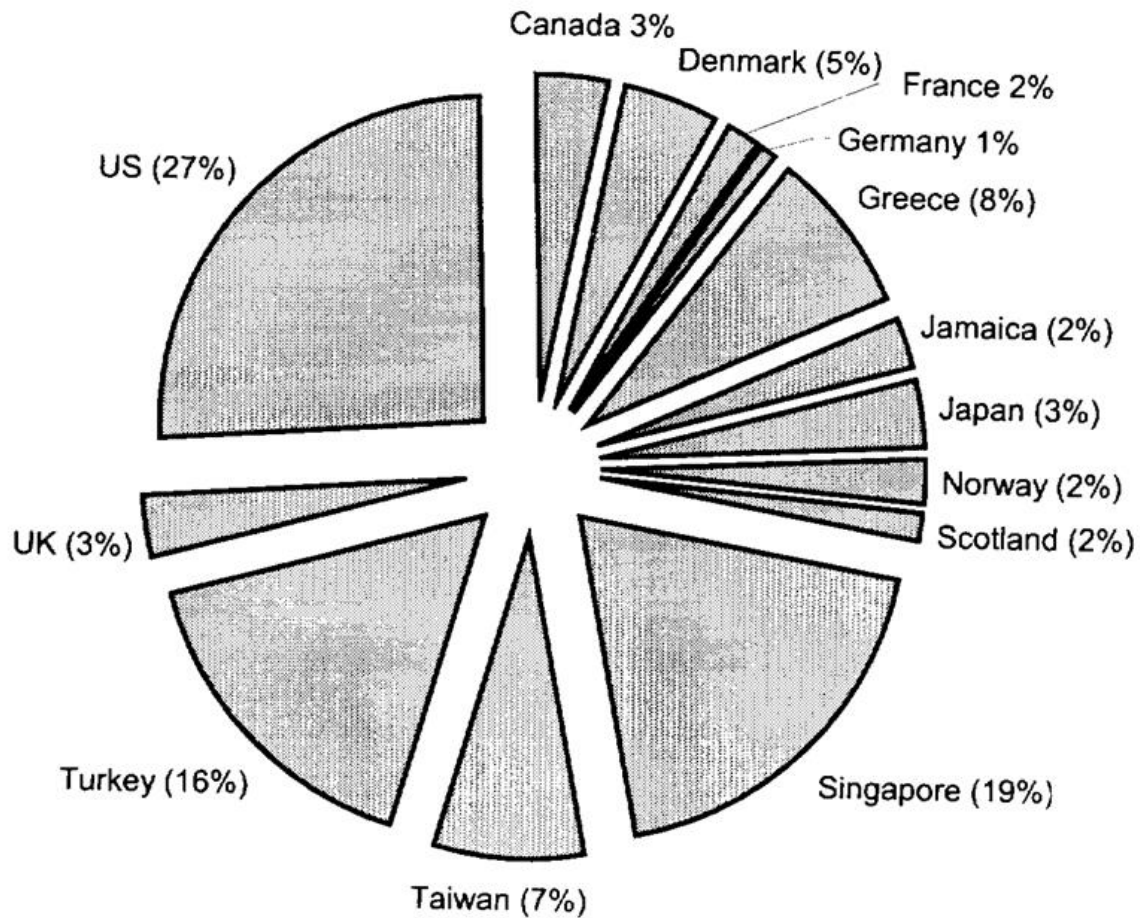
geniculate bodies

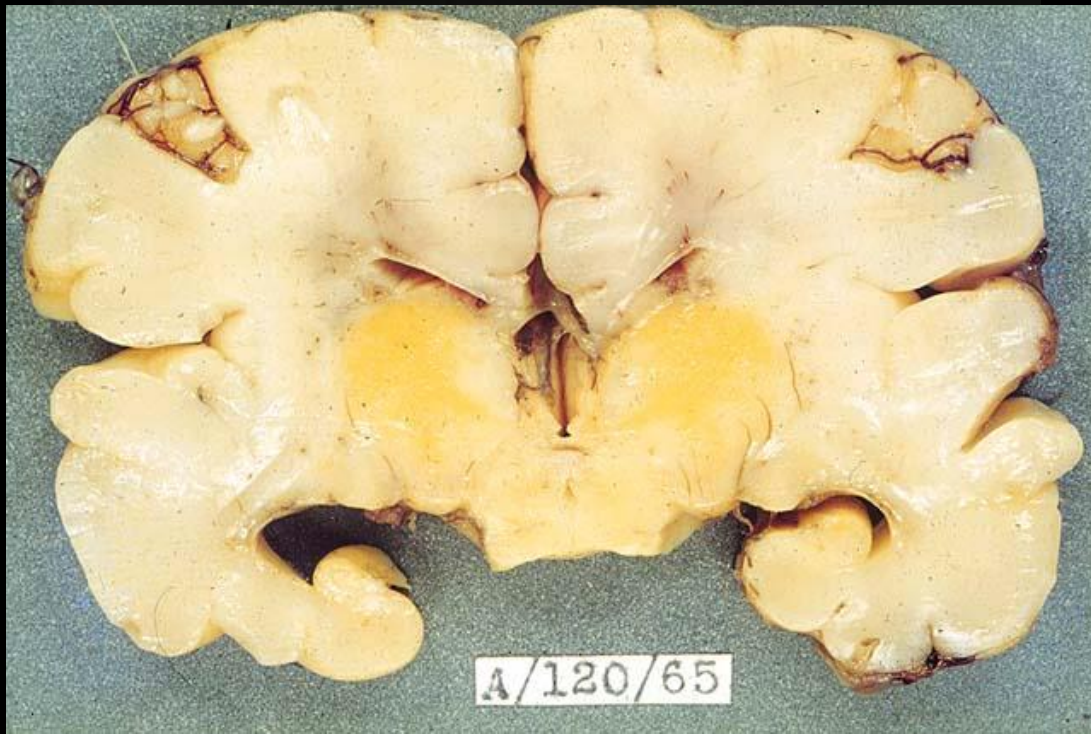
cranial nerve nuclei

Pathophysiology

- Bilirubin staining in the regions of the basal ganglia, hippocampus, substantia nigra, and brainstem nuclei
- Staining can occur in the absence of severe hyperbilirubinemia
- Characteristic patterns of neuronal necrosis

KERNICTERUS





Causes

- Severe hemolytic processes were identified 25%
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency was diagnosed in 22%
- galactosemia occurred in 2.5%
- Crigler-Najjar syndrome type I occurred in
- NO etiology for the severe hyperbilirubinemia was discovered in 73% of cases

Incidence

- Incidence of bilirubin levels $>30\text{mg/dl}$ (1/10,000)
- Do we have any registry in Saudi Arabia??
- All reported cases from Saudi literatures were secondary to Crigler Najjarr syndrome

Term Infant with Jaundice

- High pitched cry
- Arching of the baby's body into a bow
- Weakness, limpness, floppiness
- Difficulty nursing and/or sucking
- **WHAT IS THE TREATMENT ?**

KERNICTERUS

- Early symptoms-acute bilirubin encephalopathy
 - ✓ poor feeding
 - ✓ abnormal cry
 - ✓ hypotonia,
- Intermediate phase
 - ✓ -stupor, irritability, hypertonia
- Late
 - ✓ shrill cry, no feeding, opisthotonus, apnea, seizures, coma, death

Clinical Spectrum: Adverse Effects of Newborn Jaundice

Acute Bilirubin Encephalopathy

Death: respiratory failure

Chronic Post-icteric Sequelae (Kernicterus)



Auditory Neuropathy (isolated)

Subtle manifestations (extra-pyramidal and central posturing disorders) *suspected but not yet proven*

Bilirubin Induced Neurologic Dysfunction (BIND)

KERNICTERUS

➤ Late sequelae can include

- ✓ gaze abnormalities
- ✓ feeding difficulties
- ✓ dystonia
- ✓ incoordination
- ✓ choreoathetosis
- ✓ sensorineural hearing loss
- ✓ painful muscle spasms

What is bilirubin level ?

- Over 120 cases kernicterus documented since 1990
- majority term, breastfed
- Majority of those had levels in high 30s to 40s.
- Lowest level recorded in case series of 111 from 1991-2002 was 20.7
- the mean was 38.
- Many cases had no planned follow up and had been discharged early (<48 hours).

Risk Factors

- ASPHYXIA
- ACIDOSIS
- SEPSIS
- HYPOALBUMINEMIA
- YOUNG GESTATIONAL AGE
- LOW BIRTH WT
- HYPERTHERMIA
- RESPIRATORY DISTRESS



Magnetic resonance imaging of the head. Hyperintense basal ganglia lesions on T2-weighted images

Prevention

- Recommend:

- Promote and support successful breastfeeding.
- Universal systematic pre-discharge assessment.
- Provide targeted follow-up based on the risk.
- Track outcome for timely treatment to prevent excessive hyperbilirubinemia and possibly, kernicterus.

AAP 2004: RECOMMENDATIONS

- I. Primary Prevention: lactation support
- II. Risk assessment for severe hyperbilirubinemia:
- III. Interpretation of TSB values
- IV. Cause of jaundice/hyperbilirubinemia.
- V. Pre-discharge risk assessment
- VI. Hospital policies and procedures
- VII. Treatment

Summary

- Bilirubin physiology
- Prevent neurotoxicity
- Identify and treat illness associated with excess production, impaired conjugation or inadequate elimination
- Combination of therapy

MCQs

A 3-day old full term infant with hemolytic disease of the newborn due to Rh incompatibility has a serum indirect bilirubin concentration of 33 mg/dL. You perform an exchange transfusion with no further elevations of bilirubin above 19 mg/dL. Among the following, the **MOST** appropriate study to use to follow up on this infant is:

- A. Another Coomb's test
- B. Brainstem auditory evoked response
- C. Computed tomography of the head
- D. Hemoglobin electrophoresis
- E. Indirect retinoscopy

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7-day old breastfeed infant born at term has had decreased appetite, irritability and vomiting for 24 hours. On Physical examination, the infant appears listless. Respiratory Rate: 40/min, Heart Rate : 160/min, and blood pressure: 68/38 mm Hg. The skin and sclera are icteric but no other abnormalities noted. Laboratory studies reveal: Hemoglobin: 12 gm/dL. Urinalysis is negative for reducing substances. Of the following, the **MOST** likely diagnosis is:

- A. Bacterial sepsis
- B. Blood group incompatibility
- C. Breast milk jaundice
- D. Hypothyroidism
- E. Intrauterine infection

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A 3-day old , breast fed infant develops jaundice. The serum bilirubin level is 12 mg/dL with a direct bilirubin component of 0.5 mg/dL. The infant's mother asks whether the jaundice might be associated with breastfeeding. Which of the following statements regarding hyperbilirubinaemia associated with breast feeding is **TRUE**:

- A. Indirect hyperbilirubinaemia associated with breast feeding may occur as early as the first day of life.
- B. Water supplementation in breast-fed infants will significantly reduce serum concentrations of indirect bilirubin
- C. Hyperbilirubinemia associated with breast feeding may persist for 8 to 12 weeks
- D. Decreased clearance of bilirubin may play a role in breast feeding jaundice, breast milk jaundice.

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Of the following conditions, which is the **MOST** consistent with findings of mild cholestasis without evidence of biliary atresia?

- A. Lead intoxication
- B. Chronic hemolytic disease
- C. Alpha – antitrypsin deficiency
- D. Breast milk jaundice
- E. Crigler-Najjar Syndrome

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A 4-week old, breast-fed boy has had mild jaundice since birth. Weight gain has been poor. The urine is light yellow-brown, and the stools are pale yellow-green in color. At this point, the **MOST** appropriate next step in management is to:

- A. Observe the child clinically for 2 to 4 weeks
- B. Stop breastfeeding and re-examine the child in 7 to 10 days
- C. Obtain a cholecystogram
- D. Obtain a total and direct serum bilirubin levels and studies of liver function

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You are presenting to 5th year medical student on Neonatal jaundice . Which statement is True ?

- A. Is normally excreted in the urine following its conjugation to glucuronic acid
- B. Achieve high blood levels due to haemolysis associated with glucose-6-phosphate dehydrogenase deficiency
- C. Must be prevented from reaching 340 $\mu\text{mol/L}$ in well term babies by use of exchange transfusion if necessary
- D. Results from the oxidation of haemoglobin by the enzyme glucuronyl transferase

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- Neonatal jaundice is associated with all of the following except :

A. prematurity

B. cystic fibrosis

C. Gilbert's syndrome

D. breast milk feeding

E. neonatal thyrotoxicosis

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A term baby is found to have serum bilirubin of 250 $\mu\text{mol/l}$ at 18 hours of age. Which of the following is true?

- A. Physiological jaundice is the most likely cause
- B. An urgent conjugated bilirubin level is indicated
- C. It is unlikely to be due to haemolysis
- D. The infants blood group and Coombs test are the most important investigations
- E. There is no indication to start phototherapy

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In an infant who appeared healthy at birth, vomiting and diarrhea developed at 1 week of age. She gained weight poorly despite a change from breast milk to infant formula feeding at 2 weeks of age. At 3 weeks of age, she is brought to the emergency department where she is found to be lethargic and to have hepatomegaly. *Of the following, the most likely diagnosis is*

- A) Inspissated bile syndrome
- B) Crigler-Najjar Syndrome
- C) Galactosemia
- D) Gilbert Syndrome
- E) Dubin-Johnson Syndrome

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- C) **Galactosemia**
- D) Gilbert Syndrome
- E) Dubin-Johnson Syndrome

6 week old infant presented with early signs of kernicterus. His blood work showed high indirect non hemolytic hyperbilirubinemia. The MOST likely diagnosis :

- A. G6PD
- B. Physiological Jaundice
- C. Crigler Najjer Syndrome
- D. Alpha 1 – antitrypsin

6 week old infant presented with early signs of kernicterus. His blood work showed high indirect non hemolytic hyperbilirubinemia. The MOST likely diagnosis :

A. G6PD

B. Physiological Jaundice

C. Crigler Najjer Syndrome

D. Alpha 1 – antitrypsin

An apparently term infant who was born at home was noted to be very yellow on the fifth postnatal day. He has no symptoms or clinical signs of bilirubin encephalopathy. His bilirubin concentration is 36.5 mg/dL (624.2 μ mol/L), with a direct bilirubin measurement of 1.5 mg/dL (26.7 μ mol/L). You draw blood to investigate the cause of the hyperbilirubinemia and place the infant under intense phototherapy. Of the following, the MOST appropriate treatment plan is:

- A. administration of a bolus of 20 mL/kg normal saline,
- B. administration of intravenous fluids with 10% glucose at rate of 150 mL/kg per day
- C. administration of salt-poor albumin (1g/kg) over the next hour,
- D. initiation of an exchange transfusion as soon as possible

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