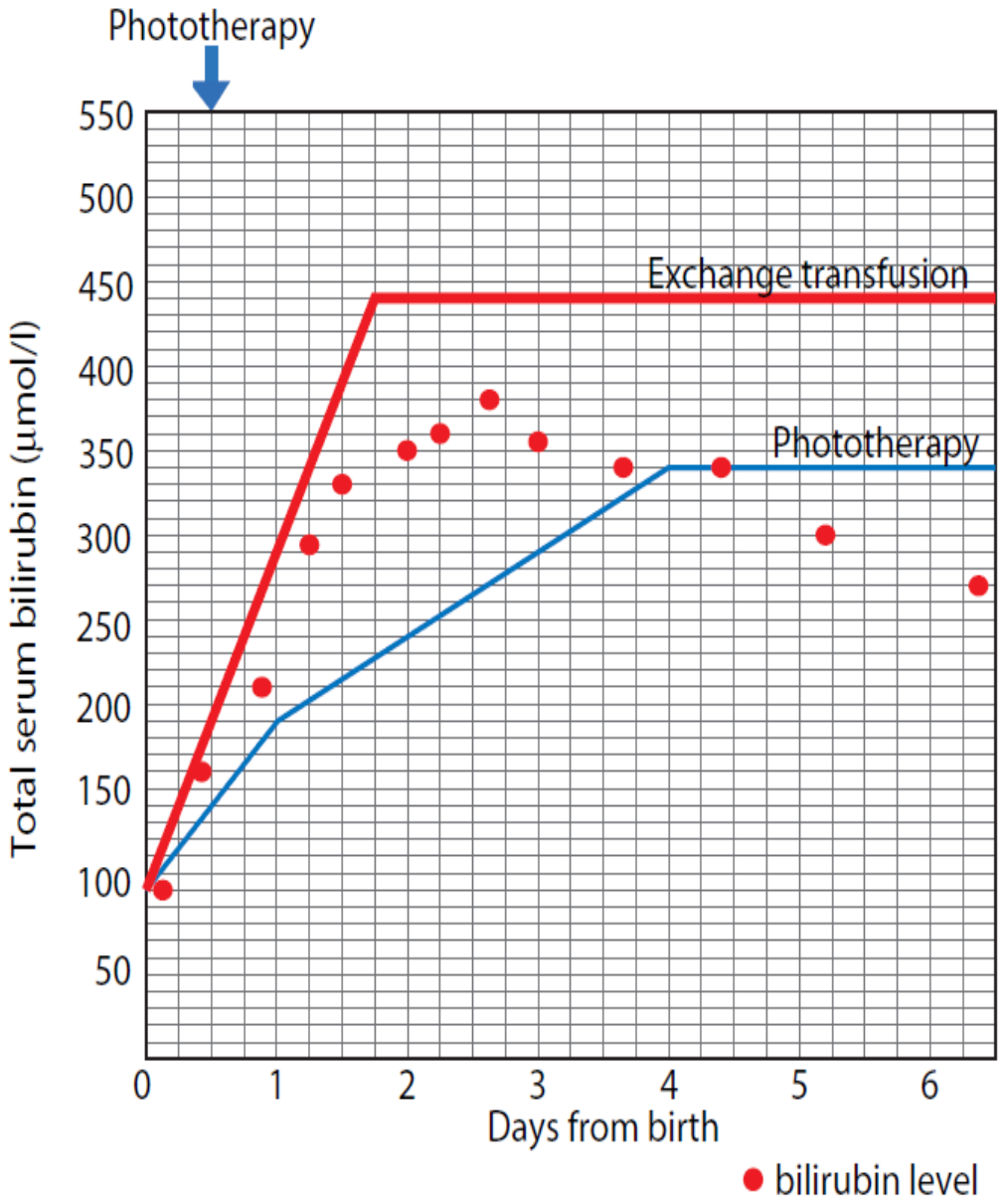
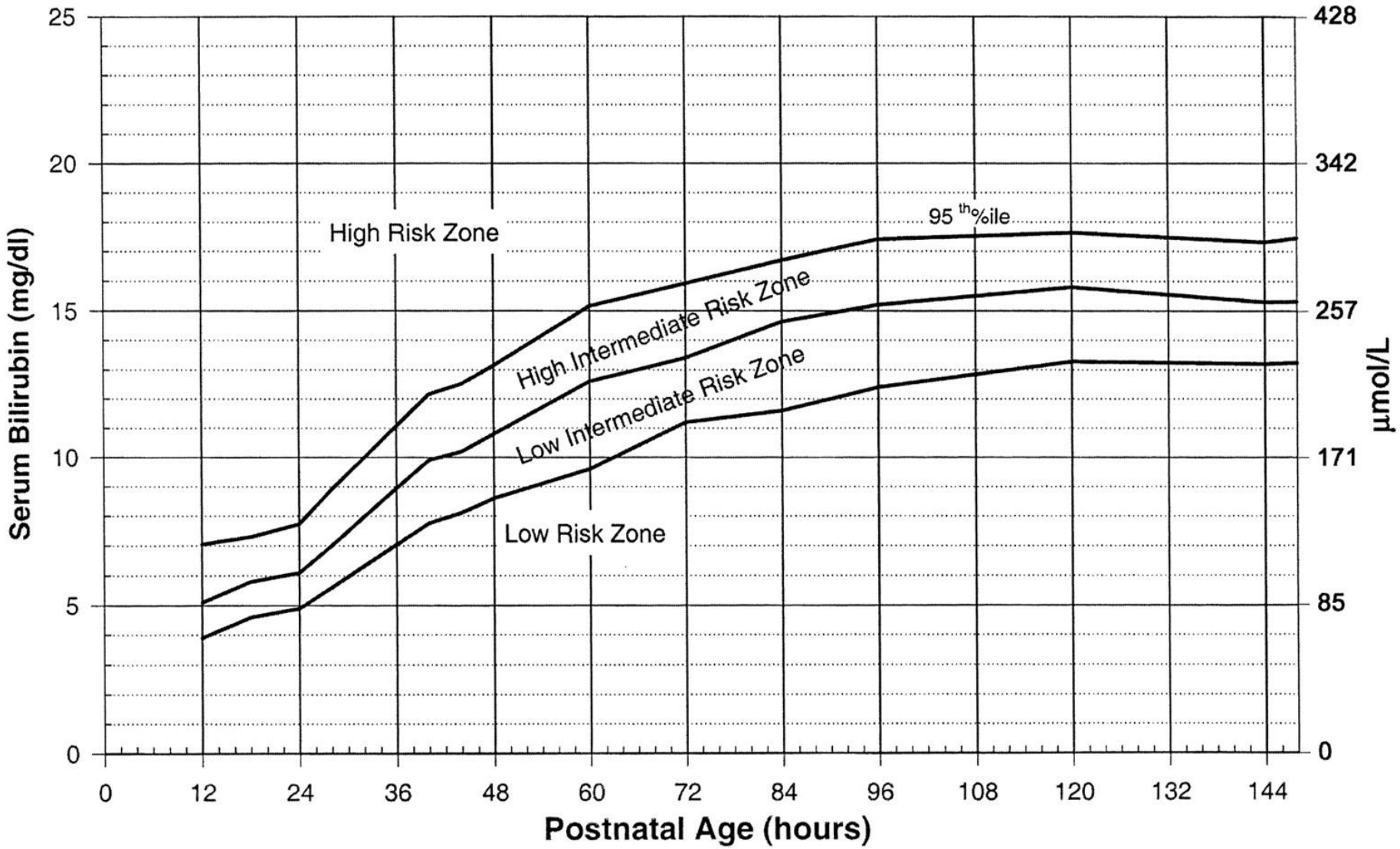
A term baby was noted to be markedly jaundiced at first day of life. Her bilirubin was 170 mmol/l, direct antibody test positive, maternal blood group O +ve, & her blood group was B +ve. A Dx of ABO incompatibility was made. She was started on intensive phototherapy & her bilirubin closely monitored & plotted on a bilirubin chart for term infants .Her condition resolved with phototherapy, so Ig therapy & exchange transfusion were not required.

Bilirubin chart of bilirubin level & time from birth. It also shows the threshold for starting phototherapy & need to do an exchange transfusion. Plotting the bilirubin values, as shown for this infant with ABO incompatibility, allows the rate of rise to be readily checked & if preparation needs to be made for an exchange transfusion.

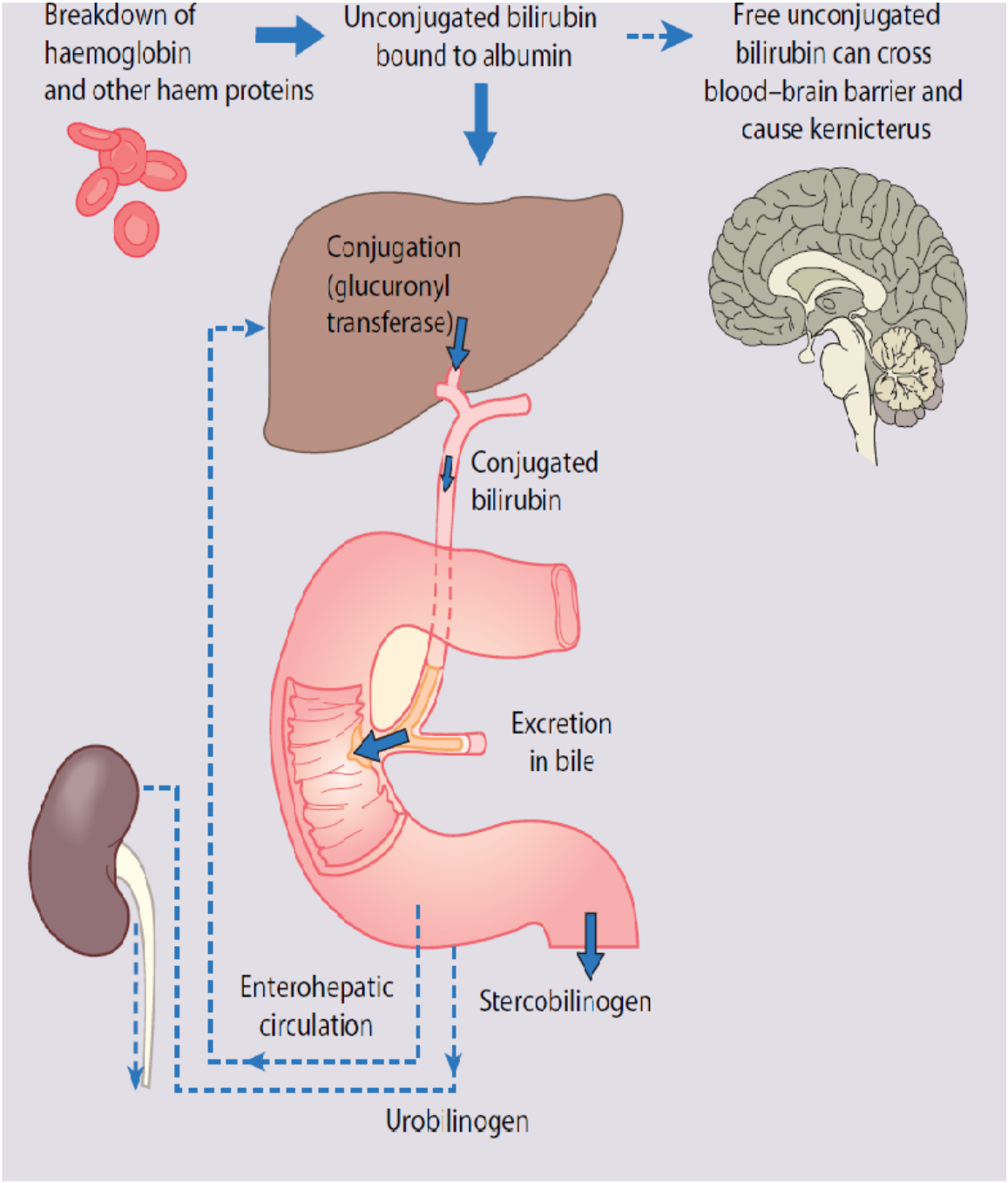
(Adapted from NICE: ***National Institute for Health and Care Excellence guideline: Jaundice in newborn babies under 28 days.*** March 2014 https://www.nice.org.uk/guidance/qs57/chapter/introduction)

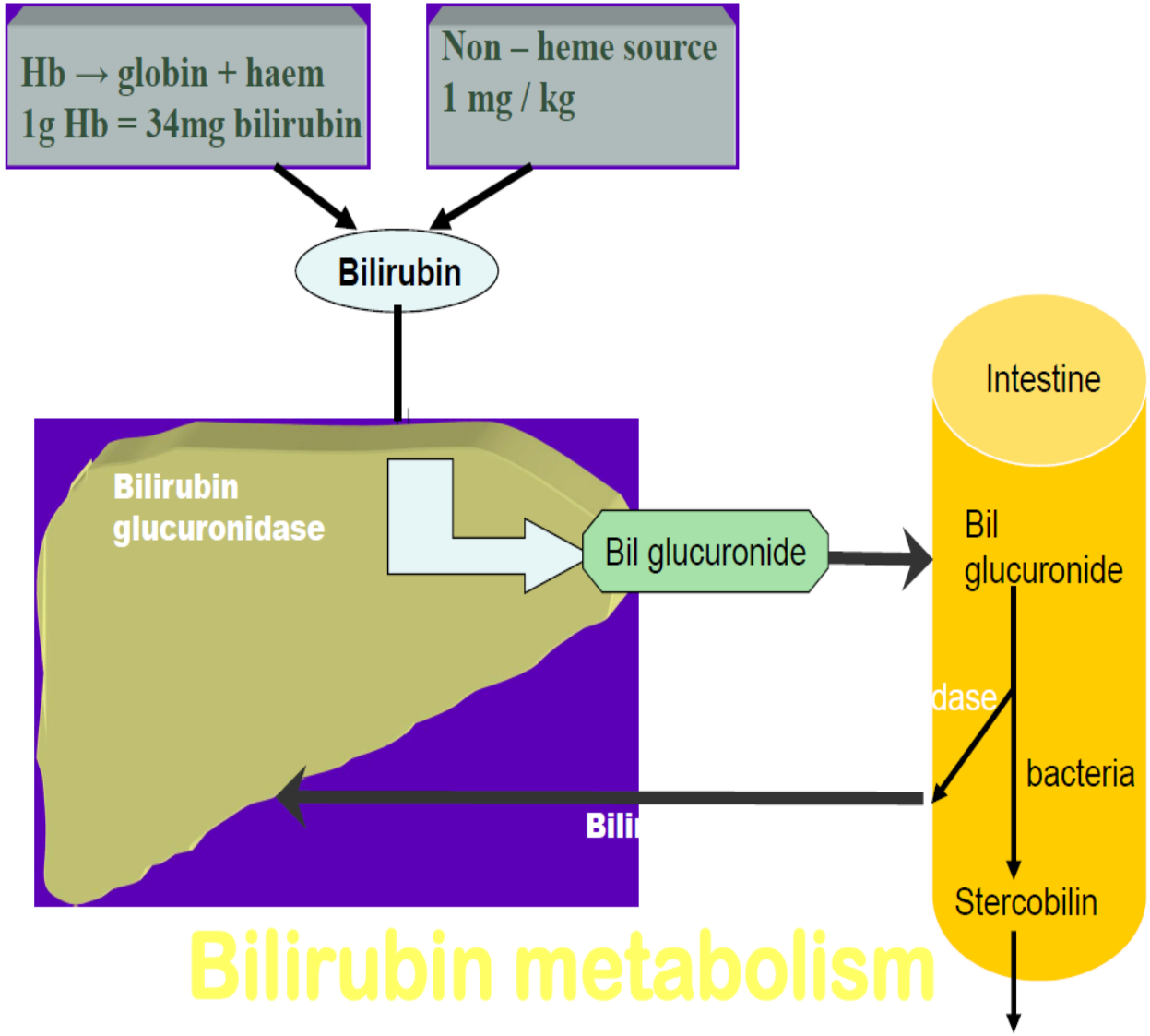



Serum Bilirubin (mg/dl)
25
20
15
10
5
0
428
342
257
171
85
0
µmol/L
High Risk Zone
95 th%ile
High Intermediate Risk Zone
Low Intermediate Risk Zone
Low Risk Zone
0
12
24
36
48
60
72
84
96
108
120
132
144
Postnatal Age (hours)

The breakdown product of Hb is ***unconjugated bilirubin*** which is *insoluble in water* but soluble in lipids. It is carried in the blood bound to albumin. free unconjugated bilirubin can cross the BBB as it is lipid soluble. *Unconjugated bilirubin* bound to albumin is taken up by the liver & conjugated by glucuronyl transferase to ***conjugated bilirubin*** ,which is water soluble & excreted in bile into the gut & then as *stercobilinogen& urobilinogen.*

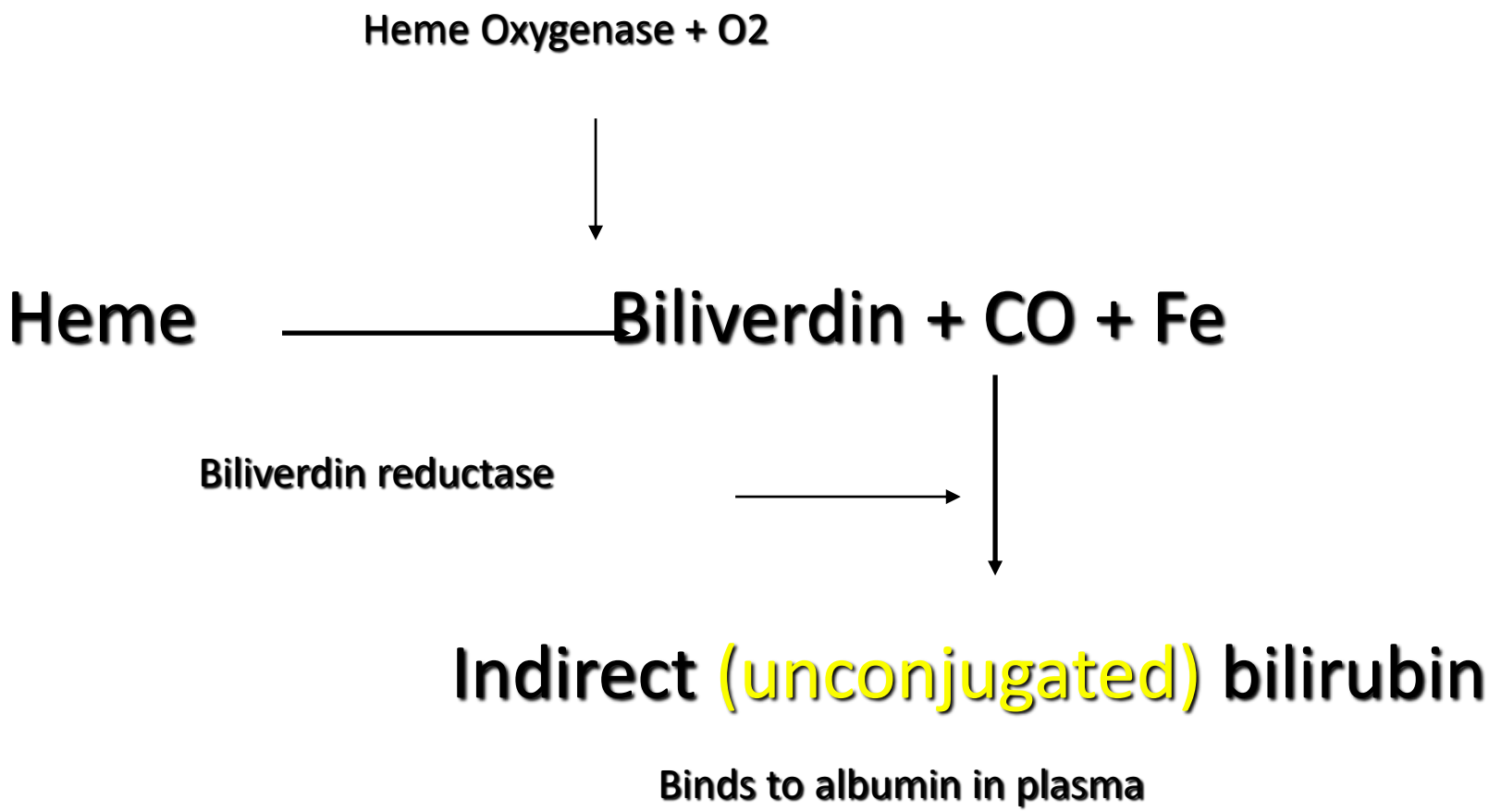
Some bilirubin in the gut is converted to unconjugated bilirubin & reabsorbed via the EHC & metabolized in the liver.



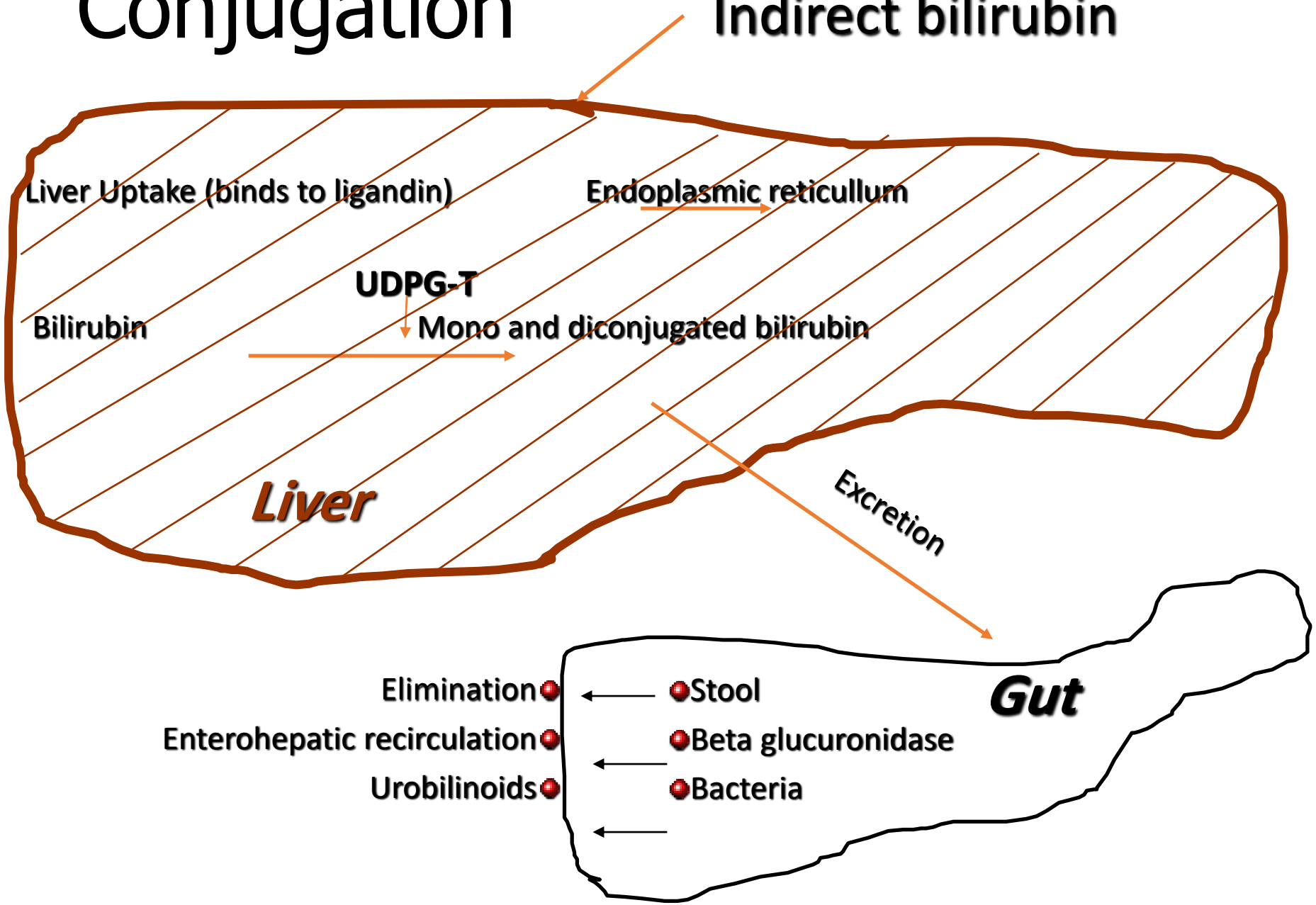


Bilirubin metabolism

Metabolism

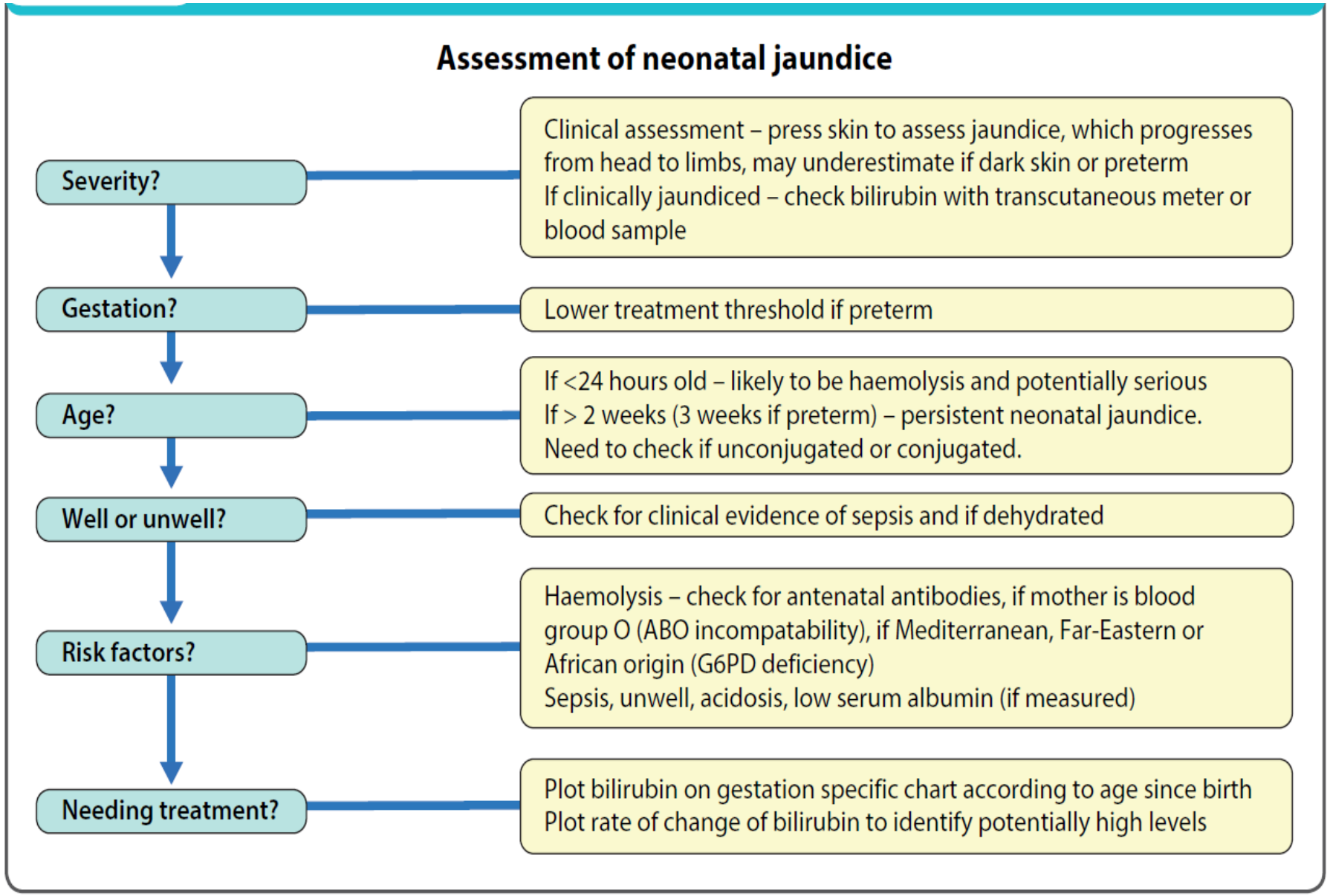

Heme Oxygenase + O2
Heme
Biliverdin + CO + Fe
Biliverdin reductase
Indirect (unconjugated) bilirubin
Binds to albumin in plasma

Conjugation

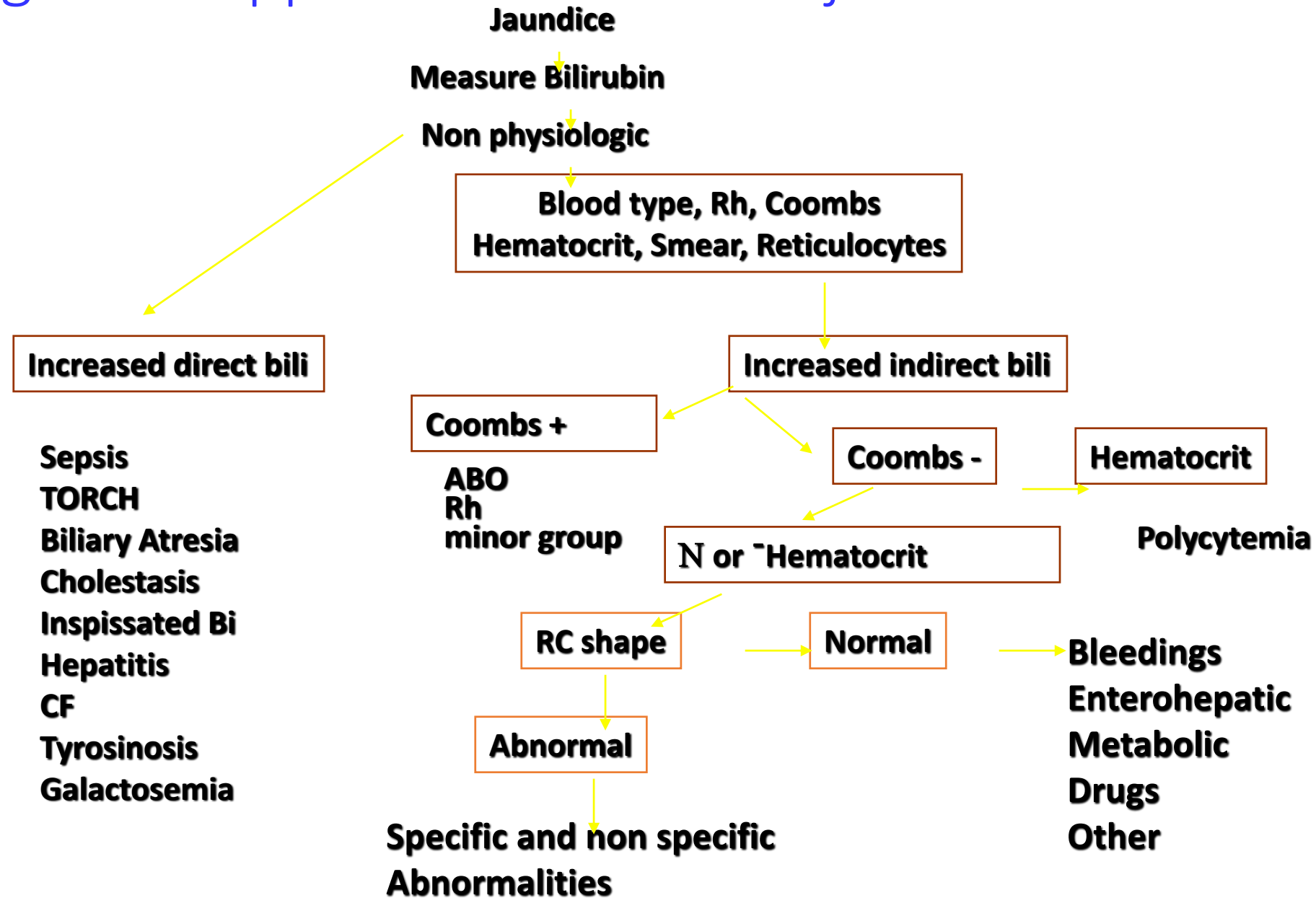


CAUSES OF NEONATAL JAUNDICE

Jaundice starting at <24 h of age	Haemolytic disorders: - Rhesus incompatibility - ABO incompatibility - G6PD deficiency - Spherocytosis, pyruvate kinase deficiency Congenital infection
Jaundice at 24 h to 2 weeks of age	Physiological jaundice Breast milk jaundice Infection, e.g. urinary tract infection Haemolysis, e.g. G6PD deficiency, ABO incompatibility Bruising Polycythaemia Crigler–Najjar syndrome
Jaundice at >2 weeks of age	Unconjugated: - Physiological or breast milk jaundice - Infection (particularly urinary tract) - Hypothyroidism - Haemolytic anaemia, e.g. G6PD deficiency - High gastrointestinal obstruction, e.g. pyloric stenosis Conjugated (>25 μmol/l): - Bile duct obstruction - Neonatal hepatitis


Assessment of neonatal jaundice
Severity?
Clinical assessment – press skin to assess jaundice, which progresses from head to limbs, may underestimate if dark skin or preterm
If clinically jaundiced – check bilirubin with transcutaneous meter or blood sample
Gestation?
Lower treatment threshold if preterm
Age?
If <24 hours old – likely to be haemolysis and potentially serious
If > 2 weeks (3 weeks if preterm) – persistent neonatal jaundice.
Need to check if unconjugated or conjugated.
Well or unwell?
Check for clinical evidence of sepsis and if dehydrated
Risk factors?
Haemolysis – check for antenatal antibodies, if mother is blood group O (ABO incompatability), if Mediterranean, Far-Eastern or African origin (G6PD deficiency)
Sepsis, unwell, acidosis, low serum albumin (if measured)
Needing treatment?
Plot bilirubin on gestation specific chart according to age since birth
Plot rate of change of bilirubin to identify potentially high levels

Diagnostic approach to neonatal jaundice



Why does physiological jaundice develop?

- Increased bilirubin load.
- Defective uptake from plasma.
- Defective conjugation.
- Decreased excretion.
- Increased entero-hepatic circulation.

Mechanism

- Production:
  - Volemia, ↑ ↑
  - RBC span (90 days) ↓
  - Ineffective erythropoiesis ↑
  - Turnover of non Hb heme proteins ↑

Mechanism

- ↑ Enterohepatic recirculation:
  - ↑ Glucuronidase
  - ↑ Bilirubin monoglucuronide
  - ↓ Intestinal bacteria
  - ↓ Intestinal motility and stooling

Mechanism

- ↓Bilirubin Uptake : ligandin ↓
- ↓Conjugation : ↓UDPG-T activity
- ↓Hepatic excretion of bilirubin

Jaundice

- Yellowish discoloration of skin +/- sclera of newborns due to bilirubin
- Affects nearly all newborns
- Peak: 48-120 hours, typically 5-6 mg/dL, usually does not exceed 17-18 mg/dL
- Pathologic: TSB exceeds age (in hours) specific 95th percentile according to Bhutani nomogram

Evaluation

- Transcutaneous bilirubin
- Total serum bilirubin
- End-tidal carbon monoxide
- Blood type, direct Coombs test
- CBC, peripheral blood smear
- Reticulocytes, G6PD screen
- Serum albumin

Evaluation of Hyperbilirubinemia

- Mother’s blood type and antibody screen
- Baby’s blood type and Direct Coombs
- CBC, reticulocyte count (hemolysis)
- Total and Direct Bilirubin
  - Remember: “One bilirubin leads to another”
    - Head to toe progression
    - Transcutaneous bilirubin meter

Pathological jaundice

- Appears within 24 hours of age.
- Increase of bilirubin > 5 mg/dl/day.
- Serum bilirubin > 15 mg/dl.
- Jaundice persisting after 14 days.
- Stool clay/white colored &urine staining clothes yellow.
- Direct bilirubin > 2 mg/dl.

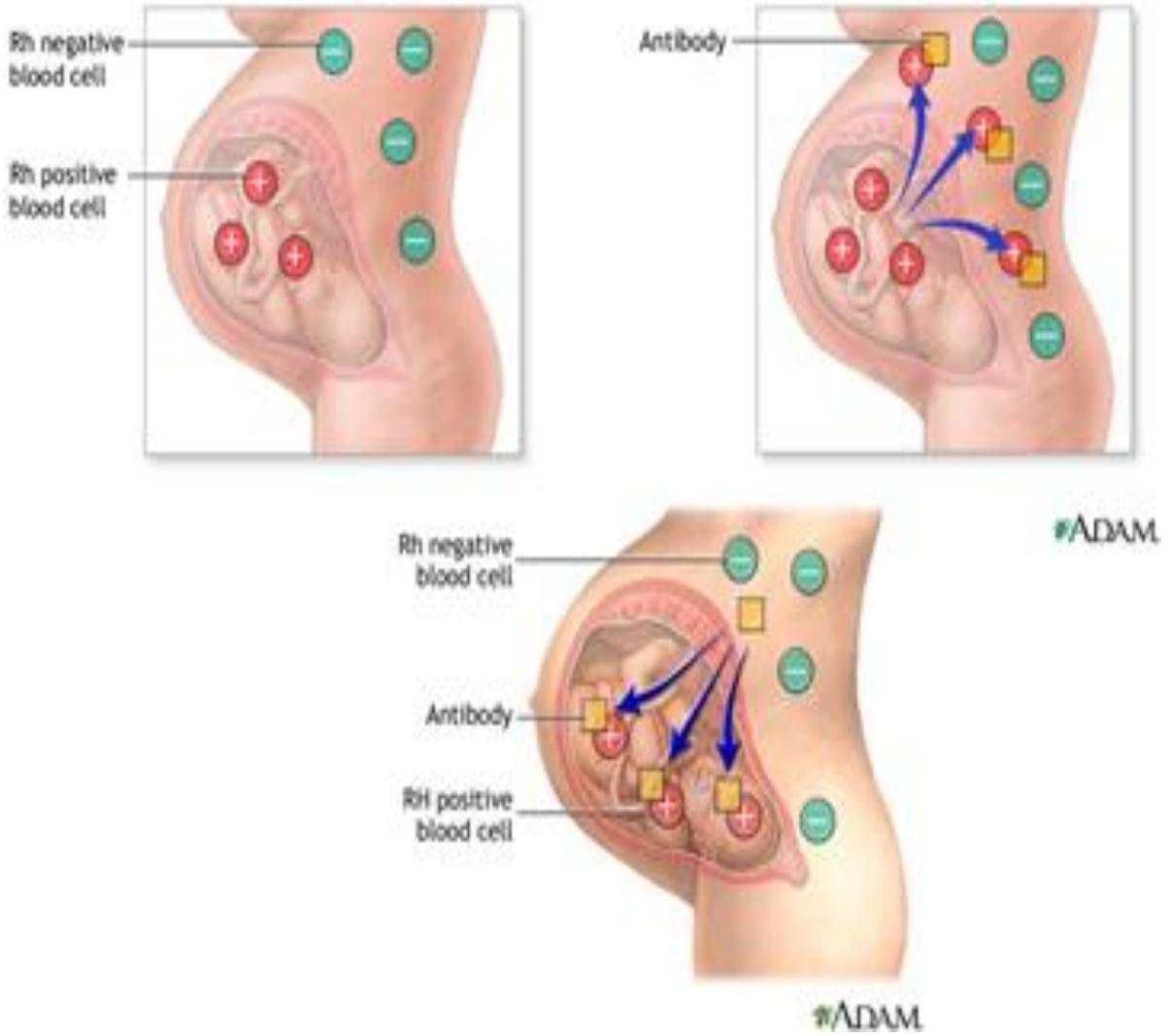
Causes of jaundice

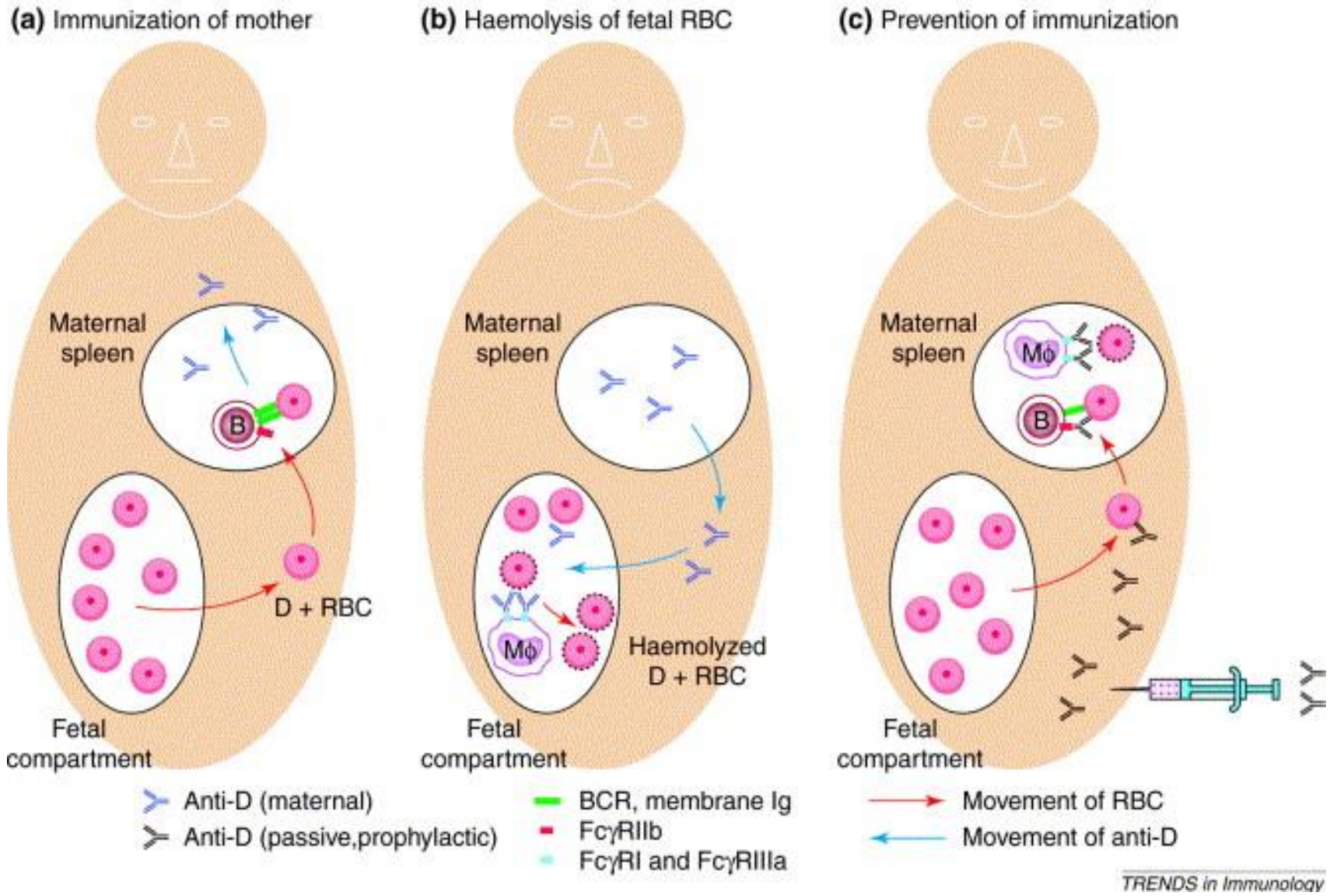
Appearing within 24 hours of age

- Hemolytic disease of NB: Rh, ABO
- Infections: TORCH, malaria, bacterial
- G6PD deficiency.

- **T** – **T**oxoplasmosis / Toxoplasma gondii
- **O** – Other infections
- **R** – **R**ubella
- **C** – **C**ytomegalovirus
- **H** – **H**erpes simplex virus or neonatal herpes simplex

Pathological Jaundice Secondary to Rh Incompatibility




(a) Immunization of mother
(b) Haemolysis of fetal RBC
(c) Prevention of immunization
Maternal spleen
B
D + RBC
Fetal compartment
Mϕ
Haemolyzed D + RBC
Anti-D (maternal)
Anti-D (passive,prophylactic)
BCR, membrane Ig
FcγRIIb
FcγRI and FcγRIIIa
Movement of RBC
Movement of anti-D
TRENDS in Immunology

Causes of jaundice

Appearing between 24-72 hours of life

- Physiological
- Sepsis
- Polycythemia
- Intraventricular hemorrhage
- Increased entero-hepatic circulation

Causes of jaundice

After 72 hours of age

- Sepsis
- Cephalhematoma
- Neonatal hepatitis
- Extra-hepatic biliary atresia
- Breast milk jaundice
- Metabolic disorders (G6PD).

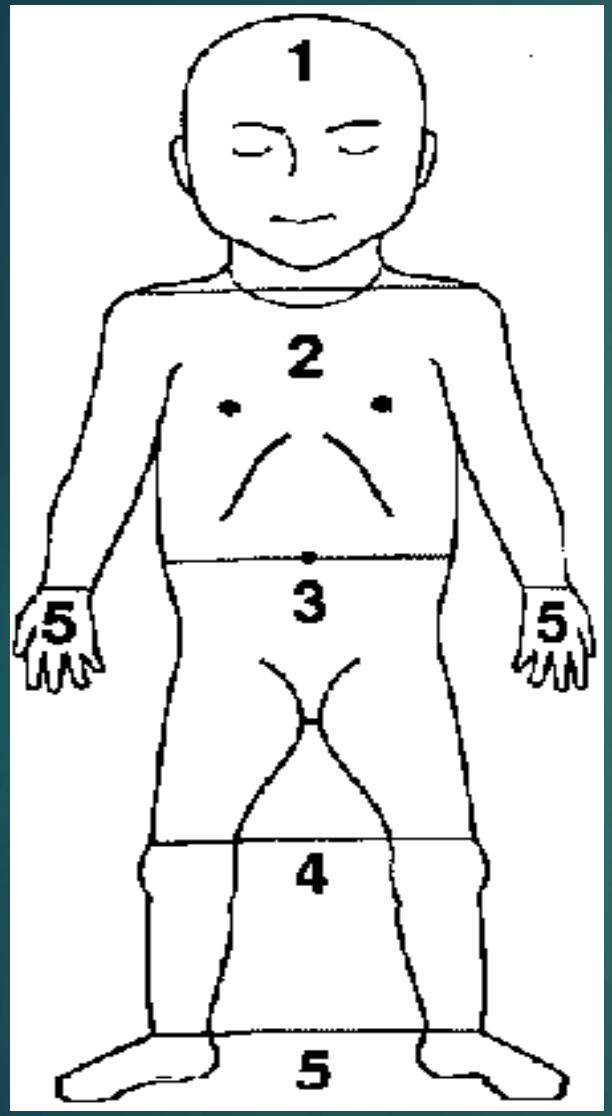
OTHER CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA

- BREAST MILK JAUNDICE
- DEFECTS OF CONJUGATION
  - #Crigler Najjar Syndrome I & II
  - #Gilbert Syndrome
- METABOLIC DISORDERS
  - #Glactosemia
  - #Hypothyroidism
- POLYCYTHEMIA

Impaired bilirubin conjugation:

Physiologic jaundice
Breast milk jaundice
Genetic deficiency of glcuronosyl transferase
Decreased expression of glcuronosyl transferase
Diffuse hepatocellular diseases

Dermal Zones of Jaundice

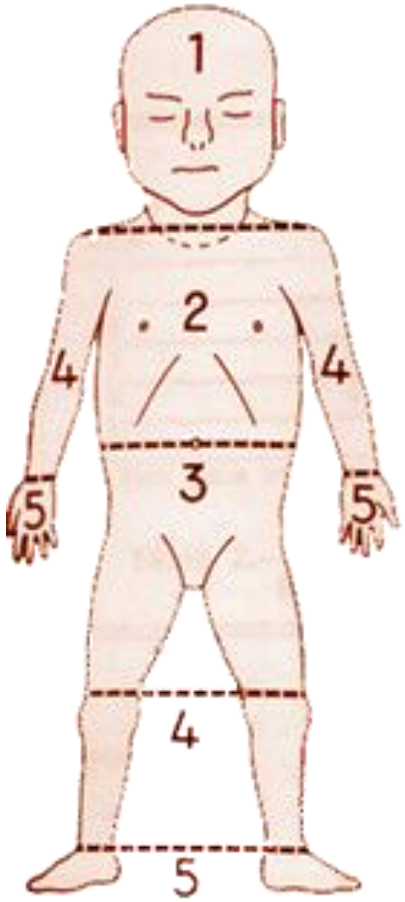


After leaving RES bilirubin binds to albumin, initially with low affinity, thus bilirubin precipitates in the proximal parts of the body before it does it distally. So jaundice appears first proximally, and later distally.

Dermal Zone	Bilirubin range (mg%)
1	4.5-8
2	5.5-12
3	8-16.5
4	11-18
5	> 15

Clinical assessment of jaundice

Area of body	**Bilirubin levels mg/dl** (*17=umol)
1- Face	4-8
2- Upper trunk	5-12
3- Lower trunk & thighs	8-16
4- Arms and lower legs	11-18
5- Palms & soles	> 15



Jaundice of Prematurity

- Jaundice appears at a level of 6-8mg/dL
- No relationship between kernicterus at autopsy & bilirubin level
- So if they are jaundiced treat them with phototherapy until it resolves

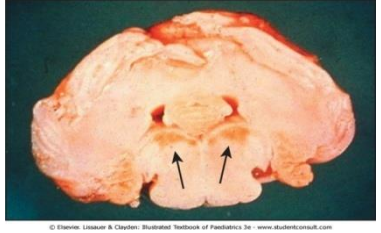
> 50% of all NN infants become visibly jaundiced This is because:

- There is marked physiological release of Hb from the breakdown of RBCs because of the high Hb conc. at birth
- The RBC lifespan of NN infants (~90 days) is markedly shorter than that of adults (120 days)
- Hepatic bilirubin metabolism is less efficient in the first few days of life.

Neonatal jaundice is important as:

- it may be a sign of another disorder, e.g. hemolytic anemia, infection, inborn error of metabolism, liver disease
- unconjugated bilirubin can be deposited in the brain, esp. in the basal ganglia, causing kernicterus.

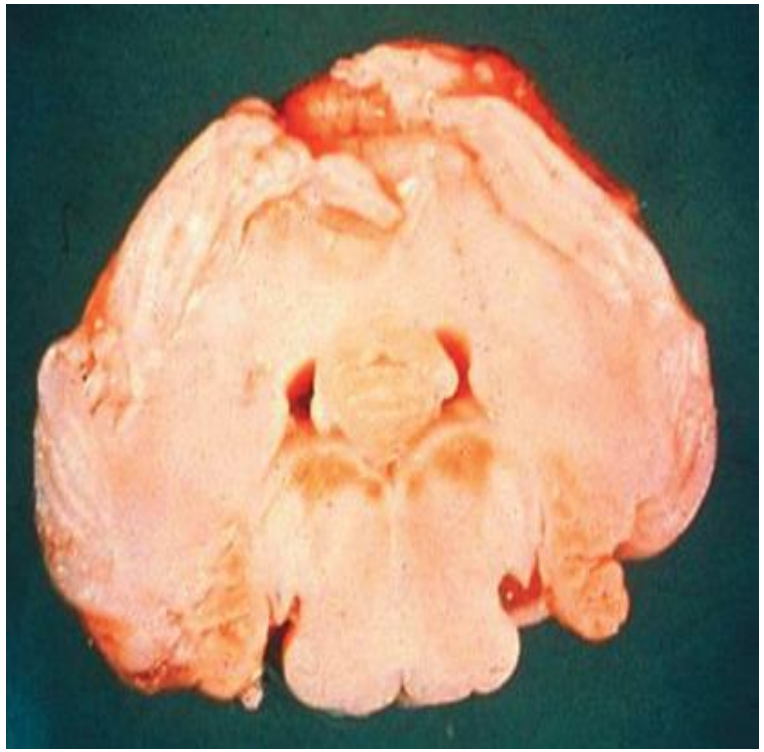
Bilirubin Encephalopathy

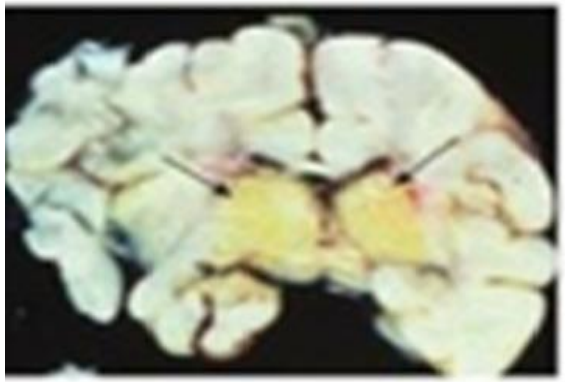


- Deposition of unconjugated bilirubin in the basal ganglia & brainstem nuclei causing neurotoxic effects
- Acute manifestations are lethargy & poor feeding , hypotonia
- Severe cases, irritability, ↑ muscle tone opisthotonos, seizures & coma
- Survivors may develop choreo-athetoid cerebral palsy (due to damage to the basal ganglia), learning difficulties & sensorineural deafness

Postmortem of brainstem & cerebellum showing kernicterus with yellow bilirubin staining of brainstem nuclei (arrows).

illustrated textbook of pediatrics 5th ed.





Cross-section of the brain at autopsy showing yellow staining, predominantly in basal ganglia from deposition of unconjugated bilirubin.

Special circumstances

- Jaundice in 1st 24 hours
  - Frequently due to hemolysis
  - Require immediate evaluation & close surveillance
- Other reasons for ↑ bilirubin production
  - Cephalohematoma, extensive bruising, conjugation disorders

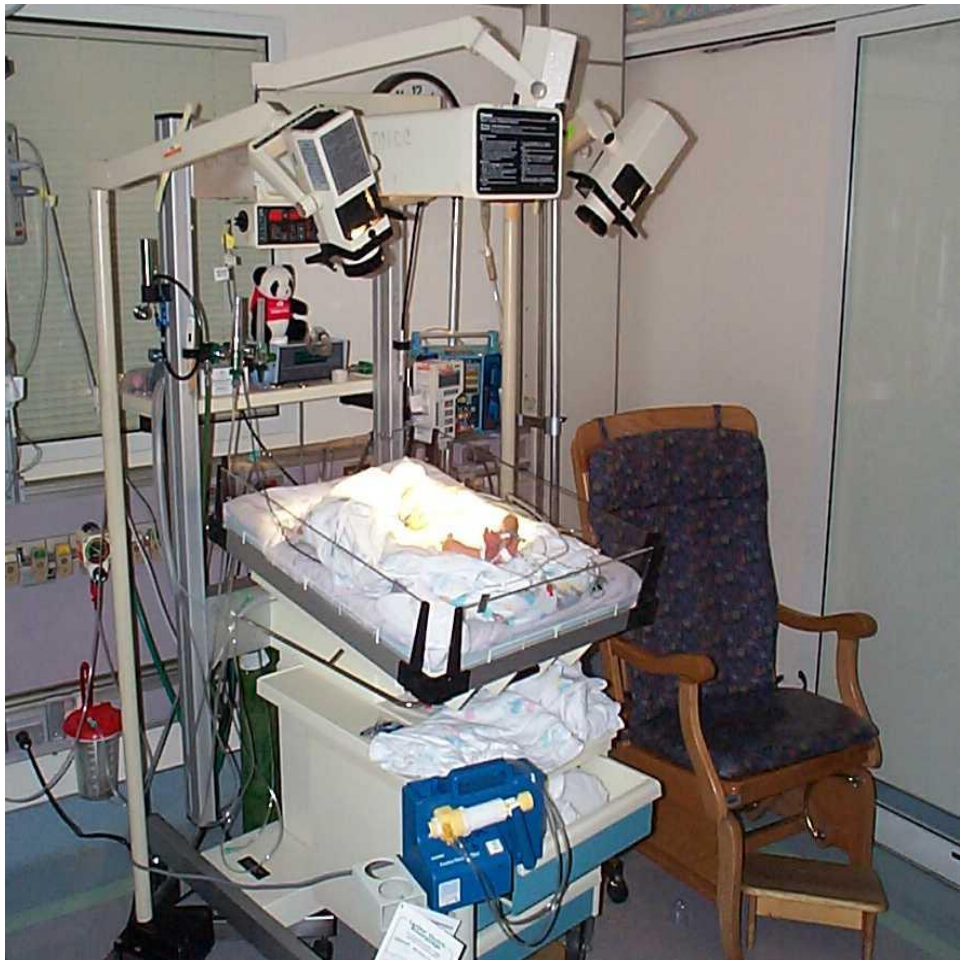
Management

- Phototherapy
  - Mechanisms
    - Structural isomerization
    - Photoisomerization
    - Photo-oxidation
  - Irradiance
  - Initiation if bilirubin exceeds the 95th percentile for hour-specific TSB concentration & risk category

Risk categories-phototherapy

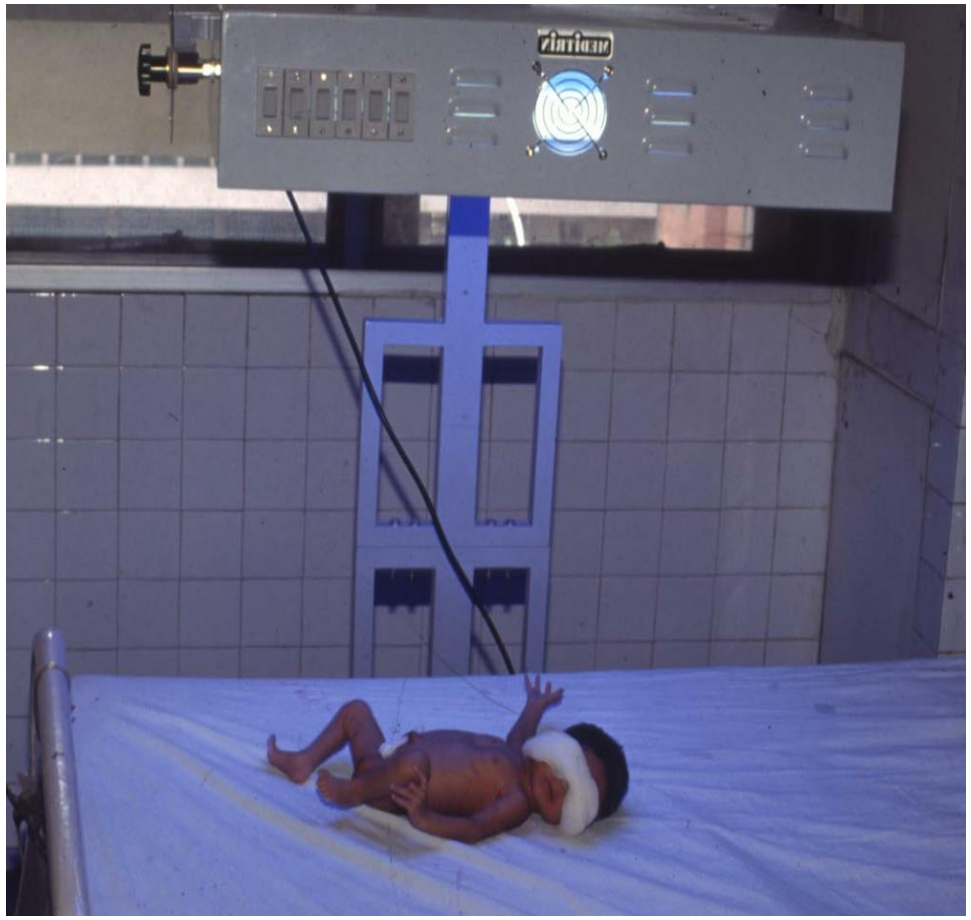
- Lower risk: at least 38 weeks gestation, no risk factors
  - >12 mg/dL at 24 hours, >15 mg/dL at 48 hours, >18 mg/dL at 72 hrs
- Medium risk: at least 38 weeks with risk factors or 35-38 weeks without risk factors
  - >10 mg/dL at 24 hours, >13 mg/dL at 48 hours, >15 mg/dL at 72 hours
- Higher risk: 35-38 weeks with risk factors
  - >8 at 24 hours, >11 at 48 hours, >13.5 at 72 hours

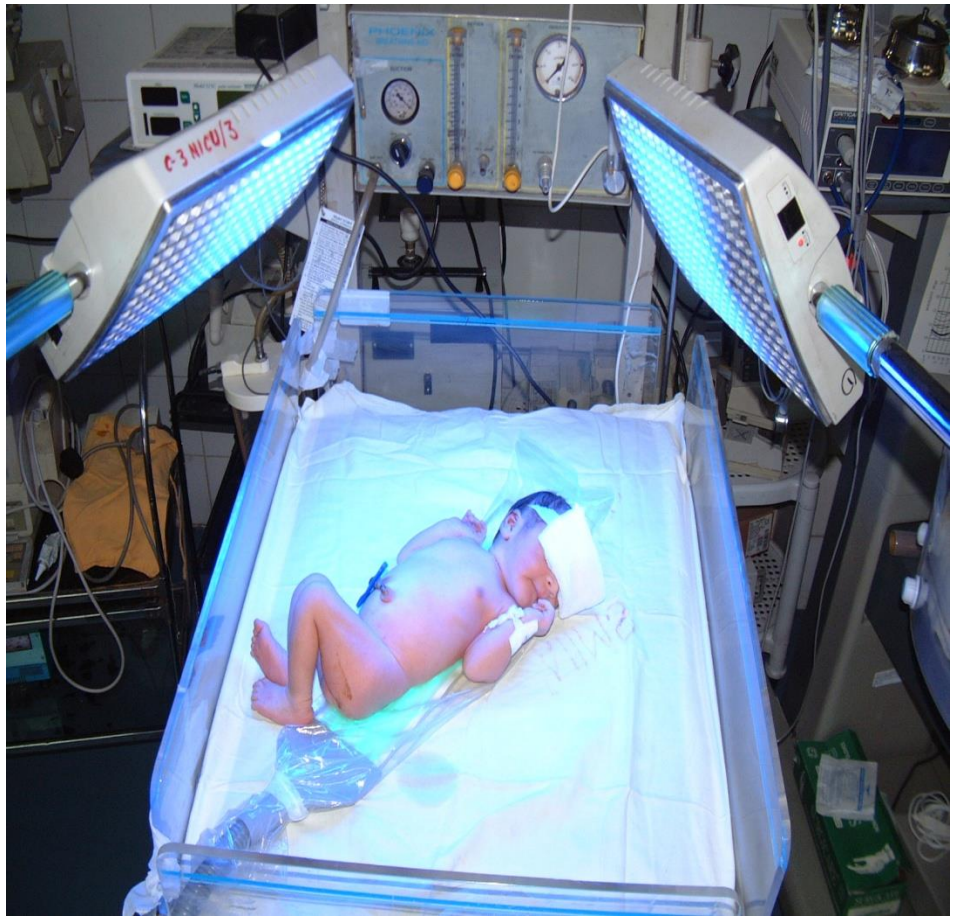
Phototherapy

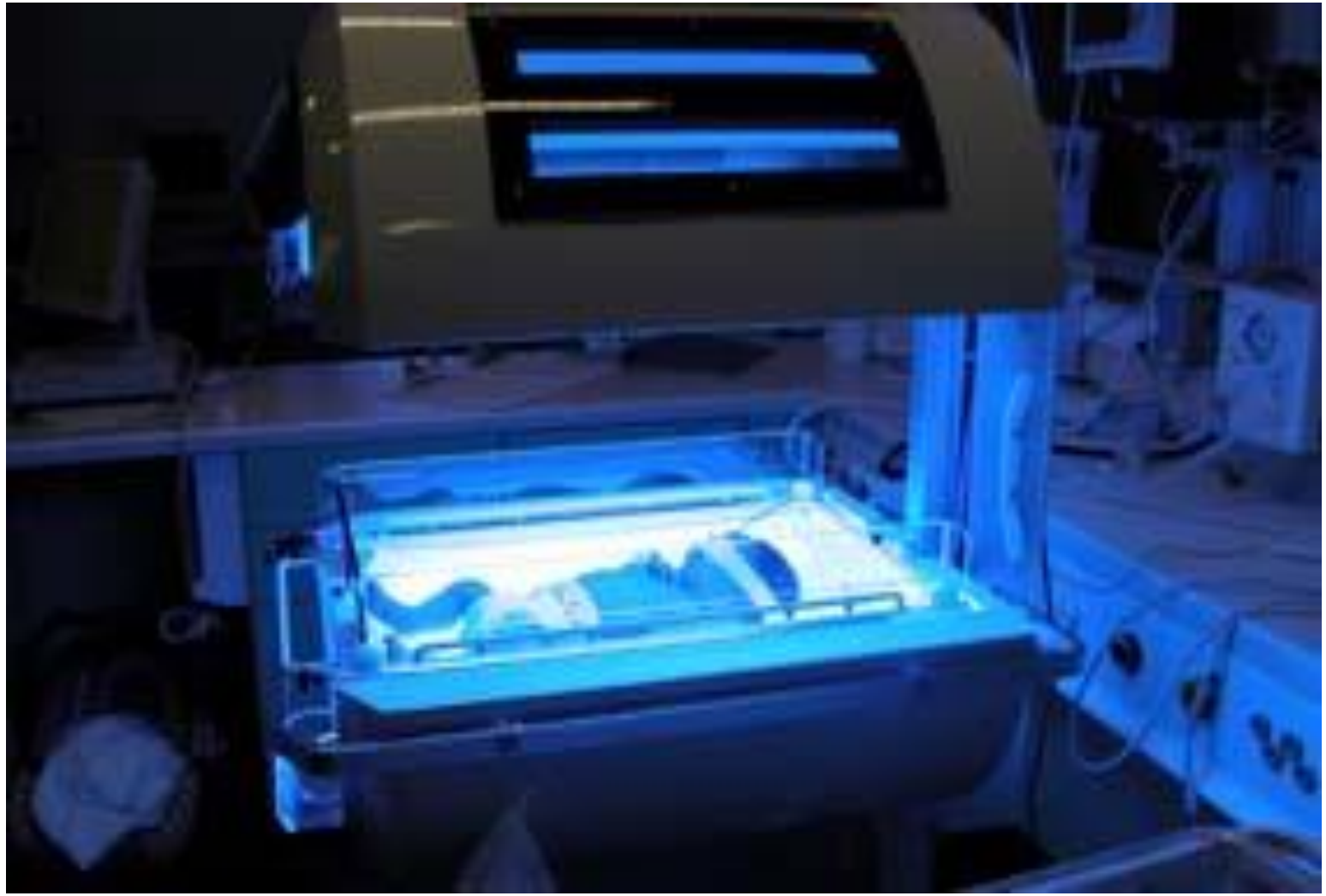


- Fast application, available everywhere
- Use “blue light” 420-475 nm with spectral irradiance of at least 20 uW/cm^2/nm
- All that is needed for most preemies, physiologic/ breast feeding jaundice, most ABO incompatibility
- Assess effectiveness of therapy

Babies under phototherapy







Treatment: Phototherapy

- Bilirubin best absorbs light at 450 ηm.
- The best is to provide it with blue light.
- White range: 380-700 ηm also adequate.
- Irradiation generates photochemical reaction in the extravascular space of the skin
- A higher illuminated area increases effectiveness

Treatment: *Phototherapy Mechanism*

- Photoisomerization:
  - Natural Isomer 4Z,15Z ↔ 4Z,15E hydrosoluble → blood → biliar secretion (unconjugated)
  - Slow excretion and fast reisomerization → reabsorbed.

- Photo-oxidation: Small polar products. Slow

Treatment: *Phototherapy mechanism*

- Structural isomerization:
  - Cyclization to lumirubin (irreversible) → bile & urine
    - Fast excretion not reabsorption.
    - Related to dose of phototherapy (intensity of light)

Management

- Rate of decline of TSB
  - Irradiance
  - Surface area
  - Initial TSB
- Discontinuation
  - TSB level below 95th percentile for age
  - Is less than 13 mg/dL

Phototherapy: Side effects

- Increased water loss
- Diarrhea
- Retinal damage
- Bronze baby, tanning
- Mutations in DNA? → shield scrotum
- Disturb of mother-infant interaction.

Management

- Exchange transfusion
  - Hyperbilirubinemia unresponsive to phototherapy
  - Especially useful with immune-mediated hemolysis
    - Removal of circulating antibodies and sensitized RBCs
  - For TSB > 25 mg/dL
  - Presence of bilirubin neurotoxicity

Case 2

- Six days old term male born at home to a G6P5A1 mother. Noted to be jaundiced on 3rd day of life. On day of admit had apneic/cyanotic episode. At local ED, total bili was 42.9 with direct of 4.4 & coombs test was +ve. Baby was opisthotonic with tongue thrusting. 2 exchange transfusions &aggressive phototherapy performed. Total bili down to 16 after first exchange. Baby died of kernicterus several months later.

Risk categories- exchange transfusion

- Lower risk: at least 38 wks gestation, no risk factors
  - >19 mg/dL at 24 hrs, >22 mg/dL at 48 hrs, >24 mg/dL at 72 hours
  - TSB/Albumin>8.0
- Medium risk: at least 38 wks with risk factors or 35-38 wks without risk factors
  - >16.5 mg/dL at 24 hrs, >19 mg/dL at 48 hrs, >21 mg/dL at 72 hrs
  - TSB/Albumin>7.2
- Higher risk: 35-38 wks with risk factors
  - >15 at 24 hrs, >17 at 48 hrs, >18.5 at 72 hrs
  - TSB/Albumin>6.8

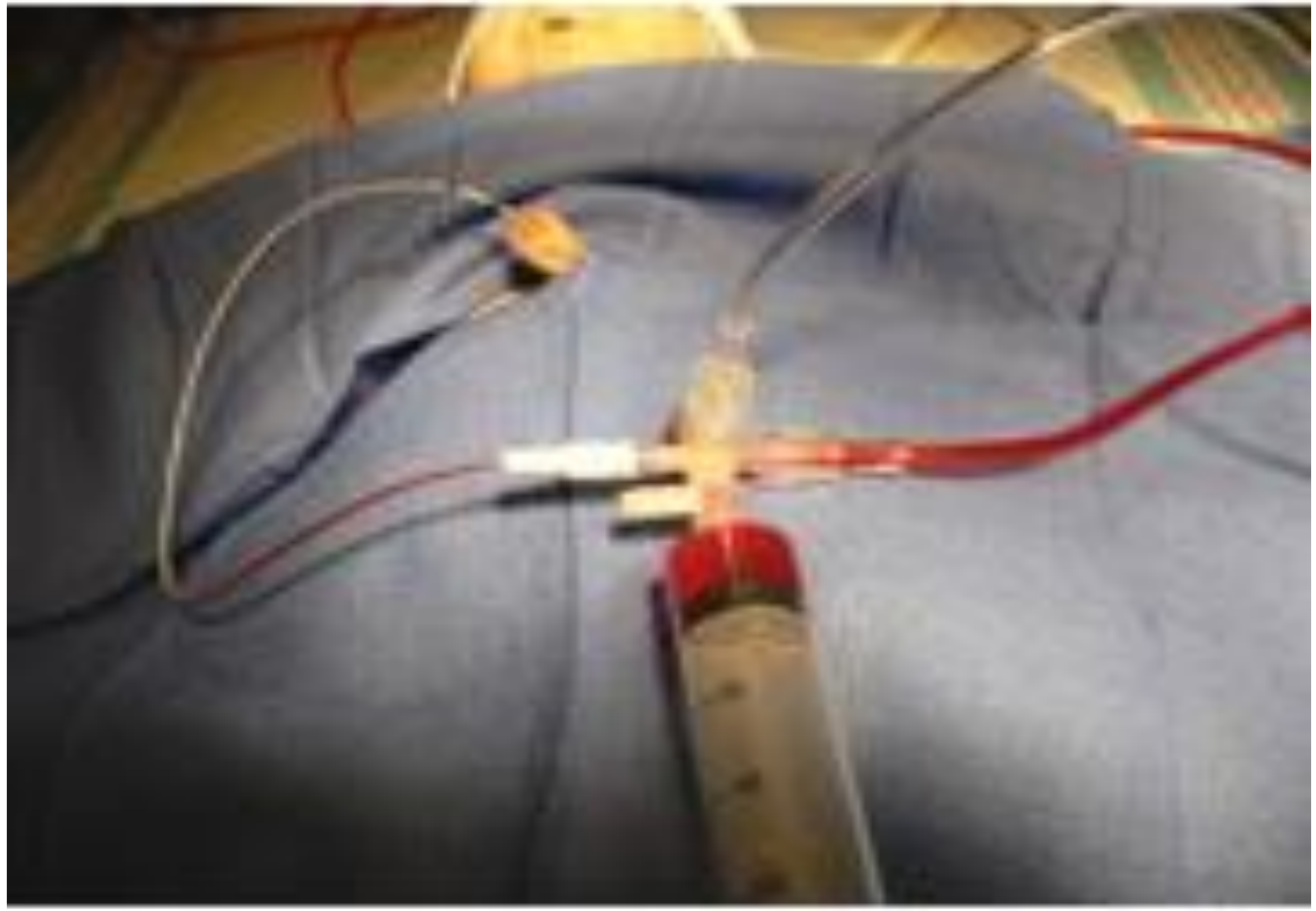
Exchange transfusion: Complications

- Hypocalcemia-hypomagnesemia
- Hypoglycemia (monitor Dx after exchange)
- Acid base disturbances
- Hyperkalemia
- Cardiovascular:
  - *Embolizations, arrhythmia, perforation, arrest*.

Exchange transfusion: Complications

- Bleeding
  - Thrombocytopenia, loss of factors.
- Infections
- Hemolysis
- GVHD
- Other
  - Fever, hypothermia, NEC?

Exchange Transfusion




...Exchanged Transfusion..
limshouzhi's photography

Case 4

- Twenty day old former term male recovering from extensive subgaleal hematoma. Has Total bilirubin level of 53.8. Treated with phototherapy only.
- Does he develop kernicterus?
- No, he has a direct bilirubin fraction of 37.0. (so, unconjugated fraction is only 16.2)

Extra hepatic biliary obstruction:

- **Extra hepatic biliary atresia**
- **Biliary stricture & choledochal cyst**

HISTORY

- ***onset / duration***
- ***nausea & vomiting***
- ***loss of weight***
- ***itching***
- ***color of stool***
- ***color of urine***
- ***family history***

EXAMINATION

- ***color of skin***
- ***severity of jaundice***
- ***anemia***
- ***liver***
- ***spleen***
- ***gall bladder***
- ***ascites***

INVESTIGATION

- ***CBC***
- ***LFT***
- ***Prothrombin time***
- ***Alfa feto proteins***
- ***U/S***
- ***ERCP & PTC***
- ***Liver biopsy***

Summary

- Neonatal jaundice is a fairly common condition
- Keep a vigilant eye
- Try to differentiate physiological from pathological jaundice
- Early and effective phototherapy
- Prevent BIND (bilirubin induced neurologic dysfunction)

NEONATAL JAUNDICE

Objectives:

Define the concept

Describe the pathophysiology of jaundice

Identify the etiology of NN jaundice

Describe the types of NN jaundice

Identify the Risk factors of NN jaundice

Describe the clinical approach to NN jaundice

Outline the management of NN jaundice

Explain the effects, Mechanism & complications of Phototherapy

Enumerate the indications & complications of Exchange transfusion