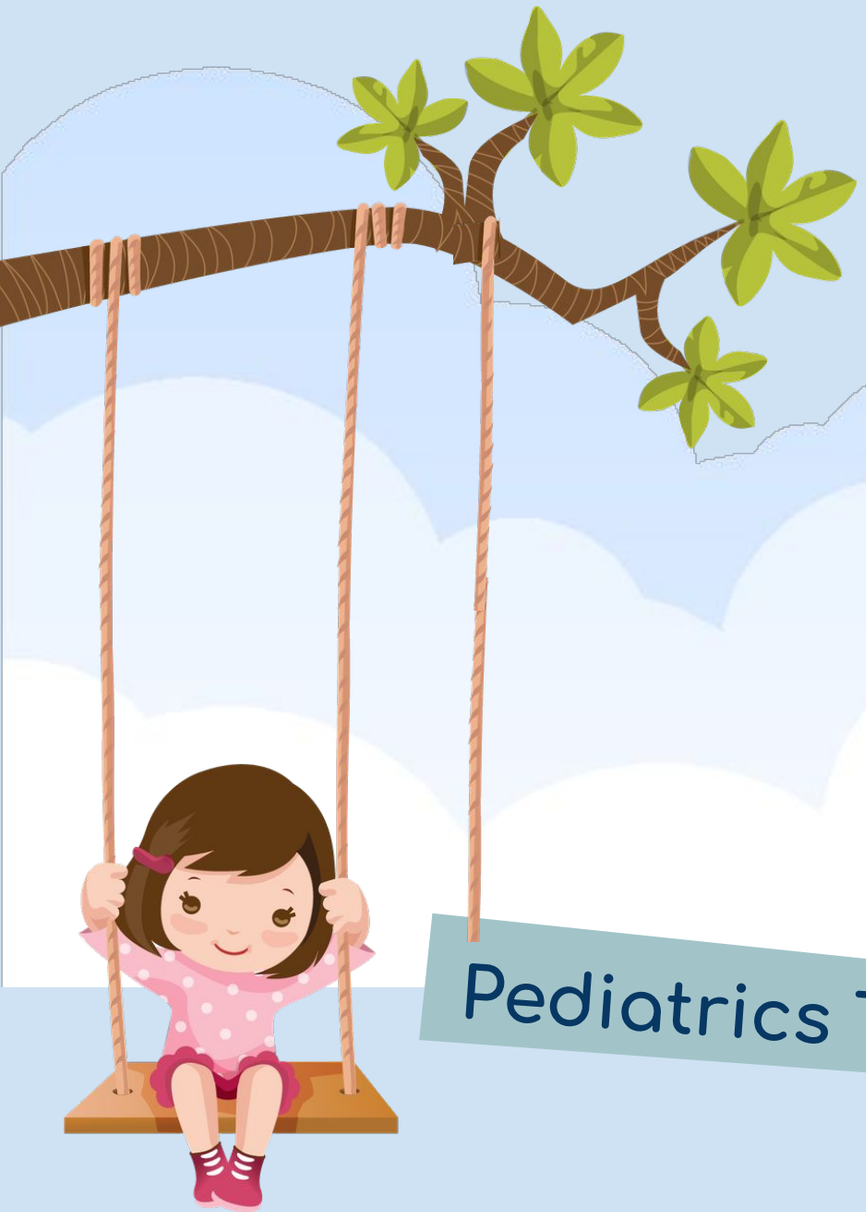

Pediatrics TeamWork 437

# Neonatal Jaundice

## Objectives

1. Summarize the metabolism of bilirubin and causes of neonatal indirect hyperbilirubinemia.
2. Describe screening methods and treatment for indirect hyperbilirubinemia.
3. Identify the complication and risk for Kernicterus .


**Done by:**

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**Revised by:**

Aseel Badukhon

**Team Leader:**

Aseel Badukhon


Notes  Previous Notes  Book  Important!

# Introduction

## Indirect Hyperbilirubinemia (IHB)

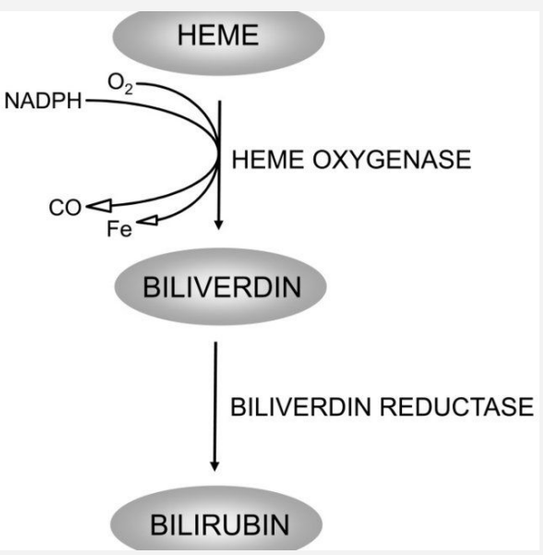
- It is one of the most common clinical phenomena encountered in newborns
  - 70% of newborns, 65% of all readmissions in the first week after birth, and 8% of readmissions in the second week after birth, are the result of severe IHB
- It may be a sign of another illness
- It may lead to catastrophic complication (kernicterus)
- Yellow-orange pigment (Icterus - bilirubin ) in the skin and sclera
- It most commonly happens on the first day, but if it happens later like on the second, its usually a pathological yet benign cause that needs treatment.

# Clinical Physiology

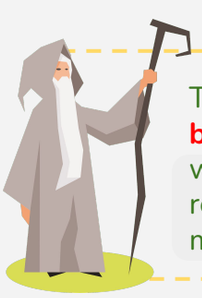
## Bilirubin Production

**What is (are) the source(s) of Bilirubin ?** Billirubin comes from the RBC

1. Degrading heme from hemoglobin-containing RBCs ( 80% ),
2. 20% from ineffective erythropoiesis
3. Turnover of other hemoproteins (e.g., myoglobin, catalase, nitric oxide synthase, peroxidases, and cytochromes).



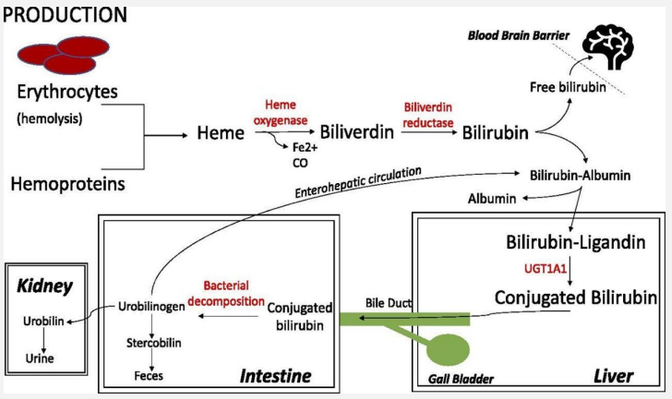

This free bilirubin penetrates the BBB easy , goes to basal ganglia , brainstem , brain nuclei -> kernicturus
V. imp for it to attach to albumin for it to be bigger so it won't penetrate BBB



The best marker for **high bilirubin in hemolysis is CO**. you will have low Hgb ,high reticulocytes, and CO good marker

## Bilirubin Transportation

- It binds reversibly to albumin (bilirubin:albumin) MCQs
  - (about 0.8 - 7 mg of bilirubin per gram of albumin)
- Low Albumin level and low affinity of binding sites are both risk factors be careful of meds that displaces bilirubin from albumin .Bilirubin goes to the brain -> kernicterus
- Free" bilirubin is hydrophobic (lipid soluble)
- The movement of bilirubin from the circulation into tissue cross blood brain barrier,




There are receptors on the livers surface, allows bilirubin-albumin to enter. ( Z-billirubins) when absent it can't go in.

## Conjugation

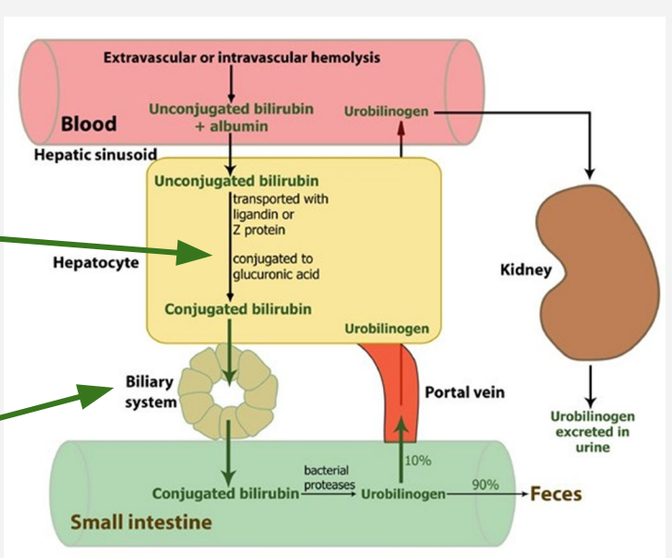
- Conjugation of bilirubin with glucuronic acid (water-soluble, non-neurotoxic bilirubin)
- Uridine diphospho - Glucuronosyl Transferase (UDGT) transfers indirect bilirubin to direct. Absent in Criglar-najjar syndrome.
- Why does the neonate develop jaundice?
  - Slower rate of hepatic uptake of free bilirubin from the blood
- Decreased concentrations and activity of (UDGT) ?

## Bilirubin Excretion

- Conjugated bilirubin enter the bile ducts and are excreted with the bile into the intestinal tract. obstructive diseases elevated DIRECT billirubin
- Mono or Diglucuronide > unconjugated Bili
- In the colon, bacterial flora in older neonates hydrogenate bilirubin >
- urobilinogen, urobilins, and stercobilins (stool color) obstruction in the intestines cause hyperbilirubinemia

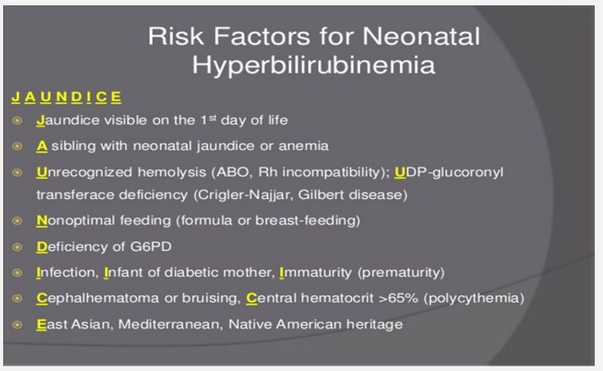
Gilbert syndrome Crigler najjar

Obstruction such Biliary atresia ;
2 weeks
Yellow
High conjugated bilirubin
Very pale stool
Very dark urine



## Risk factors

- Gestational Age more in premature
- Race (Genetic & environmental)
- Maternal illness DM & Blood group (ABO or Rhs)
- Family history of jaundice requiring phototherapy
- Family Hx of Hemolysis (G6PD, Spherocytosis)
- Severe bruising
- Breastfeeding



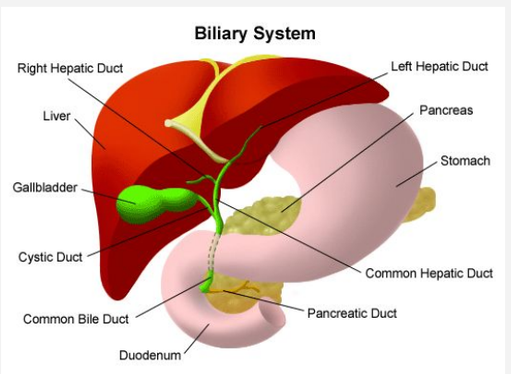

## Etiological classification

MCQs know each category and causes

Bilirubin Production

Binding

Entero-hepatic conjugation




Hour- Specific Bilirubin load

Bilirubin Elimination

**Increased bilirubin load (production)**

1. Haemolytic causes
   - Coombs' test positive: like different maternal and fetal blood types commonly as ABO incompatibility / rhesus incompatibility
   - Coombs' test negative: like G6PD and Spherocytosis

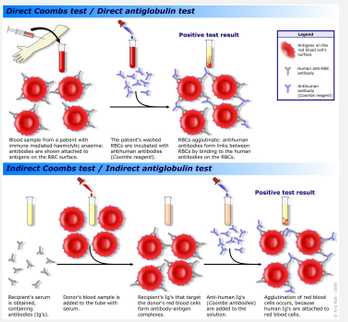
- red blood cell membrane defects (spherocytosis AD, elliptocytosis), RBCs enzyme defects (G6PDutiallnyd pyruvate kinase deficiency)

**We do not include thalassemia or SCD. why?**

Because they are related to the beta chain of hemoglobin which isn't in neonates HgbF does not have beta chain

-Early jaundice (1st 24 hours) 1st question: ask mom's blood group if O or Rhesus - go check baby's blood type. Order Combs test if + or - . then do phototherapy
-G6PD during the attack will be normal

## 1. Haemolytic Disease




- Jaundice in the first 24 hours of age
- Blood group incompatibility (1ABO, 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) v imp to rule out; eating well? Breathing well? Breathing well? Cause in sepsis any can be affected

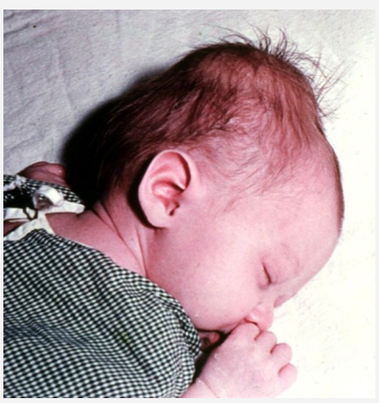
## 2. Non-hemolytic Jaundice

Increased unconjugated bilirubin level, normal percentage of reticulocytes or Co:

1. Physiological Jaundice the most common ( > 24 hours)
2. Extra vascular sources like a cephalic hematoma
3. Polycythemia hematocrit more than 60 or 70
4. Exaggerated Entero- hepatic circulation

## 3. Decreased Bilirubin Conjugation

1. Physiologic jaundice not true anymore
2. Crigler-Najjar syndrome absence of conjugation, only cure is transplant
3. Gilbert syndrome
4. Hypothyroidism will be jaundiced until given thyroxine
5. Breast milk jaundice

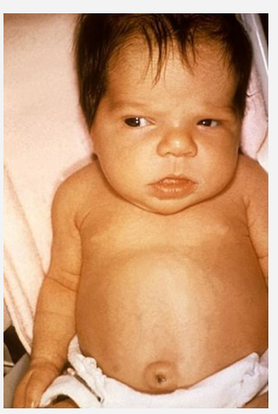


TERM INFANT BORN NSVD DEVELOPED JAUNDICE AT 24 HOURS OF AGE WHAT IS THE MOST LIKELY CAUSE OF JAUNDICE ?

### Case Scenario

6week male infant with prolonged N.J, started on the 4th day or life, but it continued, and he has coarse facia features and an umbilical hernia , protruding tongue , shallow breathing , low cry.

- What is your diagnosis?
  - hypothyroidism
- How do you manage this infant?
  - Just give thyroxine



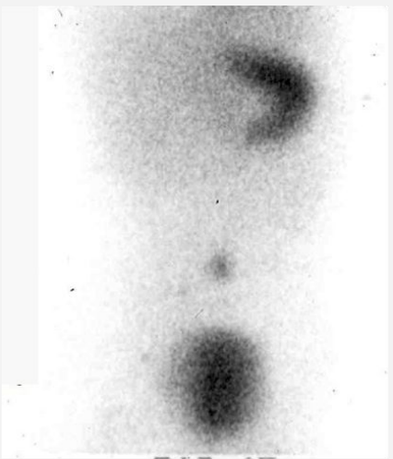
## 4. Impaired Bilirubin Excretion

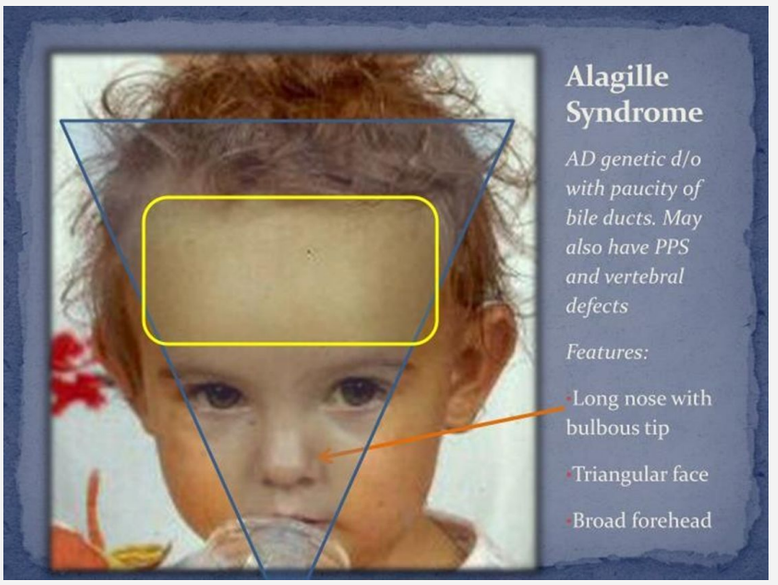
Direct hyperbilirubinemia obstruction. Happens 2-3 weeks

- Conjugated bilirubin level of >2 mg /dL (34 µmol/ 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

Important to catch early and treat early






What is this test? What is the indication?

### Case Scenario MCQs

Term male newborn, presented on the second day of life with jaundice, otherwise is normal, baby looks well (physiological)

- What farther questions do you want to obtain?
  - Everything will be normal, probably will have family Hx of a
  - sibling with neonatal jaundice that only required phototherapy
- Clinical signs you want to elicit?
- How do you manage such neonate?
  - Conservative therapy (rehydration, feeding) or phototherapy if the level of bilirubin exceeds a certain level

Commonest cause of jaundice in neonates? Physiological. Remember it has a criteria

- 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 in healthy neonates?
  Physiological jaundice! (excluded if the baby presented before 24 hours)
- Which one of the following is NOT included in the criteria for physiological jaundice?
  1. Onset within 24 hours! NOT PHYSIOLOGICAL!
  2. Rate of TSB increment is 5mg/dl/day
  3. Level of TSB reaching 20 mg/dl
  4. TSB is mainly indirect non conjugated

# Criteria for Physiological Jaundice

1. Onset >24 hours of birth
2. Rate of TSB increment ( 5mg/dl/day)
3. Level of TSB
4. Type of Bili indirect
5. Duration (Less than 2wks in term and 3wks in preterm Neonates)

If 1st day or Direct or Indirect but symptomatic( crying , not eating..)
NOT PHYSIOLOGICAL
<24 hour -> #1 ask mom blood group if O or - look for baby's and then do combs test + or-
Look for G6Pd ..

# Jaundice and Breastfeeding

- 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. The material in the breast milk that interferes with conjugation is so far unknown. It occurs later when the babyingested enough breast milk

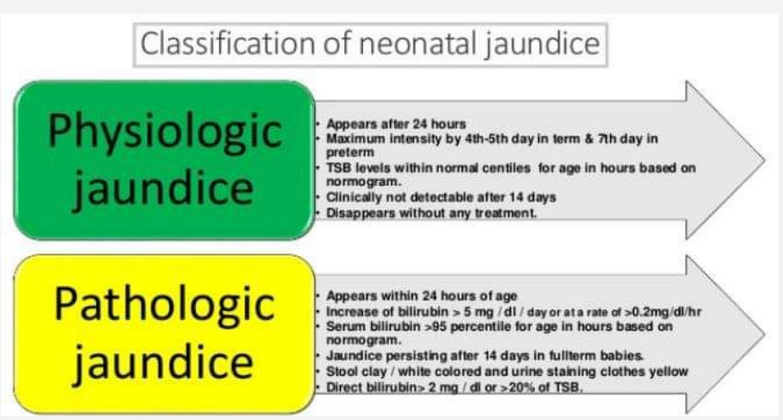
# Pathological Jaundice

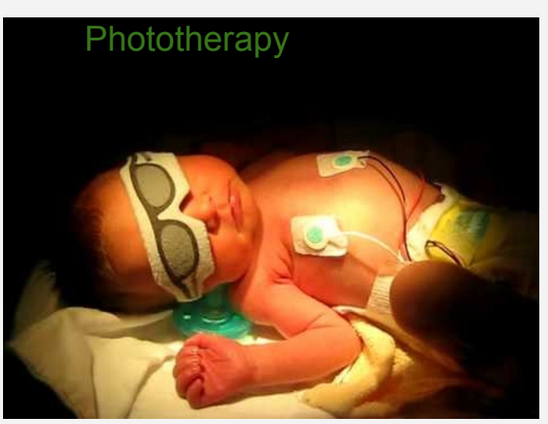
All etiologies of jaundice beyond
1. physiologic
2. breastfeeding or
3. breast milk jaundice
   Are considered Pathological

Breastfeeding Jaundice
Feeding failure

Happens early
in 48 hours

Milk Jaundice
Baby has enough milk but material in milk permits conjugation
Happens later



# 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 sever then Rhesus
- Hb. is usually normal or slightly reduced
- No hepato-splenomegaly

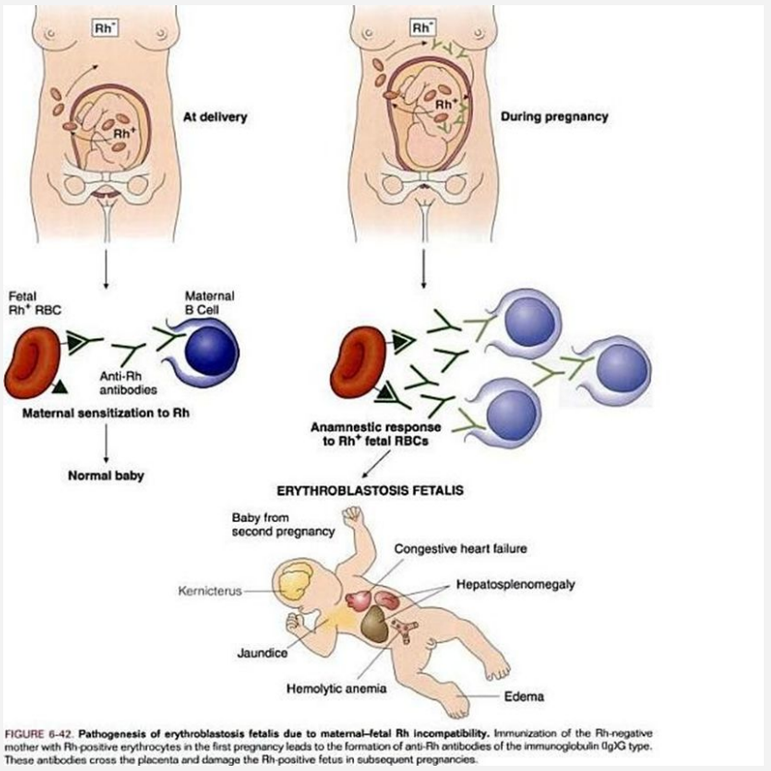
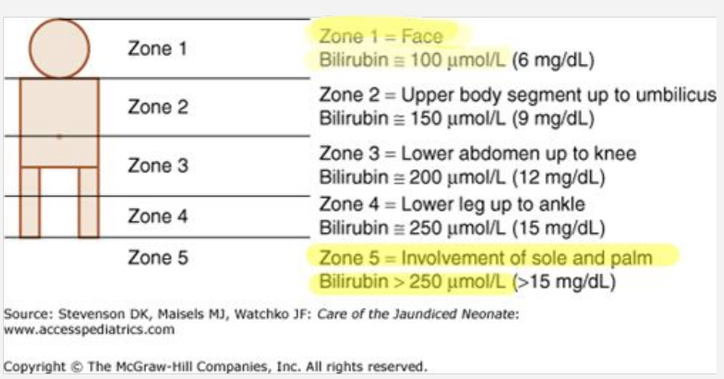


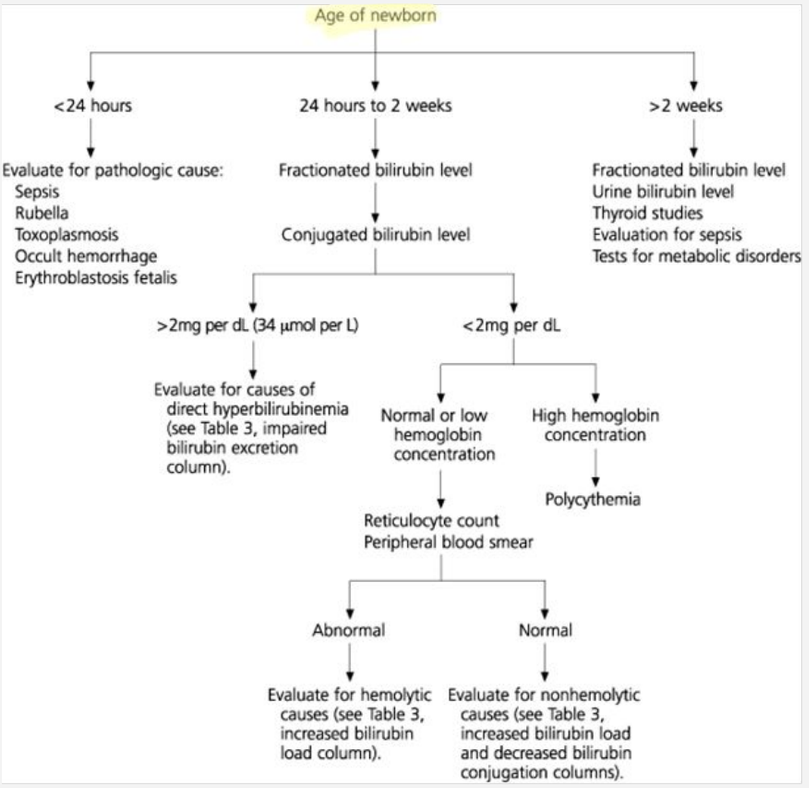

FIGURE 6-42. **Pathogenesis of erythroblastosis fetalis due to maternal-fetal Rh incompatibility.** Immunization of the Rh-negative mother with Rh-positive erythrocytes in the first pregnancy leads to the formation of anti-Rh antibodies of the immunoglobulin (Ig)G type. These antibodies cross the placenta and damage the Rh-positive fetus in subsequent pregnancies.

# Diagnosis

- History onset , associates symptoms, feeding and hydration statues
- Physical Examination in the sunlight, and assess zones
- Investigation TSB ( direct and indirect) , CBC, combs test




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



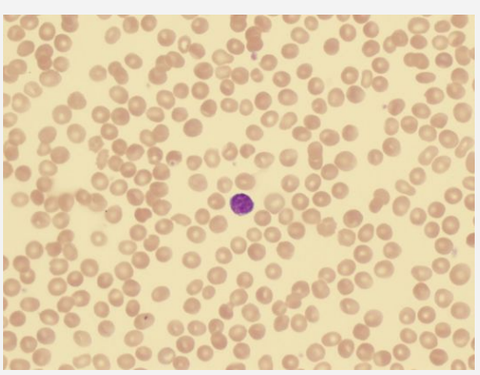

# Laboratory

## Laboratory Evaluation of Term Newborn With Jaundice

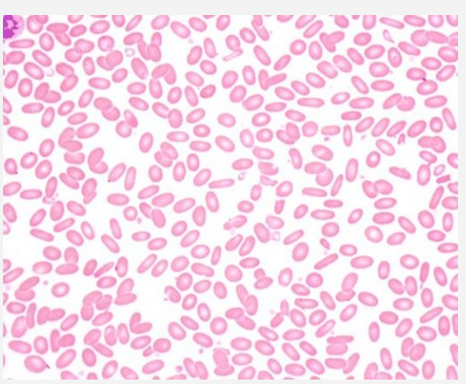
- TOTAL SERUM BILIRUBIN (TSB)
- Bilirubin fraction (conjugated OR non conj.)
- Blood group and coombs test
- CBC. Diff. Reticulocytes
- G6PD level can be normal in hemolysis
- Peripheral blood smear
- Blood and urine culture IF sepsis is suspected
- Thyroid function & LFT

We do these. The rest depends on the scenario


New device called bilirubinometry from above the skin. Gives us a rough estimation of TSB.



- Spherocytosis.
- It is autosomal dominant.



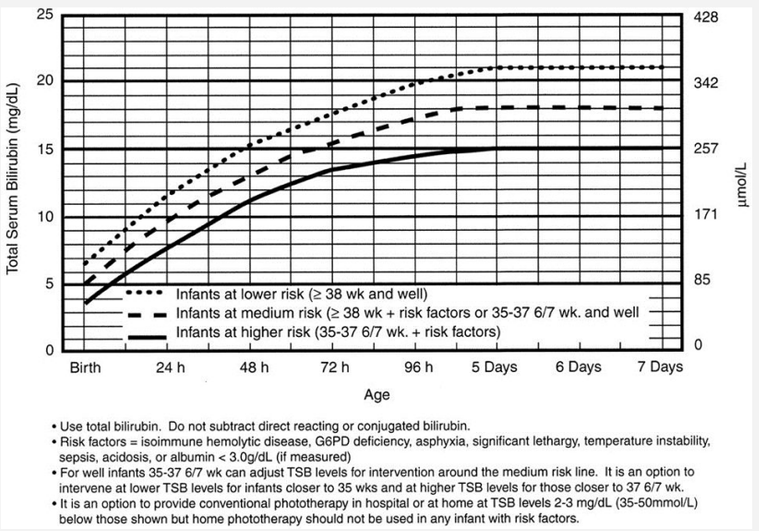
- Elliptocytosis.
- It is autosomal dominant.

Sometimes the patient continues to have jaundice even though phototherapy and transfusion so do smear

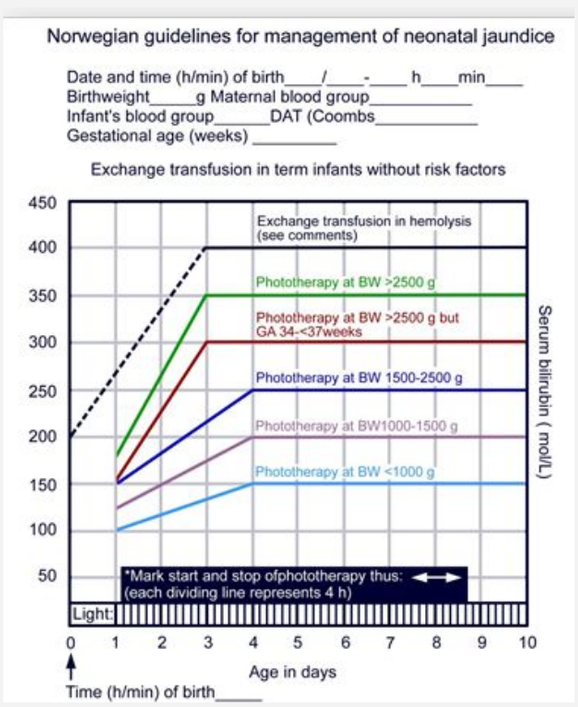
# Management

- 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 breastfeeding/ milk doesn't reach to this although there are some case reports
    - 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

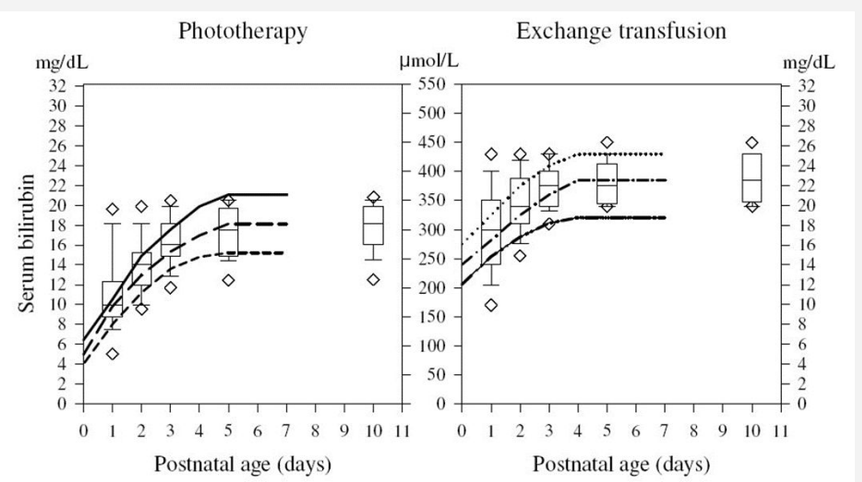



## Guidelines for Management




You order phototherapy #1 if bilirubin didn't drop and it kept increasing to 400 thats when youre in the exchange zone
so #2 exchange transfusion

## APP Recommendation



# 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)
- Changes the isomerization of bilirubin


- 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.

Know it

## Side effects of phototherapy

- **Increased insensible water loss**: Frequent Breast feeding. They get dehydrated
- **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.

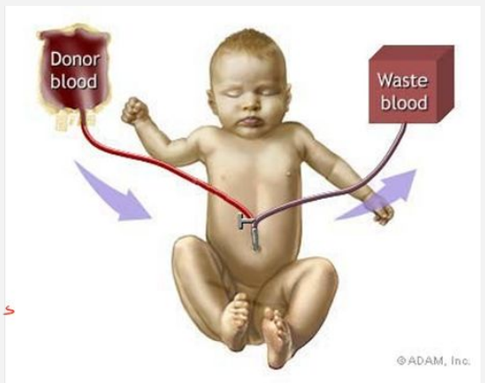
**The therapeutic effect** of phototherapy depends on

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

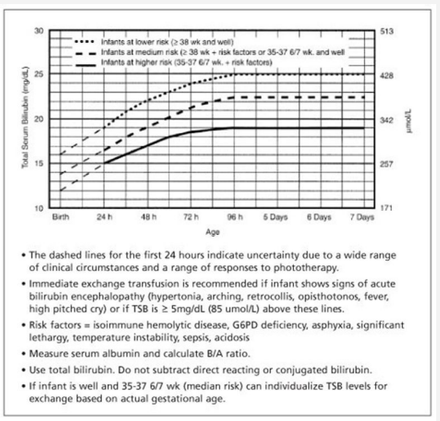
**During phototherapy :**

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

# Exchange Transfusion




Blood bolus is 80 ml /kg




Some indication when patient present with kernicterus even if bilirubin is not that high

**Exchange transfusion**

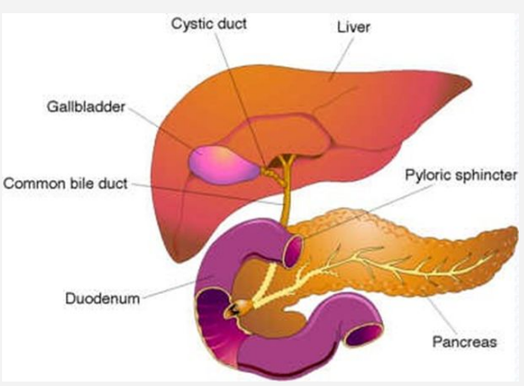
- **From the procedure.**
  **Embolization with air or thrombi, thrombosis, arrythmia, overheparinization, apnea, bradycardia, cyanosis, vasospasm, hypothermia, volume overload, arrest,**
- **From blood products.**
  **Hyperkalemia, hypernatremia, hypocalcemia, acidosis, coagulation disturbance, blood-borne infections.**

***Monitoring of electrolytes, platelet count, coagulation parameters, and arterial blood gases is recommended.**

Read about side effects
(the pic is from internet)

# Other Treatments

- Immunoglobulin help in ABO incompatibility , when you want to shorten the phototherapy or help when the patient isn't in the exchange zone.
- Albumin transfusion
- antibiotic
- Fluid and Electrolytes
- D5% water sun exposure
- Phenobarbital ?
- Mesoporphyrin Still under investigation
- Thyroxine in hypothyriodism




Conjugated Hyperbili
When biliary atresia we refer to surgery.
Choledochal cyst or pancreatic tumor also

# Kernicterus

Basal Ganglia

Hippocampus

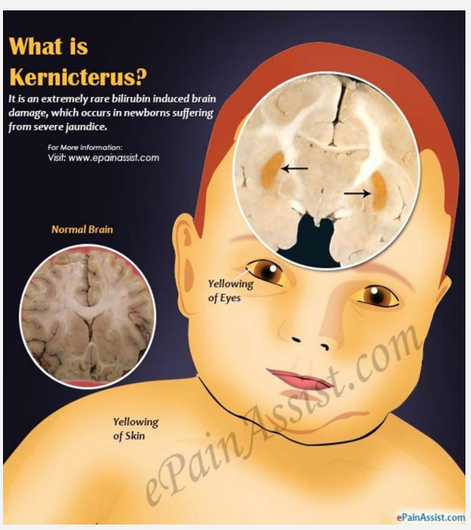
Geniculate Bodies

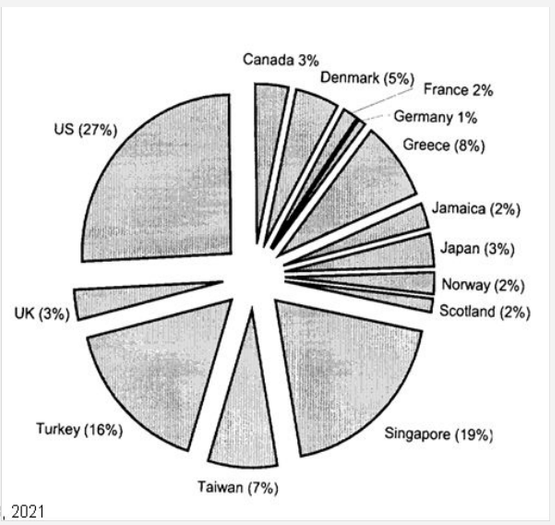
Cranial Nerve Nuclei

- Increased awareness, validated screening nomograms, and phototherapy (PT), KSD still occurs in highly resourced countries and is associated with a 10% mortality and 70% morbidity rate
- Happens when there is excessive indirect hyperbilirubinemia. In cranial nerve most common is the 8th -> hearing will be affected. If in hippocampus ; we'll have pyramidal manifestation.

## 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

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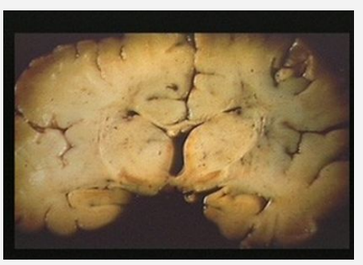
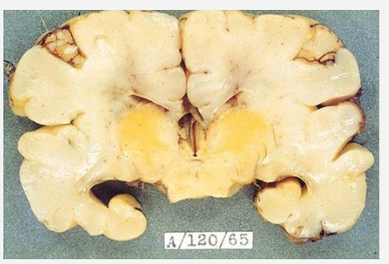





## Causes

- #1 causes worldwide is hemolytic 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 (no treatment available)
- type I
- NO etiology for the severe hyperbilirubinemia was discovered in 73% of cases

## Incidence

- Incidence of bilirubin levels >30mg/dl ( 1/10,000)
- Do we have any registry in Saudi Arabia?? No.
- All reported cases from Saudi literatures were secondary to Crigler Najjarr syndrome

## Case Scenario

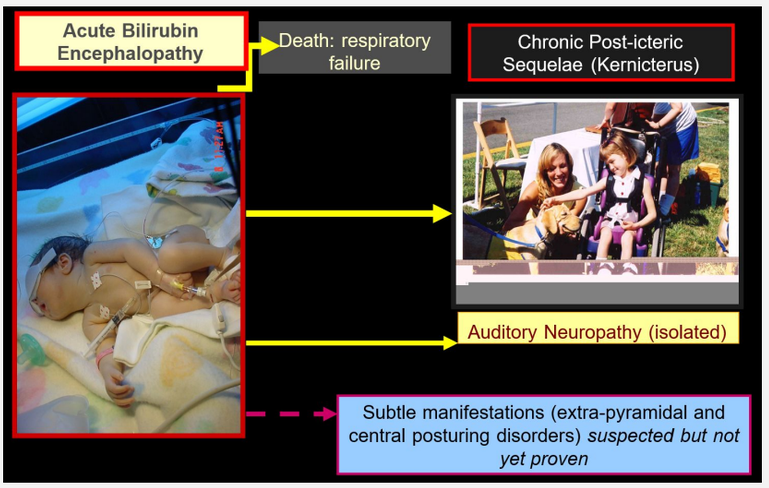
Term Infant with Jaundice

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

## Symptoms and Presentation

- 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 Death: respiratory failure




## Late sequelae can include

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

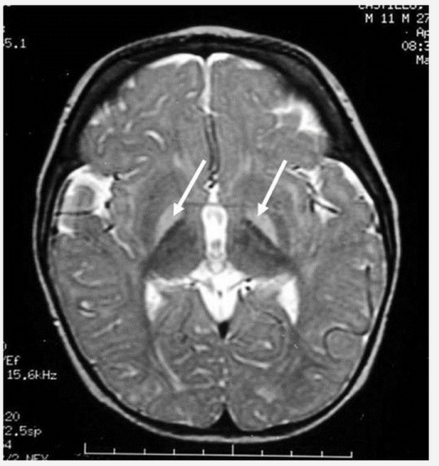
Jaundice + spastic -> encephalopathy

## 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

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

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. mTahney 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. Direct 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 ginno breast feeding jaundice, breast milk jaundice.

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

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

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 umol/L in well term babies by use of exchange transfusion if necessary
D. Results from the oxidation of haemoglobin by the enzyme glucuronyl transferase

# MCQs

-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

A term baby is found to have serum bilirubin of 250 umol/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

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 mcmol/L), with a direct bilirubin measurement of 1.5 mg/dL (26.7 mcmol/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

# Book!

- **ABO incompatibility:** Haemolysis can cause severe jaundice but it is usually less severe than in rhesus disease. The infant's haemoglobin level is usually normal or only slightly reduced and, **in contrast to rhesus disease, hepatosplenomegaly is absent**. The direct antibody test (Coombs test), which demonstrates antibody on the surface of red cells, is positive. The jaundice usually peaks **in the first 12 hours to 72 hours.**
- **Congratulations infection:** Jaundice at birth can also be from congenital infection. In at **24 h to this case**, the bilirubin is **conjugated and the infants have 2 weeks of other abnormal clinical signs**, such as growth restriction, age hepatosplenomegaly and thrombocytopenic purpura.
- **Infection (jaundice at 2 days - 2 weeks):** An infected baby may develop an unconjugated hyperbilirubinemia from poor fluid intake, haemolysis, reduced hepatic function and an increase in the enterohepatic circulation
- Although jaundice from haemolysis usually presents in the 1st day of life, it may occur during the 1st week
- Bruising after birth + polycythemia (venous hematocrit > 0.65 ) will exacerbate infant's jaundice
- Infants who experience severe hypoxia, hypothermia or any serious illness may be more susceptible to damage from severe jaundice. Drugs that may displace bilirubin from albumin, e.g. sulphonamides and diazepam, are avoided in newborn infants.
- In rhesus haemolytic disease, it was found that kernicterus could be prevented if the bilirubin was kept below 340 "mol/l (20 mg/dl).
- Jaundice in babies >2 weeks old (3 weeks if preterm) is called **persistent or prolonged neonatal jaundice**:

However, in most infants with persistent neonatal jaundice, the hyperbilirubinaemia is unconjugated, but this needs to be confirmed on laboratory testing.

In prolonged unconjugated hyperbilirubinaemia:

- 'breast milk jaundice' is the most common cause, affecting up to 15% of healthy breastfed infants; the jaundice gradually fades and disappears by 12 weeks of age
- infection, particularly of the urinary tract, needs to be considered if the infant is unwell
- congenital hypothyroidism may cause prolonged jaundice before the clinical features of coarse facies, dry skin, hypotonia and constipation become evident. Affected infants should be identified on routine neonatal biochemical screening (Guthrie test).

- Conjugated hyperbilirubinemia ( >25 "mol/l) is suggested by the baby passing dark urine and unpigmented pale stools. Hepatomegaly and poor weight gain are other clinical signs that may be present. Its causes include neonatal hepatitis syndrome and biliary atresia (**BA is imp to exclude in any baby with prolonged jaundice!!!!**)