

# A simple case of neonatal unconjugated hyperbilirubinaemia?



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# Case

- Neonate hospitalised at age 12 days for prolonged neonatal jaundice – total bilirubin 627 (conj 12) umol/L;
- Referred to RXH at 7 weeks – having received phototherapy, phenobarbitone, immunoglobins and exchange transfusion; breast feeding stopped → minimal change to bilirubin levels
- Birth history
  - Uncomplicated pregnancy
  - NVD at 38 weeks; birth weight 2950g; APGARS 9 & 10
  - Discharged age 1 day, breastfeeding
- Clinically:
  - “deeply jaundiced”; brown stool; yellow urine
  - No congenital abnormalities
  - Abd – palpable liver (1-2cm); no splenomegaly
  - CNS- initially hypotonic with head lag, moving all limbs; later hypertonic; brisk reflexes; “cycling and fisting”, chorea-athetoid movements; evolving cerebral palsy; ?hearing loss;
  - BIND –bilirubin induced neurological dysfunction

## Effects of Bilirubin Toxicity in Newborns

### Early

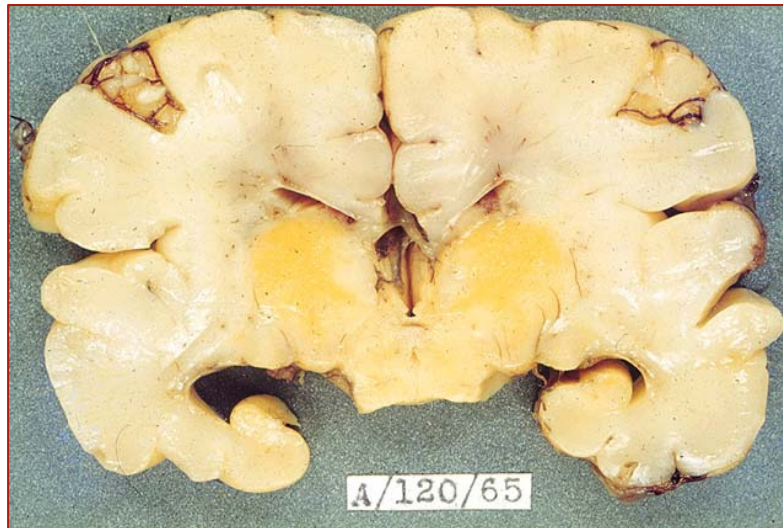
Lethargy  
Poor feeding  
High-pitched cry  
Hypotonia

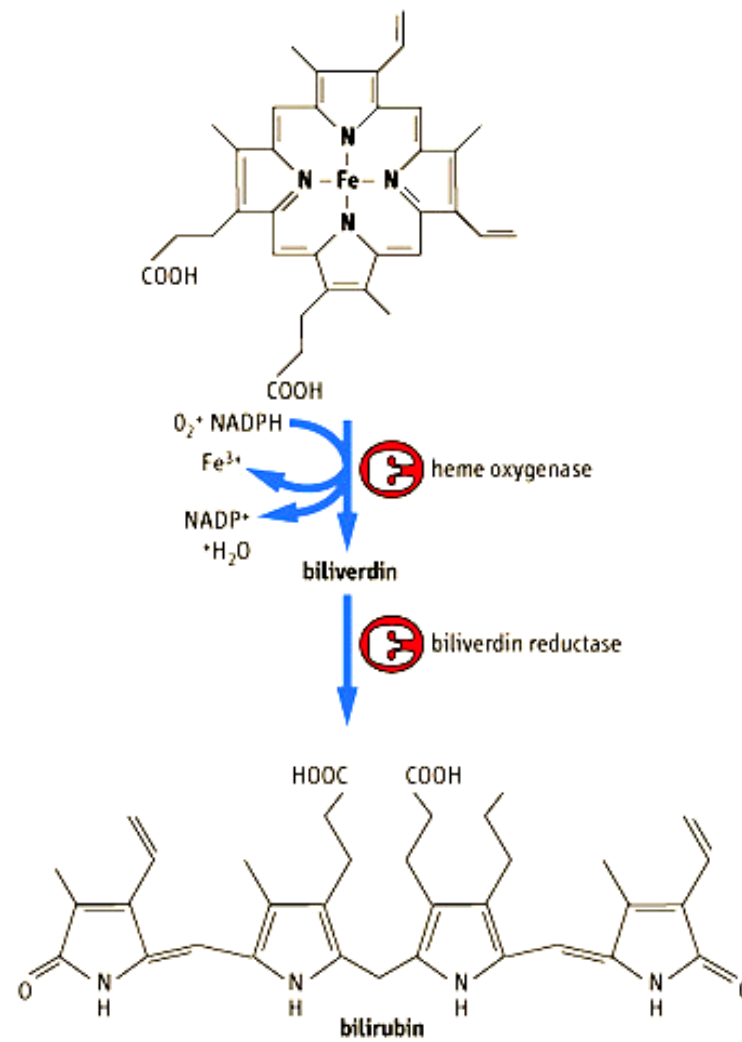
### Late

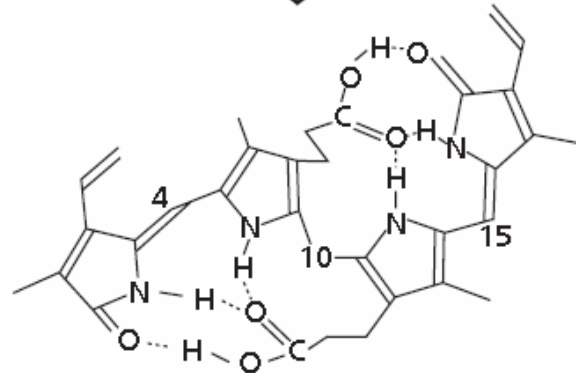
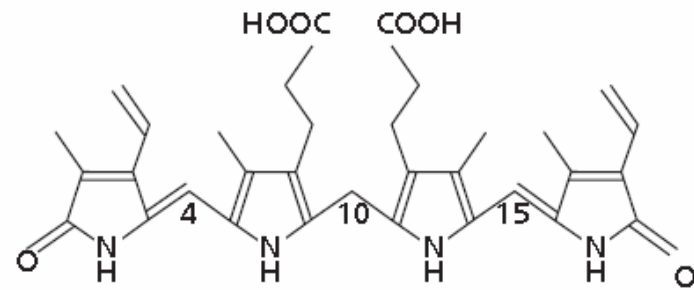
Irritability  
Opisthotonos  
Seizures  
Apnea  
Oculogyric crisis  
Hypertonia  
Fever

### Chronic

Athetoid cerebral palsy  
High-frequency hearing loss  
Paralysis of upward gaze  
Dental dysplasia  
Mild mental retardation

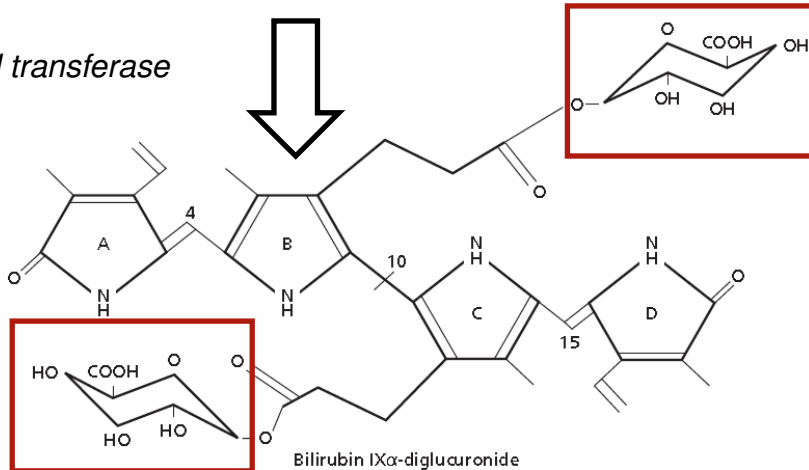
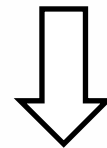




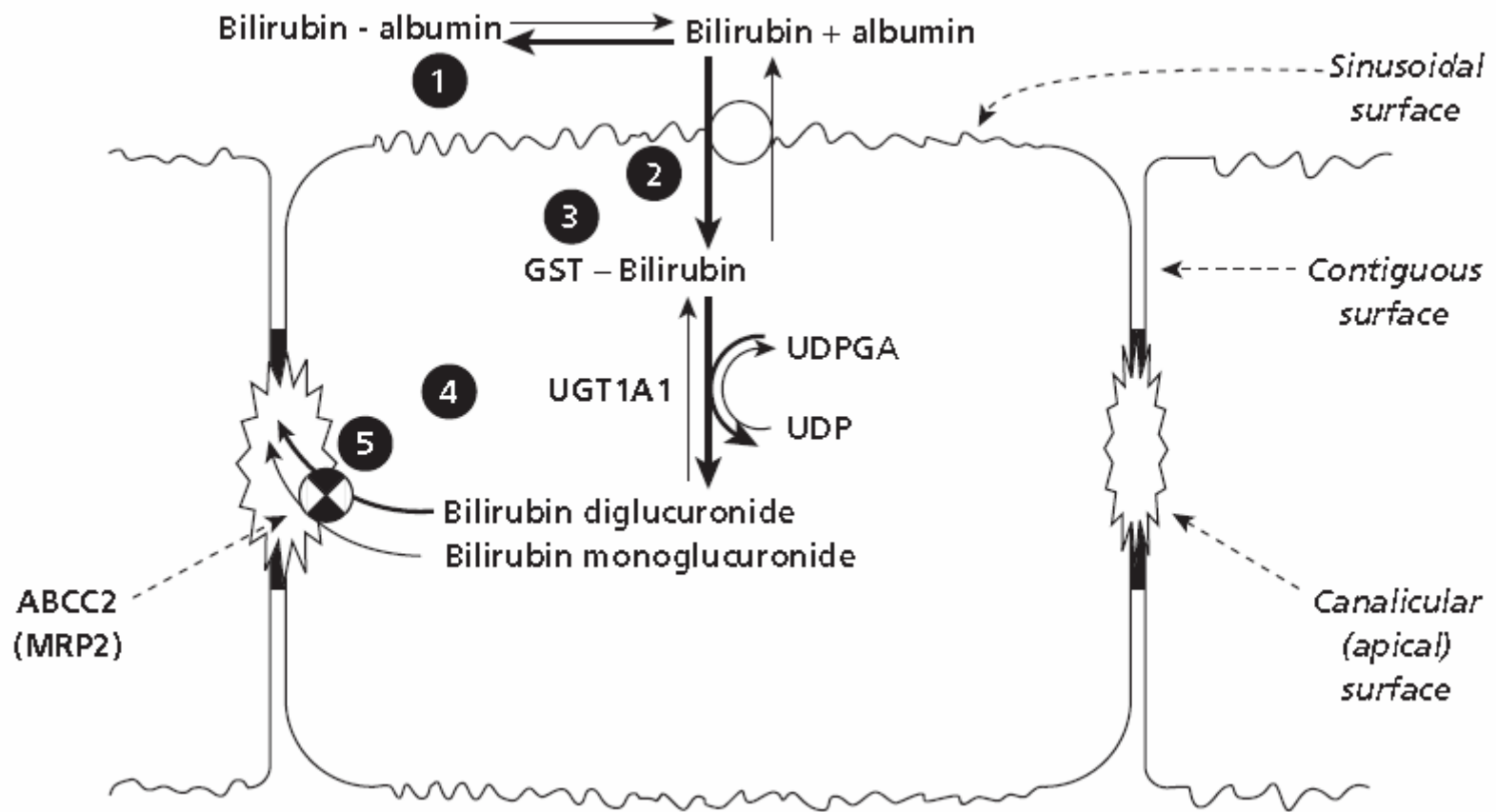


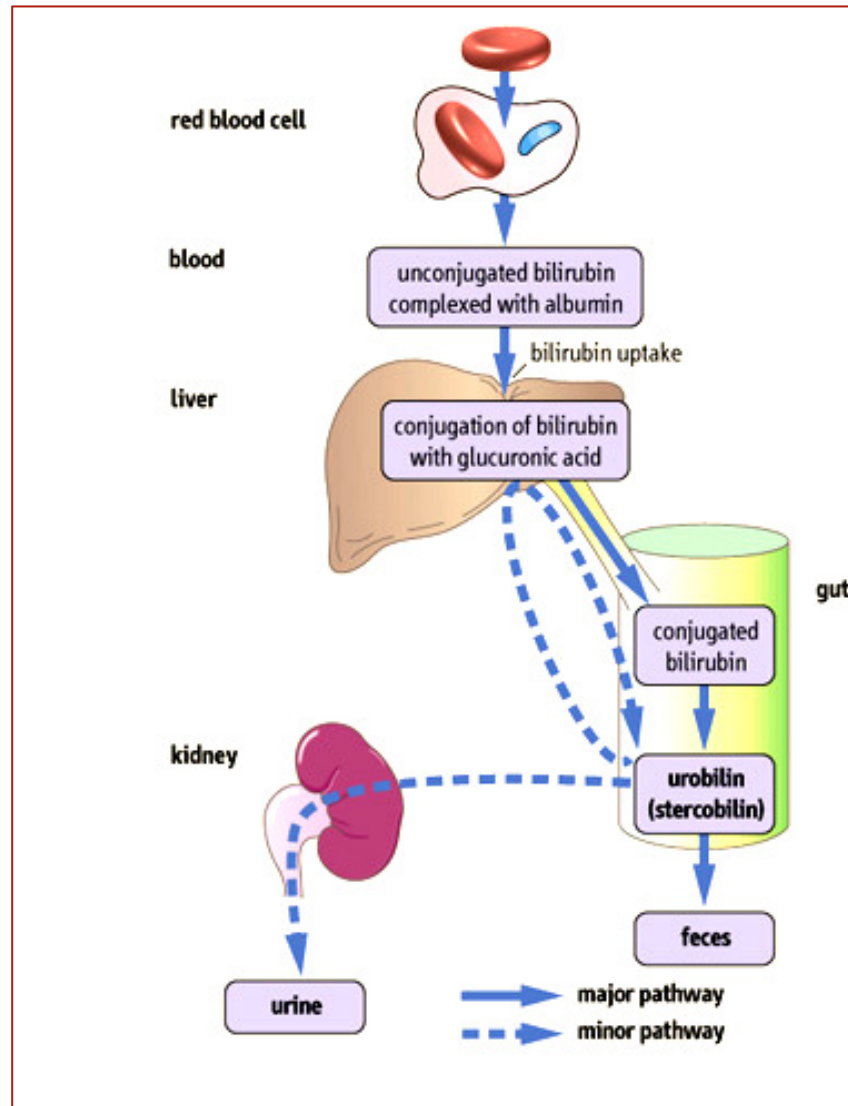
Bilirubin IX $\alpha$ -4Z,15Z

*UDP-glucuronyl transferase*



Bilirubin IX $\alpha$ -diglucuronide



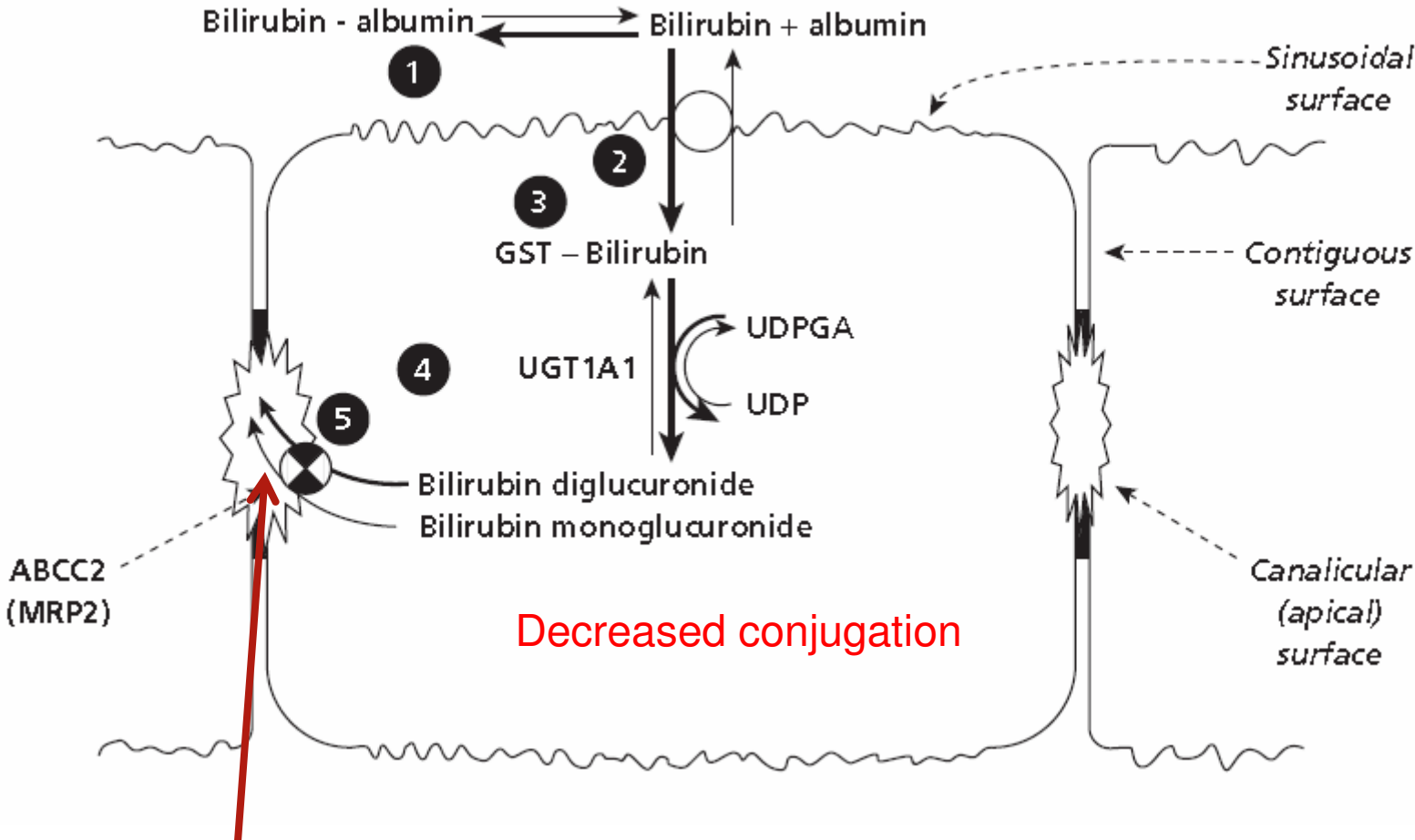


Increased bilirubin load

Decreased conjugation

Decreased excretion

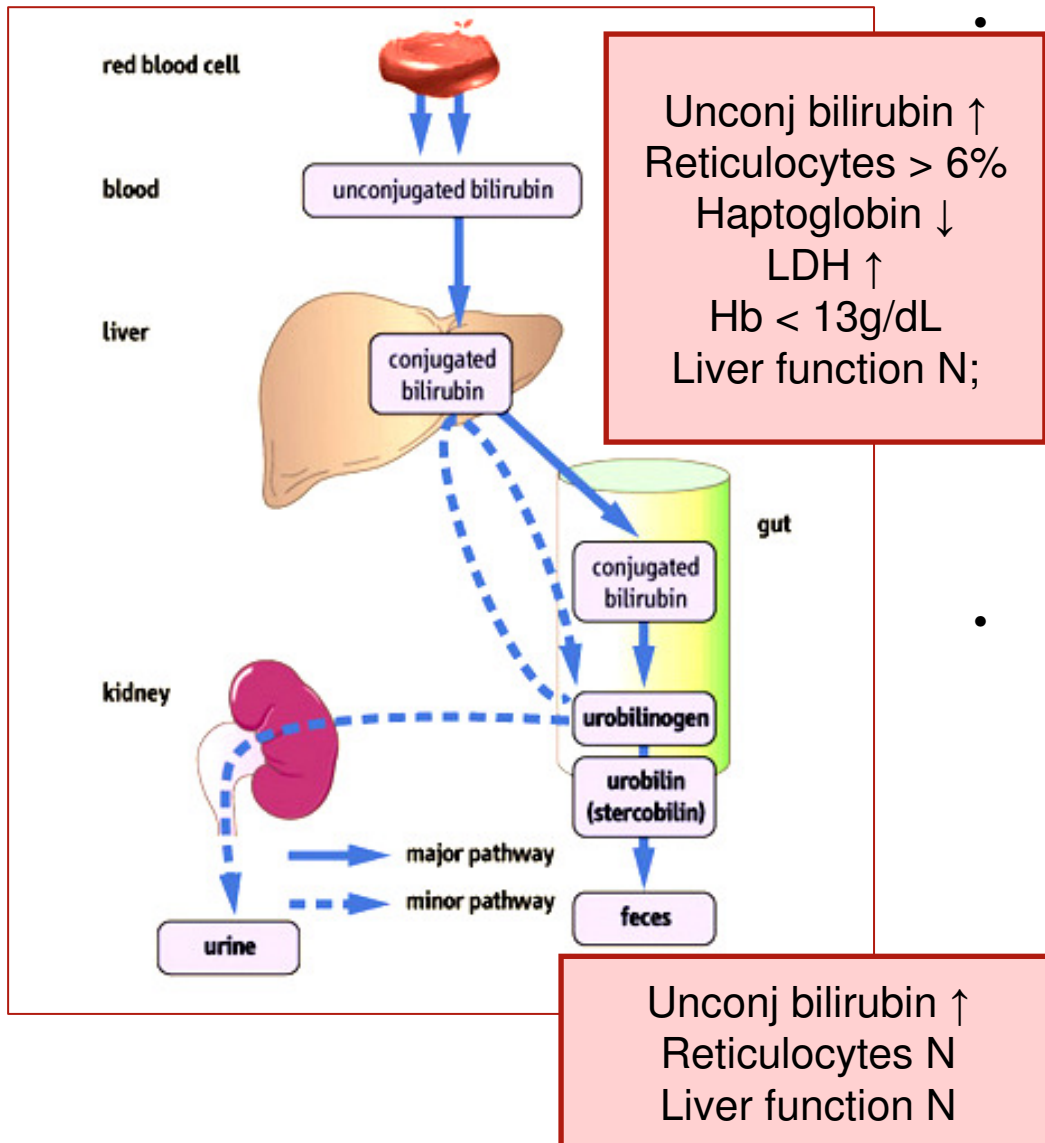
Increased bilirubin load



Decreased conjugation

Decreased excretion

## Increased bilirubin load



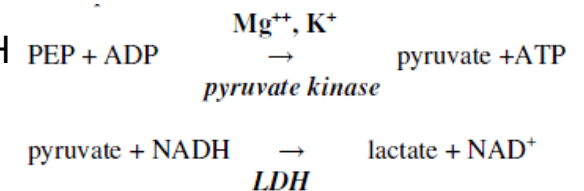
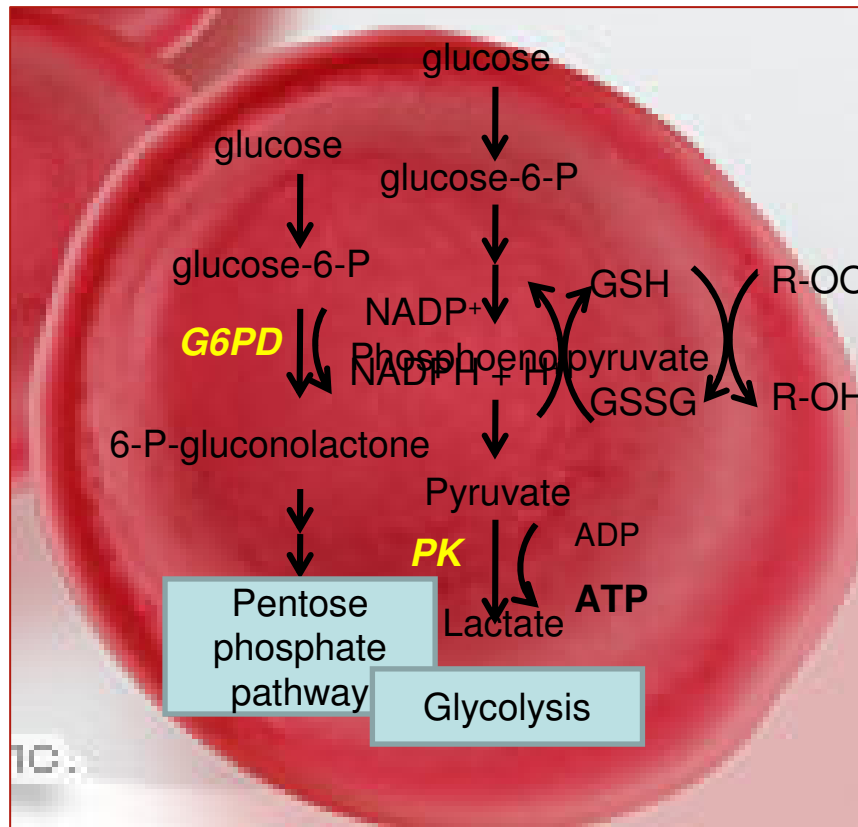
- Excessive production of bilirubin – beyond liver’s ability to conjugate
- Haemolytic
  - *Coombs’ positive*
    - Haemolytic disease of newborn – ABO; Rh –
  - *Coombs’ negative*
    - RBC enzyme deficiencies e.g. G6PD deficiency; pyruvate kinase deficiency
    - RBC membrane abnormalities e.g. Hereditary spherocytosis
    - Haemoglobinopathies e.g. Sickle cell anaemia
    - Sepsis
    - Drugs
- Non- haemolytic
  - Extravascular sources
    - Cephalohaematoma; bruising; CNS haemorrhage
    - Swallowing blood
  - Polycythaemia
    - Fetal-maternal transfusion; delayed cord clamping
    - Twin-twin transfusion
  - Exaggerated enterohepatic circulation
    - Cystic fibrosis
    - Ileal atresia
    - Breast milk

# Glucose 6 Phosphate Dehydrogenase Deficiency

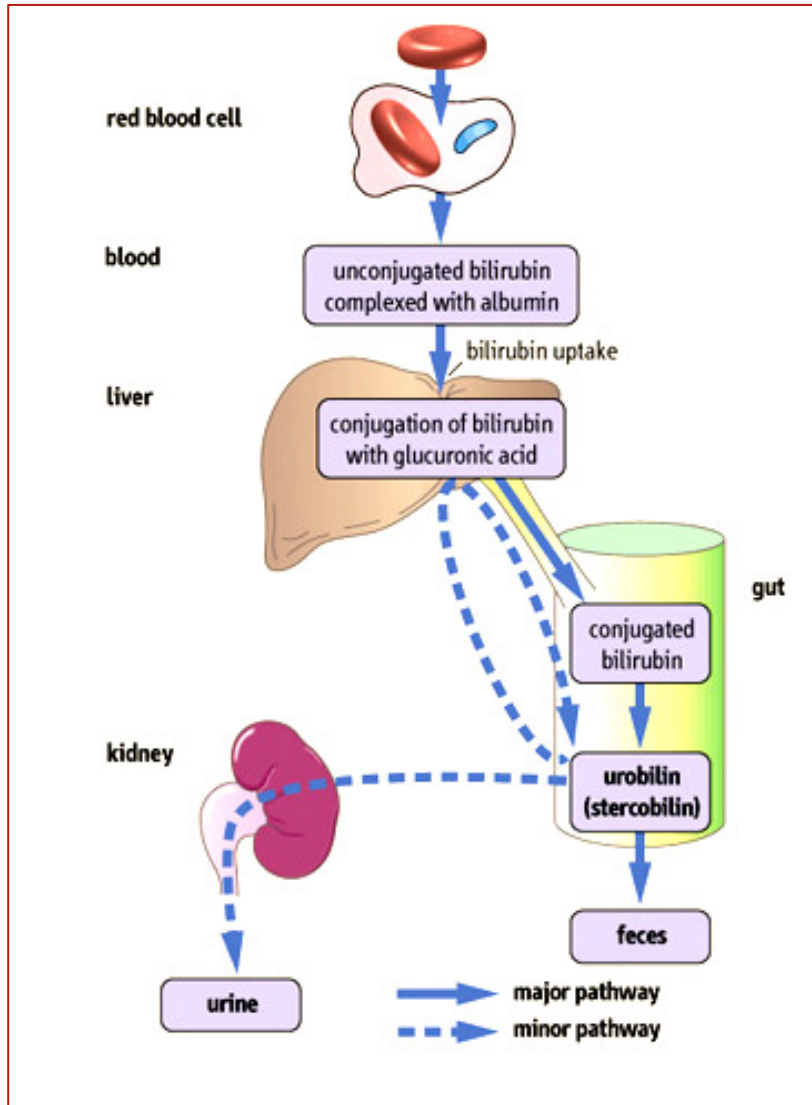
- X-linked recessive
- Common 400 million people worldwide
- Usually asymptomatic; neonatal jaundice
- Lab diagnosis via fluorescence of NADPH – offered at RXH

# Pyruvate kinase deficiency

- Autosomal recessive
- Common
- Varied age of onset
- Dysmorphism – frontal bossing
- Splenomegaly
- Lab diagnosis easy – enzymatic assay – offered at IMD Lab



## Decreased bilirubin conjugation



Decreased uptake and conjugation by hepatic cells.

- Physiological jaundice
- Breast milk jaundice
- Hypothyroidism
- Gilbert's Syndrome
- Crigler-Najjar

Unconj bilirubin ↑  
Hb N  
Reticulocyte % N  
Liver function N

## Physiological jaundice

- Due to:
  - Relative polycythaemia
  - Shorter rbc lifespan (80 vs 120 days)
  - Immature hepatic uptake and conjugation
  - Increased enterohepatic circulation
- vs Pathological:
  - Starts before 24 hours
  - Last longer than age 10 days
  - Rise rate > 85umol/L/day
  - Total bilirubin > 289umol/L (term) / 170umol/L (pre-term)
  - Conjugated >20% of total bilirubin
  - Evidence of underlying illness

## Breast milk jaundice

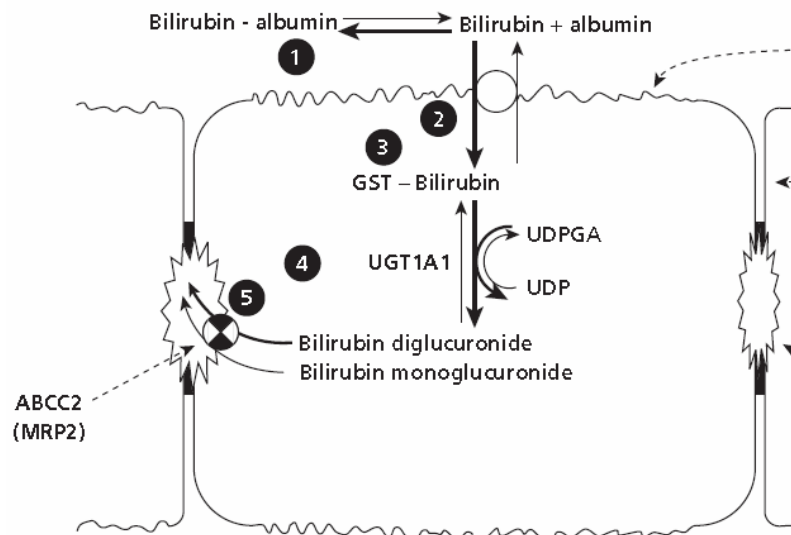
- Early – first few days – 4-7 days (up to 260umol//L) or late –after 2 weeks (up to 340umol/L) onset
- Persists longer than physiological jaundice
- B-glucuronidase – deconjugates bilirubin

## Hypothyroidism

- Decreases conjugation of bilirubin

## Gilbert's Syndrome

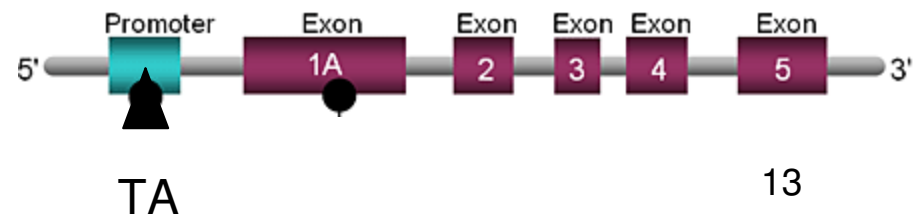
- Also called benign unconjugated hyperbilirubinaemia ; Familial non-haemolytic jaundice
- 1901 Augustine Gilbert
- Autosomal recessive
- 3 – 7 % US; Males > females (2-7:1)
- Benign - Mild jaundice (usually <51umol/L , up to 102umol/L)
- Precipitants: dehydration, fasting, stress
- Neonatal jaundice (esp breast fed)
- Abnormal UGT1A1 TATA region (promotor) → decreased expression



## Crigler Najjar Syndrome

- Also called Hereditary unconjugated hyperbilirubinaemia
- More severe deficiency of the same enzyme
- Severely elevated unconjugated bilirubin usually starting within first 2 weeks of life
- Autosomal recessive; mutation UGT1A1
- Rare 1:1 000 000
- Type 1 – more severe, fatal in early childhood (liver transplant) -lifelong risk of developing kernicterus especially when phototherapy is stopped or during infections or other stress (e.g. fasting)
- Type 2 – milder, may present later in infancy (phenobarbitone)

- **Diagnosis of exclusion (other causes of unconjugated bilirubin incl haemolysis)**
- **All other biochemical findings (hepatic) normal**
- **Persistent bilirubin > 340umol/L after first week of life (otherwise normal) suggests Crigler Najjar**



## Increased bilirubin load

- **Excessive production of bilirubin – beyond liver’s ability to conjugate**
- Haemolytic
  - *Coombs’ positive*
    - Haemolytic disease of newborn – ABO; Rh –
  - *Coombs’ negative*
    - RBC enzyme deficiencies e.g. G6PD deficiency; pyruvate kinase deficiency
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    - Sepsis
    - Drugs
- Non- haemolytic
  - Extravascular sources
    - Cephalohaematoma; bruising; CNS haemorrhage
    - Swallowing blood
  - Polycythaemia
    - Fetal-maternal transfusion; delayed cord clamping
    - Twin-twin transfusion

## Decreased bilirubin conjugation

- **Decreased uptake and conjugation by hepatic cells.**
- Physiological jaundice
- Hypothyroidism
- Breast milk jaundice
- Gilbert’s Syndrome
- Crigler-Najjar

### OUR PATIENT

No other biochemical abnormalities

LFT	Normal
Hb	Normal
Reticulocyte count	Normal
Coombs	Negative
G6PDD	Negative
Thyroid function	Normal
TORCHES	Negative

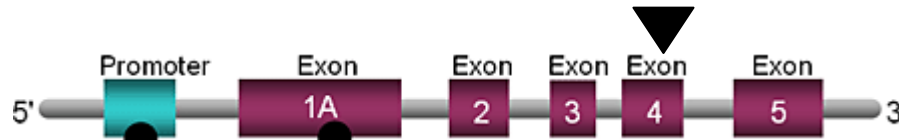
# Confirming diagnosis of metabolic disease:

1. Hallmark metabolite
2. Enzyme activity
3. Genetic Mutation

**Bilirubin**

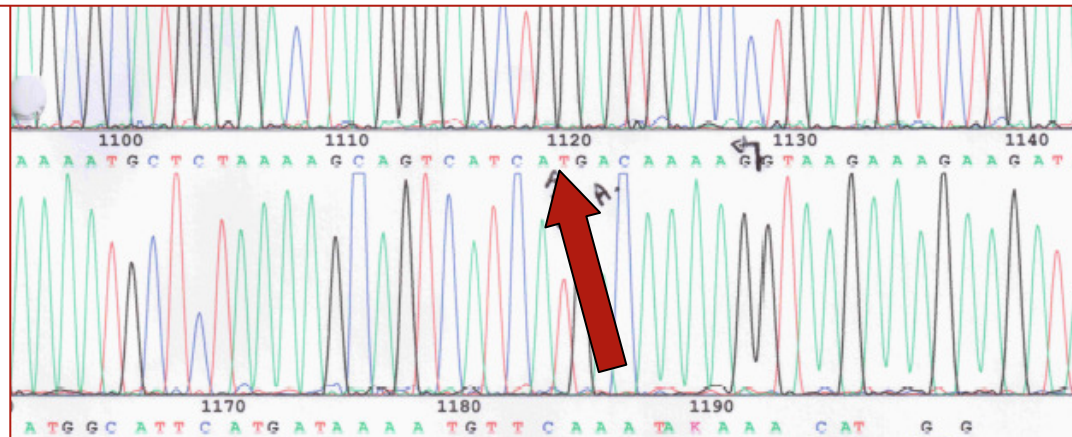
**UDP-glucuronyltransferase**

**UGT1A1**

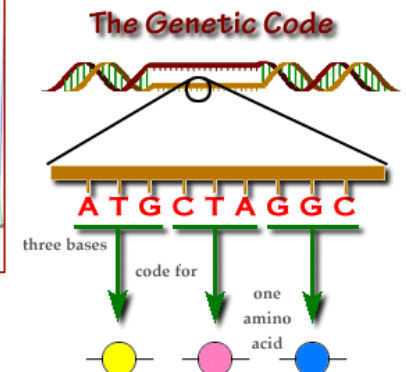


1281 AAAAGCAGTCAT**CAAT**GACAAAAGTTACAAGGAGAACATCATGCGCCTCTCCAGCCTTCA  
 427 --K--A--V--I--**N**--D--K--S--Y--K--E--N--I--M--R--L--S--S--L--H

1281 AAAAGCAGTCAT**CAT**GACAAAAGTT**CA**AGG**AGA**ACAT**CAT**GCGCCTCT**CC**AGCCTTCA  
 427 --K--A--V--I--**M**--T--K--V--T--R--R--T--S--C--A--S--P--A--F--



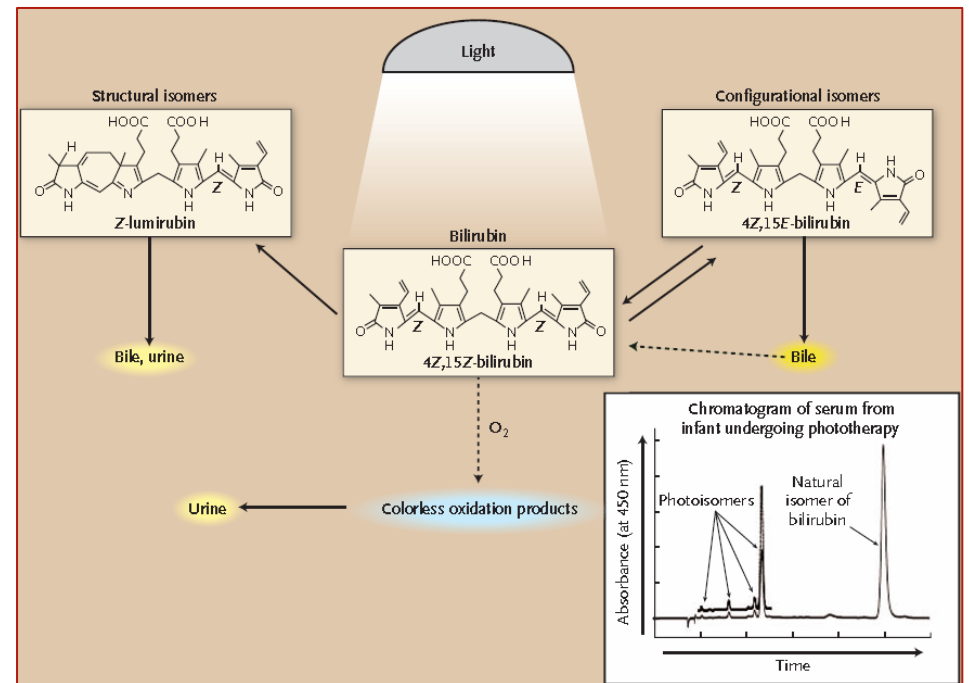
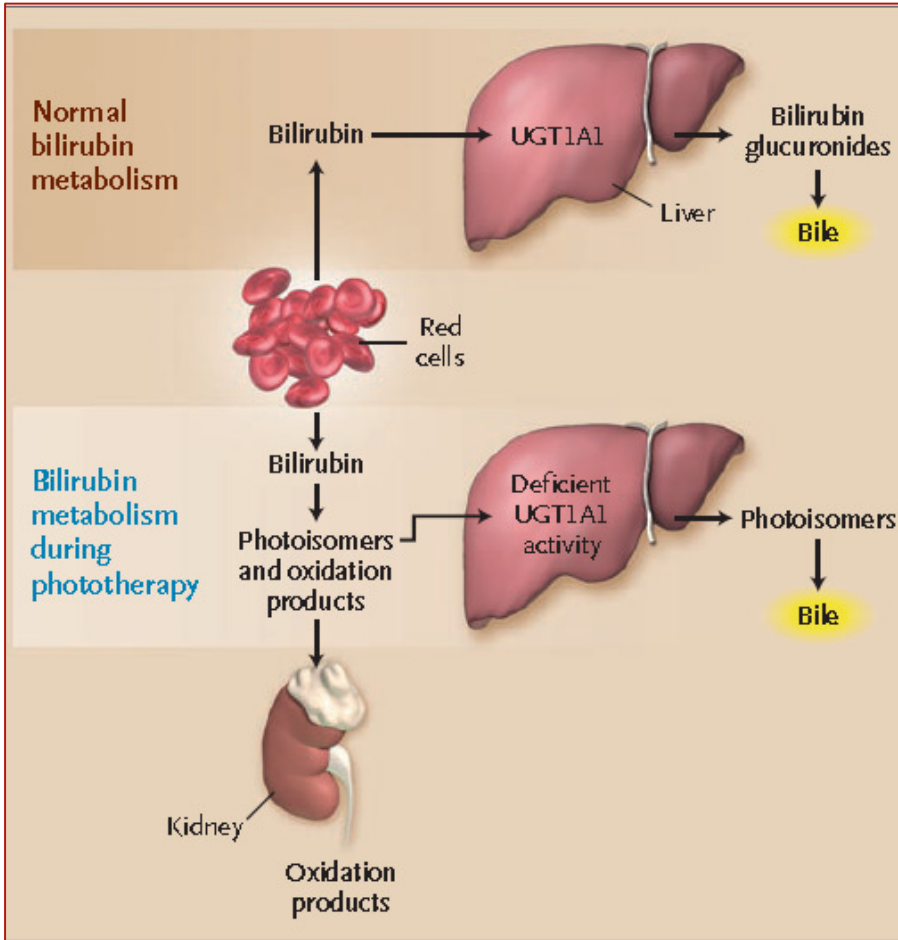
Homozygous del A position 1295 →  
 Asn432Meth → Sequence change thereafter



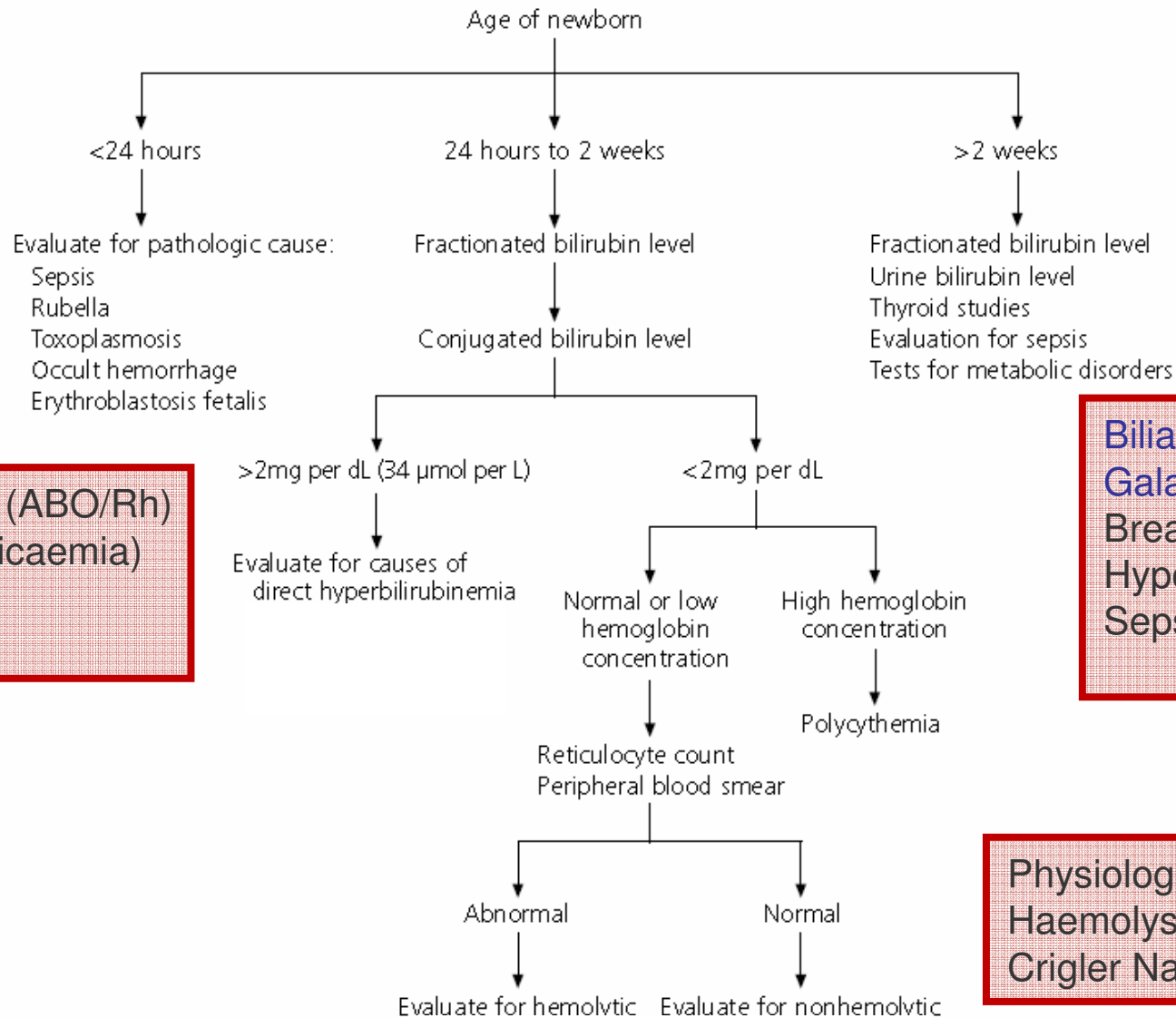
# Further management

- Diagnosis: Crigler-Najjar Syndrome Type I
- Discharged to local hospital on phenobarbitone, cholestyramine, overnight phototherapy and antibiotics (Klebs sepsis) (bilirubin on discharge 400umol/L).

# Effect of phototherapy



## Laboratory Evaluation of Term Newborn with Jaundice



Haemolysis (ABO/Rh)  
Sepsis(septicaemia)  
TORCHES

Biliary atresia  
Galactosaemia  
Breast milk jaundice  
Hypothyroidism  
Sepsis(UTI)

Physiological  
Haemolysis  
Crigler Najjar syndrome

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- Surita Meldau  
*Medical Scientist, NHLS, GSH*

TABLE 3

**Classification of Neonatal Hyperbilirubinemia Based on Mechanism of Accumulation****Increased bilirubin load**

## Hemolytic causes

- Characteristics: increased unconjugated bilirubin level, >6 percent reticulocytes, hemoglobin concentration of <13 g per dL (130 g per L)
- Coombs' test positive: Rh factor incompatibility, ABO incompatibility, minor antigens
- Coombs' test negative: red blood cell membrane defects (spherocytosis, elliptocytosis), red blood cell enzyme defects (G6PD deficiency, pyruvate kinase deficiency), drugs (e.g., sulfisoxazole acetyl with erythromycin ethylsuccinate (Pediazole), streptomycin, vitamin K), abnormal red blood cells (hemoglobinopathies), sepsis

## Nonhemolytic causes

- Characteristics: increased unconjugated bilirubin level, normal percentage of reticulocytes
- Extravascular sources: cephalohematoma, bruising, central nervous system hemorrhage, swallowed blood
- Polycythemia: fetal-maternal transfusion, delayed cord clamping, twin-twin transfusion
- Exaggerated enterohepatic circulation: cystic fibrosis, ileal atresia, pyloric stenosis, Hirschsprung's disease, breast milk jaundice

**Decreased bilirubin conjugation**

- Characteristics: increased unconjugated bilirubin level, normal percentage of reticulocytes
- Physiologic jaundice
- Crigler-Najjar syndrome types 1 and 2
- Gilbert syndrome
- Hypothyroidism
- Breast milk jaundice

**Impaired bilirubin excretion**

- Characteristics: increased unconjugated and conjugated bilirubin level, negative Coombs' test, conjugated bilirubin level of >2 mg per dL (34  $\mu$ mol per L) or >20% of total serum bilirubin level, conjugated bilirubin in urine
- Biliary obstruction: biliary atresia, choledochal cyst, primary sclerosing cholangitis, gallstones, neoplasm, Dubin-Johnson syndrome, Rotor's syndrome
- Infection: sepsis, urinary tract infection, syphilis, toxoplasmosis, tuberculosis, hepatitis, rubella, herpes
- Metabolic disorder: alpha<sub>1</sub> antitrypsin deficiency, cystic fibrosis, galactosem, glycogen storage disease, Gaucher's disease, hypothyroidism, Wilson's disease, Niemann-Pick disease
- Chromosomal abnormality: Turner's syndrome, trisomy 18 and 21 syndrom
- Drugs: aspirin, acetaminophen, sulfa, alcohol, rifampin (Rifadin), erythromycin, corticosteroids, tetracycline

G6PD = glucose-6-phosphate dehydrogenase.

Information from Siberry GK, Iannone R, eds. *The Harriet Lane handbook: a manual for pediatric house officers*. 15th ed. St. Louis: Mosby; 2000:257-8.