




# Prolonged Neonatal Jaundice

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# Definition

- Prolonged jaundice is defined as a serum bilirubin level higher than 5 mg/dl, which persists at postnatal 14 days in term infants and 21 days following the birth in preterm infants.
- It affects up to 15% of all newborns and 40% of breastfed infants.

- Although underlying cause can not be found in the majority of prolonged jaundice cases, this may also be the first sign of a serious causative pathology.
- The difficult task facing primary care providers is discriminating between serious conjugated hyperbilirubinemia and benign unconjugated jaundice because in the early stage, the infants can look very well except for their jaundice.
- Early identification of infants with cholestatic liver disease is critical so that a correct diagnosis is made and the appropriate therapy is instituted.

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- Tests performed to determine the underlying cause and failure to determine the etiology cause anxiety for both families and physicians.
  - The most important point is to determine whether prolonged jaundice is of a benign cause or is due to a substantial disease.
  - For this reason, health care providers should not take unnecessary tests in normal infants, but should also recognize infants with a causative pathology.
  - Neonatal jaundice still maintains its importance in neonatal clinical practice, since early diagnosis and treatment is feasible.

# Direct/indirect hyperbilirubinemia,

- Although jaundice in early infancy is predominantly caused by indirect hyperbilirubinemia, it can also be seen as direct hyperbilirubinemia.
- Distinguishing between these types of jaundice is crucial in determining the etiology of prolonged jaundice.

# Causes of indirect hyperbilirubinemia in neonatal prolonged jaundice

- Breast milk jaundice
- Sepsis
- Hemolytic diseases
- Congenital hypothyroidism
- Urinary tract infection
- Extravascular blood collection
- Pyloric stenosis
- Gilbert syndrome
- Crigler najjar syndrome

# Breast milk jaundice

- To date, the most common cause of prolonged jaundice of indirect hyperbilirubinemia has been identified as breast milk jaundice.
- The cause of prolonged jaundice seen in 15–40% of newborns is breastfeeding.
- Besides, breast milk jaundice may extend up to the twelfth week of life.
- However, the diagnosis of breast milk jaundice is made by excluding other causes.

# *Gilbert's syndrome*

- In Gilbert's syndrome, both hepatocytes' bilirubin uptake is decreased and UDPGT activity is decreased.
- It is inherited in autosomal dominant or autosomal recessive.
- It has a prevalence of 2–6%.
- It is thought that hyperbilirubinemia, which is observed in newborns with weight loss after insufficient caloric intake, also has a similar etiologic mechanism to Gilbert's syndrome.
- Phenobarbital can be used as treatment in selected cases of Gilbert's syndrome.



# *Crigler Najjar syndrome type 1*

- Crigler-Najjar Syndrome type 1 is caused by the complete absence of the hepatic glucuronyl transferase enzyme and is inherited autosomal recessively.
- It is a chronic non-hemolytic indirect hyperbilirubinemia syndrome and has a severe clinical course.
- In the homozygous form, severe indirect hyperbilirubinemia, which may progress to kernicterus, develops within the first three days of life.
- Diagnosis is made by percutaneous liver biopsy. UGT activity is measured in the biopsy sample/specimen.
- Phenobarbital is not an effective treatment of choice in Crigler-Najjar Syndrome type 1 syndrome

# *Crigler Najjar Syndrome type 2*

- Crigler Najjar Syndrome Type 2 is more common than Type 1.
- The clinical course is better.
- The reason for this is that the activity of the UDPGT enzyme is partially present in Type 2.
- It has an autosomal dominant inheritance.
- Although indirect bilirubin levels start to increase in the first days of life, they usually do not go above 20 mg/dl levels.
- Unlike type 1, Crigler-Najjar Syndrome responds to phenobarbital. Therefore, response to phenobarbital can be used as a distinguishing strategy for type 1 and type 2 disease.
- In Crigler-Najjar syndrome type II, UDPGT activity is reduced in the same way as is found in infants with prolonged jaundice due to Gilbert's syndrome.

# *Lucey Driscoll Syndrome*

- It is a rare disease of newborn, which goes with high bilirubin levels in the postnatal first two days of life.
- Bilirubin levels are above 20 mg/dl and may rise to levels that can require exchange transfusion.
- These high bilirubin levels can persist for longer than 14 days.
- Most of these infants develop kernicterus, whether exchange transfusion is not performed.

# Hypothyroidism

- It is one of the substantial causes of neonatal prolonged jaundice.
- Prolonged jaundice is seen in approximately 10% of infants with congenital hypothyroidism.
- Decreased UGT activity is blamed for the pathophysiology of hyperbilirubinemia seen in congenital hypothyroidism.
- In this case, hyperbilirubinemia may persist for several months.
- Treatment with thyroid hormone leads rapid resolution of jaundice.

# Direct hyperbilirubinemia

- Direct hyperbilirubinemia is defined as serum direct bilirubin  $>1.5$  mg/dl or direct bilirubin  $>20\%$  of total bilirubin.
- Although rare, it usually indicates an underlying pathological cause and requires immediate investigation and prompt intervention.
- Direct hyperbilirubinemia (cholestatic jaundice) is never physiological.

# Direct hyperbilirubinemia

- It affects 1/2500 live births and should be suspected in all jaundiced infants with light colored stools and/or dark urine.
- For the early diagnosis of cholestasis, it is recommended to measure the serum total bilirubin (STB) and direct bilirubin levels of each newborn with prolonged jaundice.

# Causes of **direct** hyperbilirubinemia in neonatal prolonged jaundice

- 1- Structural
- Extrahepatic biliary atresia
- Choledochal cyst
- Caroli's syndrome
- Choledocholithiasis
- Alagille's syndrome
- Nonsyndromic bile duct paucity
- Undersized extrahepatic biliary system (biliary hypoplasia)
- Neonatal sclerosing cholangitis

# Causes of **direct** hyperbilirubinemia in neonatal prolonged jaundice

## 2-Infection

- Viral
  - - Cytomegalovirus
  - - Herpes simplex
  - - Adenovirus
  - - Enterovirus
  - - Parvovirus B19
  - - Hepatitis B virus
- Bacterial infection (sepsis or remote from liver [eg, urinary tract infection])
- Toxoplasmosis
- Syphilis



# Causes of **direct** hyperbilirubinemia in neonatal prolonged jaundice

## 3-Metabolic

- Alpha-1-antitrypsin deficiency
- Galactosemia
- Tyrosinemia
- Hereditary fructose intolerance
- Glycogen storage disease type IV
- Lipid storage disease - Niemann-Pick disease,- Gaucher's disease, Wolman's disease
- Mitochondrial enzymopathies (including fatty acid oxidation disorders)
- Peroxisomal disorders (eg, Zellweger syndrome)
- Bile acid synthesis disorders
- Urea cycle defects

# Causes of **direct** hyperbilirubinemia in neonatal prolonged jaundice

## 4-Genetic

- Cystic fibrosis
- Trisomy 21
- Trisomy 18

# Causes of **direct** hyperbilirubinemia in neonatal prolonged jaundice

## 5-Neoplastic

- Neuroblastoma
- Hepatoblastoma
- Histiocytosis X

## 6-Toxic

- Drug induced
- Total parenteral nutrition

# Extrahepatic biliary atresia

- Biliary atresia is the most common cause of neonatal cholestasis, and affected infants may appear healthy for a considerable time.
- Without therapy, its natural course is very poor, with less than 10% survival by the third year.
- Kasai hepatoportoenterostomy should be performed in the first 45 days of life to restore bile flow and reduce further damage to the liver.
- Early diagnosis of biliary atresia is the most important predictive factor in operated newborns.

# Hepatobiliary scanning

- HIDA Scan:
- Infants should receive three to five days of phenobarbital (5 mg/kg/day) to promote hepatocellular uptake of the tracer.
- Serial images are obtained evaluating hepatocellular uptake and biliary excretion into the small intestine. Hepatobiliary scanning is almost 100% sensitive for extrahepatic biliary atresia because the excretion of tracer into the small bowel almost always rules out biliary atresia. Unfortunately, a nondraining scan is not specific and it can have many different etiologies.

# cholestatic liver disease

- A thorough physical examination may provide evidence of cholestatic liver disease and its underlying etiology. Some helpful features may include
- dysmorphic faces (Alagille's syndrome),
- evidence of congenital heart disease (Alagille's syndrome, biliary atresia),
- an abdominal mass (choledochal cyst, tumour),
- hepatomegaly/splenomegaly (found with obstruction, inflammation, a storage disorder or tumour),
- failure to thrive and an abnormal respiratory examination (cystic fibrosis).
- In addition, the neuromuscular examination may reveal hypotonia or abnormal reflexes (as with mitochondrial disorders and vitamin E deficiency)

# Mixed Direct/indirect hyperbilirubinemia

- Intrauterine infections,
- Bacterial sepsis,
- Galactosemia,
- Aminoacidemias,
- congenital hypopituitarism can occur with a mixture of increased direct and indirect bilirubin.

# Infections

- In the neonatal period, infections can be accompanied by jaundice.
- Particularly, urinary tract infections, and sepsis are common causes of jaundice. Indirect hyperbilirubinemia can develop in sepsis due to hemolysis caused by endotoxins.
- The incidence of urinary tract infection in asymptomatic infants, under two months of age with jaundice, but without fever, has been shown to be 7.5%.
- Therefore, prolonged jaundice may be the unique finding in urinary tract infection.
- In a study, the most common infection associated with jaundice in the neonatal period was found to be urinary tract infection



# Diagnosis

- Global protocol for investigating prolonged jaundice is not defined yet.
- The incidence of conditions that play a role in prolonged jaundice in terms of etiology varies between countries.
- This difference is the main reason for the various protocols.
- The cost of the examinations in cases with prolonged jaundice and the differences in healthcare systems between countries also contribute to this situation.

# Initial tests in patients with prolonged jaundice

1. Direct and indirect bilirubin level
2. Complete blood count, peripheral blood smear
3. Maternal blood group, infant blood group, Direct Coombs test, G6PD enzyme level
4. TSH, fT<sub>4</sub>
5. Urinalysis, urine culture, Urine Reducing substance

# Tests for Direct Hyperbilirubinemia

1. Blood
  - Liver panel: AST, ALT ALP, gamma-glutamyl transpeptidase, total bilirubin, conjugated bilirubin and albumin
  - Coagulation studies (PT, INR, PTT)
  - Complete blood count and differential with smear
  - Toxoplasmosis, other infections, rubella, Cytomegalovirus infection and herpes simplex (TORCH) serology
  - Blood culture
  - Hepatitis B surface antigen
  - Glucose/serum lactate/serum amino acids/ammonia
  - TSH, fT<sub>4</sub>
  - Iron studies, ferritin
  - Galactosemia screen

# Tests for **Direct** Hyperbilirubinemia

## 2-Urine

- Reducing substances
- Organic acids
- Bacterial culture
- Urine Cytomegalovirus (positive result before four weeks of age is highly suggestive of congenital Cytomegalovirus)

## 3-Sweat test

# Tests for **Direct** Hyperbilirubinemia

## 4-Imaging

- Abdominal ultrasound (evaluate for mass, choledochal cyst, small gallbladder, triangular cord sign)

## 5-Hepatobiliary scanning

# Liver biopsy

- Liver biopsy is the most informative investigation in the evaluation of neonatal conjugated hyperbilirubinemia, with many centres reporting over 90% accuracy for biliary atresia.
- Some histological findings include bile ductular proliferation, bile plugging and portal fibrosis in biliary atresia, parenchymal inflammatory infiltrate and giant cell transformation in neonatal hepatitis, and portal duct hypoplasia with Alagille's syndrome. Further immunostaining, histo-chemistry and electron microscopy can assist in the diagnosis of other disorders, such as alpha-1-antitrypsin deficiency and some storage disorders.

# Treatment

- **Pharmacological treatment**
- Agents used to treat neonatal jaundice can be classified according to their action of mechanism as follows;
- Inhibition of bilirubin production (Tin protoporphyrin and mesoporphyrin, Zinc protoporphyrin and mesoporphyrin),
- accelerating bilirubin excretion process (Phenobarbital, Ethanol, Chloroquine, Antihistamines, Clofibrate, Antipyrine),
- inhibiting the enterohepatic circulation (Agar, Activated charcoal, Cholestyrylpyriron, bilirubin oxidase) and IVIG
- IVIG, phenobarbital, and metalloporphyrins are the most preferred ones in the treatment of hyperbilirubinemia.

# *Phenobarbital*

- Phenobarbital is a potent inducer of microsomal enzymes.
- It makes this strong induction by inducing the enzyme glucuronyl transferase.
- By this mechanism, it increases bilirubin conjugation, excretion and bile flow, which means that it affects all steps of bilirubin metabolism.
- In addition, phenobarbital is used in the diagnosis and treatment of Crigler Najjar disease It is recommended for use only in highrisk conditions.



