Causes of cholestasis in the newborn, which presents as direct or conjugated hyperbili
cholestasis in neonates and young infants".)

DEFINITIONS

Although there is no consensus amongst experts in the field in defining the clinical sig
levels for term and late preterm infants, the authors use the following definitions in th

- Benign neonatal hyperbilirubinemia is a transient and normal increase in bilirubir
referred to as "physiologic" jaundice.
- Significant hyperbilirubinemia in infants ≥35 weeks gestational age (GA) is define
nomogram (figure 1) [1].
- Severe neonatal hyperbilirubinemia is defined as a TB >25 mg/dL (428 micromol/L
bilirubin-induced neurologic dysfunction (BIND).
- Extreme **neonatal hyperbilirubinemia** is defined as a TB >30 mg/dL (513 microm
bilirubin-induced neurologic dysfunction (BIND).
- **BIND** is due to brain damage from free bilirubin that crosses the blood-brain barr
molecular and cytological injuries of brain cells. (See "Unconjugated hyperbilirubi
clinical manifestations", section on 'Clinical manifestations'.)
    - Acute bilirubin encephalopathy (ABE) is used to describe the acute manifestat
hyperbilirubinemia in term and late preterm infants: Epidemiology and clinica
encephalopathy'.)
    - Chronic bilirubin encephalopathy (CBE, previously referred to as kernicterus) i
bilirubin neurotoxicity. (See "Unconjugated hyperbilirubinemia in term and la
manifestations", section on 'Chronic bilirubin encephalopathy (kernicterus)'.)

BILIRUBIN METABOLISM

Knowledge of the basic steps in bilirubin metabolism is essential to the understanding
Bilirubin metabolism is briefly reviewed here and is discussed in detail separately (figu

conjugated bilirubin. The unconjugated bilirubin is reabsorbed through the intest
as the enterohepatic circulation of bilirubin.

BENIGN NEONATAL HYPERBILIRUBINEMIA

Mechanism — Benign neonatal hyperbilirubinemia (also previously referred to as "ph
reacting) bilirubinemia that occurs in nearly all newborns [2]. It is a normal transitiona
cells, the immaturity of the newborn's liver to efficiently metabolize bilirubin, and incre

Normal adult total serum or plasma bilirubin (TB) levels are <1 mg/dL, while term new
approximately 8 to 9 mg/dL because:

- Newborns have more red blood cells (hematocrit between 50 to 60 percent), and f
85 days) than those in adults. After birth there is an increased turnover of fetal re

- Bilirubin clearance (conjugation and excretion) is decreased in newborns, mainly d
diphosphogluconurate glucuronosyltransferase (UGT1A1). UGT activity in term inf
of the adult liver and does not reach adult levels until 14 weeks of age [3,4].

- There is an increase in the enterohepatic circulation of bilirubin as the amount of
conversion of conjugated bilirubin to urobilin, allowing for increased deconjugatio
This further increasing the bilirubin load in the infant. (See 'Bilirubin clearance and

Peak TB levels and time to resolution — Peak total serum or plasma bilirubin (TB) ar
gestational age (GA), likely because of differences in hepatic uptake, clearance, and ex

- Peak TB – Both the height and the timing of peak TB typically vary based on ethnic

  - In Caucasian and African American term infants, the mean TB levels peak at 4
micromol/L). The 95th percentile ranges from 13 to 18 mg/dL (222 to 308 micr

  - In some East-Asian infants, mean TB levels can peak to 10 to 14 mg/dL (171 to
120 hours of age.

- Time to resolution – Visible jaundice resolves within the first one to two weeks aft
formula-fed Caucasian and African American infants, and by the 10th day in Asian
65 percent of exclusively breastfed newborns, although approximately one in five
hyperbilirubinemia beyond two weeks of age has been labelled as prolonged hyp

production due to hemolytic disease processes, such as [8,11,12,14-18]:

- Isoimmune-mediated hemolysis (eg, ABO or Rh[D] incompatibility) [19]. (See "Mar pregnancy" and "Postnatal diagnosis and management of hemolytic disease of th
- Inherited red blood cell membrane defects (eg, hereditary spherocytosis and ellip elliptocytosis and related disorders".)
- Erythrocyte enzymatic defects (eg, glucose-6-phosphate dehydrogenase [G6PD] d erythropoietic porphyria). (See "Diagnosis and management of glucose-6-phospha deficiency" and "Congenital erythropoietic porphyria".)
- Sepsis – The mechanism is not known; however, one theory suggests that increas blood cells [8].
- Other causes of increased bilirubin production due to increased red blood cell bre within a closed space, such as in cephalohematomas. (See "Neonatal polycythemi
- Macrosomic infants of diabetic mothers (IDM) have increased bilirubin productior (See "Infants of women with diabetes".)

Decreased clearance — Inherited defects in the gene that encodes UGT1A1, which ca decrease bilirubin conjugation. This reduces hepatic bilirubin clearance and increases disorders include Crigler-Najjar syndrome types I and II and Gilbert syndrome. These detail separately. (See "Crigler-Najjar syndrome" and "Gilbert syndrome and unconjug

Crigler-Najjar syndrome — There are two variants of Crigler-Najjar syndrome. (Se

- Crigler-Najjar syndrome type I (CN-I) – This is the most severe form of inherited U severe hyperbilirubinemia develops in the first two to three days after birth. Lifelo bilirubin-induced neurologic dysfunction (BIND) unless liver transplantation is per
- Crigler-Najjar syndrome type II (CN-II) – CN-II is less severe than is CN-I. UGT activ develop severe jaundice, the hyperbilirubinemia often responds to phenobarbital recessive manner, although autosomal dominant transmission occurs in some cas

Gilbert syndrome — Gilbert syndrome is the most common inherited disorder of b gene. In white and African American patients, it results from a mutation in the promot reduced production of UGT, leading to unconjugated hyperbilirubinemia. In the East A

impaired intestinal motility caused by functional or anatomic obstruction and possibly
latter has not been confirmed.

Breast milk jaundice — Breast milk jaundice is defined as the persistence of benig
weeks of age. It typically presents after the first three to five days of life, peaks within
levels over 3 to 12 weeks [9,35]. Breast milk jaundice needs to be distinguished from b
suboptimal fluid and caloric intake during the first seven days of life. (See 'Lactation fa

In infants with jaundice who exclusively receive human milk, TB levels >5 mg/dL (86 m
Although the hyperbilirubinemia is generally mild and typically does not require interv
the unconjugated form and does not increase. If TB levels begin to increase or there is
for other causes of hyperbilirubinemia should be performed. In the case of elevated c
considered. If after evaluation human milk intake is the only remaining viable factor, h
zone with the expectation of resolution by 12 weeks of age [36]. (See "Unconjugated h
Screening" and "Causes of cholestasis in neonates and young infants" and "Approach

The underlying mechanism of "breast milk jaundice" is not conclusively known. Human
which catalyzes the hydrolysis of beta-D-glucuronic acid [37]. In contrast, there is negl
formula-fed infants have lower levels of bilirubin than those who receive human milk
glucuronic acid due to increased degradation is thought to promote an increase in int
Beta-glucuronidase inhibitors, such as enzymatically-hydrolyzed casein or L-aspartic a
been used prophylactically in breastfed newborns [40]. However, the prolonged uncon
benign, and there appears to be no benefit for the use of these agents [41]. As a resul
milk jaundice.

Another potential underlying mechanism is polymorphic mutation of the *UGT1A1* gene
jaundice, half of infants were homozygous for the *UGT1A1*6* genotype [42]. These infa
polymorphisms. The *UGT1A1*6* genotype was not detected in control infants. However
determine whether there is a causal relationship between genetic variation of the *UGT*
testing should not be used in the evaluation of breast milk-related jaundice.

Ileus or intestinal obstruction — Ileus or anatomic causes of intestinal obstructio
result in jaundice. TB levels are frequently higher with small bowel than with large bow
percent of infants with pyloric stenosis when vomiting begins. (See "Infantile hypertro

Lactation failure jaundice — Lactation (breastfeeding) failure jaundice typically occu
inadequate intake of fluids and calories resulting in hypovolemia and significant weigh

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education pieces are longer, more sophisticated, and more detailed. These articles are
for patients who want in-depth information and are comfortable with some medical ja

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also locate patient education articles on a variety of subjects by searching on "patient

- Beyond the Basics topics (see "Patient education: Jaundice in newborn infants (Be

SUMMARY

- Total serum or plasma bilirubin (TB) levels >1 mg/dL (17 micromol/L) occur in almo
severe hyperbilirubinemia (TB >25 mg/dL [428 micromol/L]) are at risk for develop
presenting acutely as acute bilirubin encephalopathy (ABE) and, if not treated app
neurologic sequelae of chronic bilirubin encephalopathy (CBE, previously referred

- Benign ("nonpathologic") neonatal hyperbilirubinemia, previously referred to as "p
caused by the turnover of fetal red blood cells, immaturity of the newborn's liver t
resulting in decreased bilirubin clearance and increased enterohepatic circulation
(indirect-reacting) hyperbilirubinemia. Mean TB levels normally peak at 7 to 9 mg/
American infants and are higher in Asian infants, 10 to 14 mg/dL (171 to 239 micro

- Hyperbilirubinemia is due to increased bilirubin load either due to an increase in b
4).

- For infants with severe and extreme hyperbilirubinemia, identification of the caus
whether therapeutic interventions are needed and their timing. (See 'Causes of sig

- Causes of significant unconjugated neonatal hyperbilirubinemia can be classified

  - Increased production of bilirubin – Hemolytic disease, polycythemia, and sequ
  production because of increased red cell breakdown. (See 'Increased producti

  - Increased enterohepatic circulation of bilirubin – Breast milk jaundice and imp
  obstruction increase enterohepatic circulation of bilirubin. (See 'Increased ent

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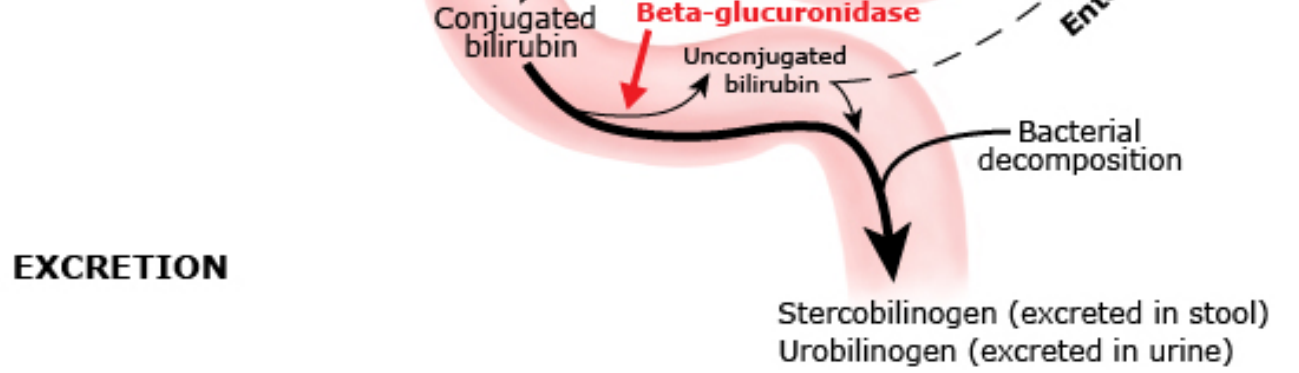

Schematic diagram demonstrating the production, metabolism, and excretion of bilirubin.

*Physiologic mechanisms that reduce the movement of free bilirubin across the blood-brain barrier include binding to plasma albumin and rapid uptake, conjugation, and clearance by the liver. These protective mechanisms are less efficient in neonates (especially preterm infants) and individuals with inherited disorders of bilirubin conjugation. As a result, these patients are at risk for bilirubin-induced neurotoxicity.

Adapted from: Hansen TWR, Bratlid D. Physiology of neonatal unconjugated hyperbilirubinemia. In: Care of the Jaundiced Neonate, Stevenson DK, Maisels MJ, Watchko JF (Eds), McGraw-Hill Companies, New York 2012.

Graphic 121543 Version 4.0

glucuronides (BG) prior to excretion. Bilirubin also enters hepatocytes by passive diffusion. Glucuronidation of bilirubin is mediated by a family of enzymes, termed uridine diphosphoglucuronosyltransferase (UGT), the most important of which is bilirubin-UGT-1 (UGT1A1). Conjugated bilirubin is secreted actively across the bile canalicular membrane of the hepatocyte against a concentration gradient that may reach 1:1000. The canalicular multi-drug resistance protein 2 (MRP2) appears to be the most important for the canalicular secretion of bilirubin. A portion of the conjugated bilirubin is transported into the sinusoidal blood via the ATP hydrolysis-couple pump, ABCC3, to undergo reuptake via OATP1B1 and OATP1B3 by hepatocytes downstream to the sinusoidal blood flow.

UDP: uridine diphosphate; UDPGA: uridine 5'-diphosphoglucuronic acid; ABCC3: ATP-binding cassette subfamily C number 3; OATP1B1: organic anion-transporting polypeptide 1B1; OATP1B3: organic anion-transporting polypeptide 1B3.

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