Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn

INTRODUCTION — Almost all newborn infants develop a total serum or plasma bilirubin (TB) level greater than 1 mg/dL (17 micromol/L), which is the upper limit of normal for adults. As the TB increases, it produces neonatal jaundice, the yellowish discoloration of the skin and/or conjunctiva caused by bilirubin deposition. Hyperbilirubinemia in infants ≥35 weeks gestation is defined as a TB >95 percentile on the hour-specific Bhutani nomogram. Hyperbilirubinemia with a TB >25 to 30 mg/dL (428 to 513 micromol/L) is associated with an increased risk for bilirubin-induced neurologic dysfunction (BIND), which occurs when bilirubin crosses the blood-brain barrier and binds to brain tissue. The term “acute bilirubin encephalopathy” (ABE) is used to describe the acute manifestations of BIND. The term “kernicterus” is used to describe the chronic and permanent sequelae of BIND. Appropriate intervention is important to consider in every infant with severe hyperbilirubinemia. However, even if these infants are adequately treated, long-term neurologic sequelae (kernicterus) can sometimes develop.

The pathogenesis and etiology of neonatal unconjugated hyperbilirubinemia is reviewed here. The clinical features, evaluation, and treatment of this disorder are discussed separately. (See "Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants" and "Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants" and "Treatment of unconjugated hyperbilirubinemia in term and late preterm infants".)

BILIRUBIN METABOLISM — Knowledge of the basic steps in bilirubin metabolism is essential to the understanding of the pathogenesis of neonatal hyperbilirubinemia. Bilirubin metabolism is briefly reviewed here and is discussed in detail separately. (See "Bilirubin metabolism".)

Bilirubin production — Bilirubin is a product of heme catabolism. Approximately 80 to 90 percent of bilirubin is produced during the breakdown of hemoglobin from red blood cells or from ineffective erythropoiesis. The remaining 10 to 20 percent is derived from the breakdown of other heme-containing proteins, such as cytochromes and catalase.

Bilirubin is formed in two steps. The enzyme heme oxygenase (HO), located in the spleen and liver as well as in all nucleated cells, catalyzes the breakdown of heme, resulting in the formation of equimolar quantities of carbon monoxide (CO) and biliverdin. Biliverdin then is converted to bilirubin by the enzyme biliverdin reductase. Measurements of CO production, such as end-tidal CO (ETCO) or carboxyhemoglobin (COHb), both corrected for ambient CO (ETCOc and COHbc, respectively), can be used as indices of in vivo bilirubin production. (See "Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants", section on 'End-tidal carbon monoxide concentration'.)

Bilirubin clearance and excretion — Clearance and excretion of bilirubin occurs in the following steps (figure 1):

- Hepatic uptake – Circulating bilirubin, which is bound to albumin, is transported to the liver. Bilirubin dissociates from albumin and is taken up by hepatocytes, where it is processed for excretion.
- Conjugation – In hepatocytes, uridine diphosphoglucuronate glucuronosyltransferase (UGT1A1) catalyzes the conjugation of bilirubin with glucuronic acid, producing bilirubin diglucuronides and, to a lesser degree, bilirubin monoglucuronides. Conjugated bilirubin, which is more water-soluble than unconjugated bilirubin, is excreted in bile.
- Biliary excretion – Conjugated bilirubin is secreted into the bile in an active process that depends upon canalicular transporters, and then excreted into the digestive tract (figure 1). Conjugated bilirubin cannot be reabsorbed by the intestinal epithelial cells. It is broken down in the intestine by bacterial enzymes and, in the adult it is reduced to urobilin by bacterial enzymes. But at birth the infant's gut is sterile and, subsequently, infants have far fewer bacteria in the gut, so very little, if any, conjugated bilirubin is reduced to urobilin. Infants have beta-glucuronidase in the intestinal mucosa.

Bilirubin metabolism
Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn

which deconjugates the conjugated bilirubin. The unconjugated bilirubin can now be reabsorbed through the intestinal wall and recycled into the circulation, a process known as the "enterohepatic circulation of bilirubin".

NEONATAL JAUNDICE — Nonpathologic jaundice is caused by normal neonatal changes in bilirubin metabolism resulting in increased bilirubin production, decreased bilirubin clearance, and increased enterohepatic circulation.

- In term newborn infants, bilirubin production is two to three times higher than in adults. This occurs because newborns have more red blood cells (hematocrit between 50 to 60 percent) and fetal red blood cells have a shorter life span (approximately 85 days) than those in adults. The increased turnover of more red blood cells produces more bilirubin.
- Bilirubin clearance is decreased in newborns, mainly due to the deficiency of the enzyme uridine diphosphoglucuronate glucuronosyltransferase (UGT1A1). UGT activity in term infants at seven days of age is approximately 1 percent of that 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, further increasing the bilirubin load in the infant. (See 'Bilirubin clearance and excretion' above.)

These perturbations generally result in the low-risk unconjugated (indirect-reacting) bilirubinemia that occurs in nearly all newborns [1].

- In Caucasian and African-American term infants, the mean peak total serum or plasma bilirubin (TB) occurs at 48 to 96 hours of age and is 7 to 9 mg/dL (120 to 154 micromol/L). The 95th percentile ranges from 13 to 18 mg/dL (222 to 308 micromol/L) [5].
- In some East-Asian infants, mean TB levels can reach 10 to 14 mg/dL (171 to 239 micromol/L) and typically occur later, between 72 and 120 hours of age.

Primary neonatal jaundice resolves within the first one to two weeks after birth, dependent on the maturation of bilirubin clearance systems.

Peak TB is also later in infants born at 35 to 37 weeks gestational age. Clinical jaundice should resolve within the first one to two weeks after birth, usually by the fifth day in Caucasian and African-American infants, and by the 10th day in Asian infants. Persistence of hyperbilirubinemia beyond two weeks of age merits further evaluation.

Ethnic variation in conjugation ability — Differences in TB levels among races may result from specific genetic variations in conjugating ability [1]. As an example, polymorphisms in the UGT1A1 gene, due to differences in the number of thymine-adenine (TA) repeats in the promoter region of the gene, vary among individuals of Asian, African, and Caucasian ancestry [6]. These polymorphisms correlate with decreases in UGT1A1 enzyme activity resulting in increased TB levels.

Another cause of racial variation in the development of neonatal jaundice results from a common mutation in the UGT1A1 gene at Gly71Arg that occurs in Eastern Asians. This mutation leads to an increased incidence of severe neonatal hyperbilirubinemia (approximately 20 percent) in Asians [7,8]. The increased frequency of this polymorphism increases the risk of hyperbilirubinemia in infants born to mothers who are Eastern Asian. (See "Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants", section on 'Risk factors'.)

HYPERBILIRUBINEMIA — Hyperbilirubinemia (defined as a total serum or plasma bilirubin [TB] >95th percentile on the hour-specific Bhutani nomogram [2]) can be caused by certain pathologic conditions or by exaggeration of the mechanisms responsible for neonatal jaundice. Identification of the cause of neonatal hyperbilirubinemia is useful in determining whether therapeutic interventions can prevent severe hyperbilirubinemia. (See "Treatment of unconjugated hyperbilirubinemia in term and late preterm infants".)

The following features suggest severe hyperbilirubinemia [9]:

- Jaundice recognized in the first 24 hours (usually caused by increased bilirubin production due to hemolysis) is a medical emergency.
- TB greater than the hour-specific 95th percentile (figure 2). The risk for severe hyperbilirubinemia and the threshold for intervention based upon the hour-specific bilirubin value may be determined using the newborn hyperbilirubinemia assessment calculator (calculator 1). (See "Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants").
- Rate of TB rise greater than 0.2 mg/dL (3.4 micromol/L) per hour.
- Jaundice in a term newborn after two weeks of age.
Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn

**CAUSES OF HYPERBILIRUBINEMIA**

**Increased production** — The most common cause of pathologic indirect hyperbilirubinemia is increased bilirubin production due to hemolytic disease processes that include the following [5-7,11-15]:

- Isoimmune-mediated hemolysis (eg, ABO or Rh(D) incompatibility). (See "Hemolytic disease of the newborn: RBC alloantibodies in pregnancy and associated serologic issues" and "Red cell transfusion in infants and children: Selection of blood products", section on 'Hemolytic disease of the fetus and newborn'.)

- Inherited red blood cell membrane defects (eg, hereditary spherocytosis and elliptocytosis). (See "Hereditary spherocytosis: Clinical features, diagnosis, and treatment" and "Hereditary elliptocytosis: Clinical features and diagnosis".)

- Erythrocyte enzymatic defects (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency [16], pyruvate kinase deficiency, and congenital erythropoietic porphyria). (See "Clinical manifestations of glucose-6-phosphate dehydrogenase deficiency" and "Pyruvate kinase deficiency" and "Congenital erythropoietic porphyria").

- Sepsis is a known cause of hemolysis. The mechanism is not known; however, one theory suggests that increased oxidative stress due to sepsis damages neonatal red blood cells that are susceptible to cell injury [5].

Other causes of increased bilirubin production due to increased red blood cell breakdown include polycythemia or sequestration of blood within a closed space, which occurs in cephalohematoma. Macrosomic infants of diabetic mothers (IDM) also have increased bilirubin production due to either polycythemia or ineffective erythropoiesis. (See "Neonatal polycythemia" and "Infant of a diabetic mother".)

**Decreased clearance** — Inherited defects in the gene that encodes UGT1A1, which catalyzes the conjugation of bilirubin with glucuronic acid, decrease bilirubin conjugation. This reduces hepatic bilirubin clearance and increases total serum or plasma bilirubin (TB) levels [17]. These disorders include Crigler-Najjar syndrome types I and II and Gilbert syndrome, which are briefly summarized below and discussed in detail separately. (See "Crigler-Najjar syndrome" and "Gilbert syndrome and unconjugated hyperbilirubinemia due to bilirubin overproduction").

**Crigler-Najjar syndrome** — There are two variants of Crigler-Najjar syndrome. (See "Crigler-Najjar syndrome").

- Crigler-Najjar syndrome type I (CN-I) — Crigler-Najjar syndrome type I (CN-I) is the most severe form of inherited UGT1A1 disorders. UGT activity is essentially absent, and severe hyperbilirubinemia develops in the first two to three days after birth. Lifelong phototherapy is required to avoid bilirubin-induced neurologic dysfunction (BIND) unless liver transplantation is performed. The mode of inheritance is autosomal recessive.

- Crigler-Najjar syndrome type II – Crigler-Najjar syndrome type II (CN-II) is less severe than is CN-I. UGT activity in this disorder is low, but detectable. Although some affected children develop severe jaundice, the hyperbilirubinemia often responds to phenobarbital treatment. CN-II usually is inherited in an autosomal recessive manner, although autosomal dominant transmission occurs in some cases.

**Gilbert syndrome** — Gilbert syndrome is the most common inherited disorder of bilirubin glucuronidation. It results from a mutation in the promoter region of the UGT1A1 gene [18]. The mutation causes a reduced production of UGT, leading to unconjugated hyperbilirubinemia. Breast milk jaundice during the second week after birth may be due to the concurrent neonatal manifestation of Gilbert syndrome.

In the United States, 9 percent of the population is homozygous and 42 percent heterozygous for the Gilbert mutation [19]. Newborns who are homozygous for the gene mutation have a higher incidence of jaundice during the first two days after birth than normal infants or those who are heterozygous [20]. Similar findings have been noted in other parts of the world, especially in Asian countries [8,21].

The Gilbert genotype alone does not appear to increase the incidence of hyperbilirubinemia. In an Italian study of 70 full-term neonates with TB ≥20 mg/dL (340 micromol/L) and matched controls with TB ≤12 mg/dL (205 micromol/L), there was no difference in the prevalence of UGT1A1 gene variants between the two groups [22]. Homozygous genotype for Gilberts was detected in 18 infants with hyperbilirubinemia and in 14 in the control group (18.6 versus 20 percent), and the heterozygous genotype was also equally distributed (44.3 versus 42.9 percent).

Rather, the Gilbert genotype appears to become clinically relevant when affected newborns have increased bilirubin...
Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn

production or enhanced enterohepatic recirculation.

- In an Israeli study, the normal Gilbert genotype did not produce an increase in the incidence of hyperbilirubinemia, defined as TB ≥15 mg/dL (257 micromol/L), in infants who were G6PD deficient compared with normal infants (9.9 versus 9.7 percent). 9.9 percent of the G6PD-normal infants had a TB ≥15 mg/dL (257 micromol/L) [23]. However, the risk of hyperbilirubinemia increased for infants with G6PD deficiency and who were either heterozygous (32 percent) or homozygous (50 percent) for the Gilbert mutations.

- In another study of male infants with G6PD deficiency, mean TB was highest in patients who were homozygotes (11.1 mg/dL [190 micromol/L]), followed by heterozygotes for the Gilbert mutation (9.1 mg/dL [156 micromol/L]), and those without the mutation (8.8 mg/dL [150 micromol/L]) [24].

The combination of a usually benign polymorphism of Gilbert genotype coupled with another factor that increases TB may be the underlying cause of some of the rare cases of infants with extremely high TB levels (>25 mg/dL [428 micromol/L]) [25]. (See “Gilbert syndrome and unconjugated hyperbilirubinemia due to bilirubin overproduction”.)

OATP-2 polymorphism — In addition to the polymorphisms of the UGT gene discussed above, a study of Taiwanese newborns reported that those with a polymorphic variant of the organic anion transporter protein OATP-2 (also known as OATP-C or solute carrier organic anion transporter 1B1 [SLCO1B1]) were more likely to develop severe hyperbilirubinemia [26]. Furthermore, the combination of the OATP-2 polymorphism with a UGT1A1 gene mutation increased this risk.

Other causes — Other causes of decreased bilirubin clearance include maternal diabetes [27], congenital hypothyroidism, and galactosemia, although in the latter case, infants typically present with elevated conjugated hyperbilirubinemia. These conditions usually are identified by metabolic screening programs; however, infants may develop severe and prolonged jaundice before screening results become available. (See "Clinical features and detection of congenital hypothyroidism" and "Galactosemia: Clinical features and diagnosis".)

Increased enterohepatic circulation — The major causes of increased enterohepatic circulation of bilirubin are breastfeeding failure jaundice, breast milk jaundice, or impaired intestinal motility caused by functional or anatomic obstruction.

Breast milk jaundice — Breast milk jaundice has been traditionally defined as the persistence of "physiologic jaundice" beyond the first week of age. It typically presents after the first three to five days of life, peaking within two weeks after birth, and progressively declined to normal levels over 3 to 12 weeks [28,29]. Breast milk jaundice needs to be distinguished from breastfeeding failure (suboptimal intake or starvation related) jaundice that occurs within the first seven days of life, resulting in excessive weight and fluid loss. (See 'Breastfeeding failure jaundice' below.)

In breast milk jaundice, infants commonly have TB levels >5 mg/dL (86 micromol/L) for several weeks after delivery [29]. Although the hyperbilirubinemia is generally mild and may not require intervention, it should be monitored to ensure that it remains unconjugated and does not increase. If TB levels begin to increase or there is a significant component of conjugated bilirubin, evaluation for other causes of hyperbilirubinemia should be performed including neonatal cholestasis. If after evaluation, breast milk intake is the only remaining viable factor, breastfeeding can continue with the expectation of resolution by 12 weeks of age and that the hyperbilirubinemia is in the safe zone [30]. (See "Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants" and "Causes of neonatal cholestasis" and "Approach to neonatal cholestasis".)

Breast milk jaundice as the primary cause of increased TB appears to be due to a factor, which has not yet been identified, in human milk that promotes an increase in intestinal absorption of bilirubin. Beta-glucuronidase is one proposed substance as it deconjugates intestinal bilirubin, increasing its ability to be absorbed (ie, increasing enterohepatic circulation) [31]. Approximately 20 to 40 percent of women have high levels of beta-glucuronidase in their breast milk. Blocking the deconjugation of bilirubin through beta-glucuronidase inhibition may provide a mechanism to reduce intestinal absorption of bilirubin in breastfed infants [32]. Although some studies have found elevated fecal levels of beta-glucuronidase in breastfed infants with hyperbilirubinemia, this has not been a consistent finding.

Another mechanism that has been proposed is polymorphic mutation of the UGT1A1 gene. In a Japanese study of 170 neonates with breast milk jaundice, half of infants were homozygous for the UGT1A1*6 genotype [33]. These infants had higher TB than infants with other genotypes. The UGT1A1*6 genotype was not detected in control infants. However, further studies in other areas of the world are needed to determine whether or not there is a causal relationship between genetic variation of the UGT1A1 gene and breast milk jaundice. Thus, currently genetic testing should not be used in the evaluation of breast milk-related jaundice.

Beta-glucuronidase inhibitors such as enzymatically-hydrolyzed casein or L-aspartic acid have been used prophylactically in breastfed newborns [32]. However, further studies are needed to determine whether these agents are effective and safe in

promoting increased fecal bilirubin excretion, thereby resulting in lower TB. We do not currently recommend these agents for breast milk jaundice.

**Intestinal obstruction** — Ileus or anatomic causes of intestinal obstruction increase the enterohepatic circulation of bilirubin and result in jaundice. TB levels are frequently higher with small bowel than with large bowel obstruction. As an example, jaundice occurs in 10 to 25 percent of infants with pyloric stenosis when vomiting begins.

**Breastfeeding failure jaundice** — Suboptimal breastfeeding compared with formula feeding is associated with an increased risk of jaundice and kernicterus.

- In a review of cases from the Pilot Kernicterus Registry, 59 of 61 infants with kernicterus were breastfed. Of the two infants who were formula-fed, both were found to have G6PD deficiency [34].
- In one report, infants who were breastfed compared with bottle-fed infants at day three of life were more likely to have TB concentrations $>13 \text{ mg/dL} \ (222 \text{ micromol/L})$, (8.9 versus 2.2 percent) [35].
- In another report, infants fed human milk compared with those fed formula had higher TB on day three of life and lower volumes of stool and urine output during the first week of life [36].

The primary mechanism for the increased likelihood of kernicterus and jaundice with breast versus formula feeding is the failure to successfully initiate breastfeeding rather than a direct effect of breast milk itself, as is seen in breast milk jaundice. A population-based study demonstrated that TB was only marginally higher in successfully breastfed compared with formula-fed infants [2].

Breastfeeding failure jaundice typically occurs within the first week of life, as lactation failure leads to inadequate intake with significant weight and fluid loss resulting in hypovolemia. This causes hyperbilirubinemia (jaundice) and in some cases, hypernatremia defined as a serum sodium $>150 \text{ mEq/L}$. Decreased intake also causes slower bilirubin elimination and increased enterohepatic circulation that contribute to elevated TB. (See "Initiation of breastfeeding", section on 'Weight loss'.)

A root cause analysis identified the following as predictors of lactation failure in infants with kernicterus [37]. (See "Initiation of breastfeeding").

- Inadequate education from clinicians and lactation consultants
- Inadequate documentation of infant latching
- Inadequate measurement of milk transfer
- Inadequate recording of urine output and stool pattern changes

In addition, maternal breastfeeding complications, such as engorgement, cracked nipples, and fatigue, and neonatal factors, such as ineffective suck, may not be properly addressed prior to hospital discharge and result in ineffective breastfeeding. (See "Common problems of breastfeeding and weaning").

Although late preterm infants (defined as gestational age between 34 weeks, and 36 weeks and 6 days) are usually able to breastfeed, they are more likely to experience difficulty in establishing successful breastfeeding than term infants. Late preterm infants may not fully empty the breast because of increased sleepiness, fatigue, and/or difficulty maintaining a latch because their oro-buccal coordination and swallowing mechanisms are not fully matured. (See "Breastfeeding the preterm infant", section on 'Late preterm infants'.)

**Prevention** — Initiation of successful breastfeeding, one of the mainstays of preventing hyperbilirubinemia, has become an increasing problem due to shortened postpartum length of stay for newborn infants and their mothers. Postnatal education, support, and care should be provided to the infant-mother dyad during the birth hospitalization and after discharge. The overall approach is briefly summarized here and is discussed in greater detail separately. (See "Breastfeeding: Parental education and support" and "Initiation of breastfeeding").

- During the first postpartum week while breastfeeding is being established, mothers should nurse whenever the infant shows signs of hunger or when four hours have elapsed since the last feeding. This will usually result in 8 to 12 feedings in 24 hours, which is usually sufficient to prevent significant hyperbilirubinemia that requires intervention [38].
- During the birth hospitalization, monitoring and assessment of breastfeeding are crucial. Problems identified in the hospital should be addressed at that time, and a documented plan for management after discharge should be communicated to both the parents and primary care provider.
- At discharge, a primary care appointment should be scheduled so that the infant-mother dyad is evaluated 24 to 48 hours after discharge, and post-discharge lactation resources provided.
At the follow-up appointment, supplementation with banked human milk or commercial infant formula is recommended when the infant has lost more than 7 percent of his/her birth weight or exhibits signs of dehydration (eg, decreased urine output), stool output is less than three small stools a day, and mother's milk supply remains limited. Glucose water or sterile water feedings should not be used, as they do not provide adequate nutrition.

Severe hyperbilirubinemia — Although genetic factors may contribute to an increase in TB, clinical factors are the major contributors to the pathogenesis of severe hyperbilirubinemia defined as a TB >95th percentile. This was illustrated in a case-control study of term infants that compared genetic and clinical factors between infants with TB levels >95th percentile and those with TB levels <40th percentile [15]. There were no differences in the frequency of G6PD, UGT1A1, and SCLO1B1 (liver transport protein) genetic variants between the two groups. Among the group with severe hyperbilirubinemia, the most common cause of an elevated TB was hemolysis due to ABO incompatibility (31 percent) followed by breastfeeding failure (22 percent), although no cause was identified in 39 percent of the cases.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: Jaundice in newborn infants (Beyond the Basics)"

SUMMARY

- Total serum or plasma bilirubin (TB) levels >1 mg/dL (17 micromol/L) occur in almost all term and near-term newborn infants. Infants with severe hyperbilirubinemia (TB >25 to 30 mg/dL [428 to 513 micromol/L]) are at risk for bilirubin-induced neurologic dysfunction (BIND), presenting acutely as acute bilirubin encephalopathy (ABE) and, if inadequately treated, long-term neurologic sequelae or kernicterus.

- Neonatal jaundice is primarily caused by normal neonatal alterations in bilirubin metabolism including increased bilirubin production, decreased bilirubin clearance, and increased enterohepatic circulation. These alterations generally result in mild unconjugated (indirect-reacting) hyperbilirubinemia with peak TB of 7 to 9 mg/dL (120 to 154 micromol/L) in Caucasian and African-American infants and higher values in Asian infants, 10 to 14 mg/L (171 to 239 micromol/L). (See 'Neonatal jaundice' above.)

- Hyperbilirubinemia is caused by exaggeration of mechanisms that cause neonatal jaundice or by pathologic conditions that increase bilirubin production, decrease bilirubin clearance, or increase the enterohepatic circulation. Identification of the cause of neonatal hyperbilirubinemia is useful in determining whether therapeutic interventions can prevent severe hyperbilirubinemia. (See 'Hyperbilirubinemia' above and "Treatment of unconjugated hyperbilirubinemia in term and late preterm infants", section on 'Prevention of hyperbilirubinemia'.)

- The following clinical findings are predictors for hyperbilirubinemia:
  - Jaundice in the first 24 hours of life.
  - TB greater than the hour-specific 95th percentile (figure 2).
  - Conjugated bilirubin concentration >1 mg/dL (17 micromol/L) if the total bilirubin is <5 mg/dL (86 micromol/L), or more than 20 percent of the total bilirubin if the total bilirubin is >5 mg/dL (86 micromol/L). Conjugated bilirubinemia suggests neonatal cholestasis. (See "Approach to neonatal cholestasis").
  - Rate of TB rise greater than 0.2 mg/dL (3.4 micromol/L) per hour.
  - Jaundice in a term newborn after two weeks of age.

- Causes of hyperbilirubinemia can be classified by pathogenesis as follows:
  - Increased production – Hemolytic disease, polycythemia, and sequestration of blood within a closed space increase bilirubin production because of increased red cell breakdown. (See 'Increased production' above.)
  - Decreased clearance – Inherited defects in uridine diphosphoglucuronate glucuronosyltransferase (UGT1A1), such
Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn

as Crigler-Najjar syndrome types I and II. In addition, metabolic disorders, such as congenital hypothyroidism, galactosemia, and infants of diabetic mothers, can decrease bilirubin clearance. (See 'Decreased clearance' above.)

- Increased enterohepatic circulation of bilirubin.
- Breast milk jaundice, and impaired intestinal motility caused by functional or anatomic obstruction increase enterohepatic circulation of bilirubin. (See 'Increased enterohepatic circulation' above and 'Breastfeeding failure jaundice' above.)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES


Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn

Schematic representation of the steps involved in bilirubin (B) throughput in hepatocytes: transport to the liver (primarily as albumin-bound bilirubin), uptake at the sinusoidal membrane, intracellular binding, conjugation (glucuronidation), and canalicular excretion. Sinusoidal bilirubin uptake requires inorganic anions such as chloride, and is thought to be mediated by carrier proteins. Within the hepatocyte, bilirubin binds to glutathione S-transferases (GSTs). GST-binding reduces the efflux of the internalized bilirubin, thereby increasing the net uptake. GSTs also bind bilirubin 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.

Graphic 52393 Version 4.0

Nomogram of hour-specific serum total bilirubin (STB)
The red, blue, and green lines denote the 95th, 75th, and 40th percentiles, respectively. Risk zones are designated according to percentile: high (STB ≥95th), high intermediate (95th > STB ≥75th), low intermediate (75th > STB ≥40th), and low (STB < 40th). Infants with values in the high risk zone are at increased risk for the development of clinically significant hyperbilirubinemia requiring intervention.


Disclosures

Disclosures: Ronald J Wong, BA Nothing to disclose. Vinod K Bhutani, MD, FAAP Nothing to disclose. Steven A Abrams, MD Grant/Research/Clinical Trial Support: Mead-Johnson (infant nutrition [specialized formulas for preterm infants]). Elizabeth B Rand, MD Nothing to disclose. Melanie S Kim, MD Employee of UpToDate, Inc.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy