Unconjugated hyperbilirubinemia in term and late preterm infants: Epidemiology and clinical manifestations

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Sep 2020. | **This topic last updated:** Feb 13, 2020.

INTRODUCTION

Almost all term and late preterm infants (gestational age ≥35 weeks) develop a total serum or plasma bilirubin (TB) value >1 mg/dL (17.1 micromol/L), which is the upper limit of normal for adults. As TB levels increase, neonatal jaundice can develop, noticeable as a yellowish discoloration of the skin and/or conjunctiva caused by bilirubin deposition. Neonates with severe hyperbilirubinemia (defined as a TB >25 mg/dL [428 micromol/L]) are at risk for developing bilirubin-induced neurologic dysfunction (BIND), which occurs when bilirubin crosses the blood-brain barrier, binds to brain tissue, and then causes neurotoxicity. Vulnerable infants are at risk for BIND at lower TB values.

The clinical manifestations of and risk factors for severe neonatal unconjugated hyperbilirubinemia in term and late preterm infants are reviewed here. The pathogenesis, etiology, evaluation, prevention, and treatment are discussed separately. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology" and "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening" and "Unconjugated hyperbilirubinemia in term and late preterm infants: Management".)

DEFINITIONS

Although there is no consensus amongst experts in the field in defining the clinical significance of varying total serum or plasma bilirubin (TB) levels for term and late preterm infants, the authors use the following definitions in this topic based on their experience.

- **Benign neonatal hyperbilirubinemia** is a transient and normal increase in bilirubin levels occurring in almost all newborn infants, which is also referred to as "physiologic jaundice.

- **Significant neonatal hyperbilirubinemia** in infants ≥35 weeks gestational age (GA) is defined as TB >95th percentile on the hour-specific Bhutani nomogram (figure 1) [1].

- **Severe neonatal hyperbilirubinemia** is defined as a TB >25 mg/dL (428 micromol/L). It is associated with an increased risk for developing bilirubin-induced neurologic dysfunction (BIND).

- **Extreme neonatal hyperbilirubinemia** is defined as a TB >30 mg/dL (513 micromol/L). It is associated with a higher risk for developing bilirubin-induced neurotoxicity and likelihood of kernicterus.

- **Bilirubin-induced neurologic dysfunction (BIND)** are due to brain damage from free bilirubin that crosses the blood-brain barrier and binds to brain tissue as evidenced by both molecular and cytological injuries of brain cells. (See 'Clinical manifestations' below.)

    - **Acute bilirubin encephalopathy (ABE)** is used to describe the acute clinical manifestations of kernicterus. (See 'Acute bilirubin encephalopathy' below.)

    - **Chronic bilirubin encephalopathy (CBE)**, previously referred to as kernicterus, is used to describe the chronic and permanent post-icteric sequelae of extreme hyperbilirubinemia. (See 'Chronic bilirubin encephalopathy (kernicterus)' below.)

CONSEQUENCES OF SEVERE HYPERBILIRUBINEMIA

The major consequence of an elevated total serum or plasma bilirubin (TB) level (hyperbilirubinemia) is a spectrum of bilirubin-associated neurotoxicity known as bilirubin-induced neurologic dysfunction (BIND). BIND occurs when unconjugated bilirubin, which is not bound to albumin (also referred to as "free" or "unbound" bilirubin or UB), crosses the blood-brain barrier, enters the brain, and causes brain injury (figure 2). BIND is an array of neurologic findings [2,3] manifested as disorders in visuocortical pathways [4], sensorineural hearing [5], proprioception (leading to gait abnormalities) [6], speech, and language [7]. Chronic bilirubin encephalopathy (CBE), previously referred to as kernicterus, is the progressive and extreme chronic form of BIND associated with permanent neurologic sequelae, such as choreo-athetoid cerebral palsy, upward gaze abnormalities, enamel dysplasia of deciduous teeth, and sensorineural impairment [1]. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Consequences of hyperbilirubinemia'.)

In the following sections, the prevalence of hyperbilirubinemia and BIND are reviewed.

EPIDEMIOLOGY

Total serum or plasma bilirubin (TB) — In the neonate, TB values vary substantially among

institutions because of differences in racial composition and prevalence of genetic factors that affect bilirubin production and metabolism, or breastfeeding practices. Risk assessments are based on TB values and not attributed to unconjugated levels alone because most elevations of TB in the first week of life are due to increased bilirubin production, resulting primarily in unconjugated bilirubin and rarely associated with cholestasis, which primarily presents with elevation of conjugated bilirubin. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Epidemiology' and "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Benign neonatal hyperbilirubinemia'.)

These factors as well as the use of different definitions to describe the severity of hyperbilirubinemia may contribute to the following observed global variations in the incidence of hyperbilirubinemia (TB >20 mg/dL [342 micromol/L]), and higher levels of bilirubin elevation.

- In studies of term or late preterm infants from a large Northern California health maintenance organization (HMO), the following incidences of hyperbilirubinemia at different TB values were reported from birth data collected between 1995 and 1998 [8,9]:
  - TB >20 mg/dL (342 micromol/L) – 2 percent [9]
  - TB >25 mg/dL (428 micromol/L) – 0.14 percent [9]
  - TB >30 mg/dL (513 micromol/L) – 0.01 percent [8]

  The risk of developing TB >20 mg/dL (342 micromol/L) was lower in infants born to mothers who were self-reported as African American than in those who were Caucasian (0.9 versus 1.5 percent, relative risk [RR] 0.62, 95% CI 0.56-0.69) [10]. However, the risk of developing TB >30 mg/dL (513 micromol/L) was higher in African American infants (0.13 versus 0.03 percent, RR 4.2, 95% CI 1.33-13.2).

  In a subsequent birth cohort of infants born between 1995 and 2011 in the same HMO network, the reported incidence of TB >30 mg/dL (513 micromol/L) was 8.6 per 100,000 live births [11].

- In a Danish population-based study from 2000 to 2015, the incidence of TB ≥26.3 mg/dL (450 micromol/L) was 0.042 percent of infants born at gestational age (GA) ≥35 weeks [12].

- In a prospective population-based study in the United Kingdom and Ireland between 2003 and 2005, the incidence of TB >30 mg/dL (513 micromol/L) was 7 per 100,000 live births (0.007 percent) [13]. The mean GA of the 108 identified infants was 38.2 weeks.

- In a prospective population-based study from Australia performed between 2010 and 2013, the incidence of TB ≥26.3 mg/dL (450 micromol/L) for newborns greater than 34 weeks GA was 9.4 per 100,000 infants (0.009 percent) [14]. (See 'Risk factors' below.)

Trends over time — The incidence of developing severe hyperbilirubinemia (TB >25 mg/dL [428

micromol/L]) is decreasing, presumably due to identifying and treating at-risk newborns. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening" and "Unconjugated hyperbilirubinemia in term and late preterm infants: Management", section on 'Criteria for intervention based on risk severity assessment'.)

- In a study that compared data from the Canadian Paediatric Surveillance Program (CPSP) with previously published reports, the incidence of TB ≥24.9 mg/dL (425 micromol/L) in Canada declined from 0.04 to 0.01 percent over a 10-year period from 2002 through 2004 to 2011 through 2013 [15].

- A report from a multicenter health care system in the United States showed a declining rate of infants with TB between 25 and 29.9 mg/dL (428 and 513 micromol/L) from 2002 to 2010 [16] (figure 3).

Bilirubin-induced neurologic injury

Acute bilirubin encephalopathy — There is a paucity of data on the incidence of acute bilirubin encephalopathy (ABE). However, based on information from the previously discussed population-based studies, the estimated risk for ABE varies from 2 to 10 percent for newborn infants with TB >30 mg/dL [513 micromol/L] in developed countries.

- In the previously discussed cohort of infants from the North California HMO study born between 1995 and 2011, 47 of 525,409 infants (0.01 percent) developed a TB >30 mg/dL (513 micromol/L). Four of these 47 patients (9 percent) clinically presented as ABE and all had TB levels >35 mg/dL (599 micromol/L) [11].

- In the Danish population study, five of the 224 infants (2 percent) with a TB ≥30 mg/dL (513 micromol/L) developed ABE; three with severe ABE had peak TB levels of 38 to 57.7 mg/dL (650 to 992 mmol/L) that resulted in kernicterus or CBE [17].

- In the population study from the United Kingdom and Ireland, 14 of 108 infants (13 percent) with a TB >30 mg/dL (513 micromol/L) showed evidence of ABE including three who died [14].

The risk may be higher with resource-constrained healthcare systems. In an observational case series from Egypt of 249 infants with unknown duration of a TB >25 mg/dL (428 micromol/L), moderate or severe ABE was diagnosed in 44 infants (18 percent) and mild ABE in 55 infants (22 percent) based on neurologic assessment using an objective bilirubin-induced neurologic dysfunction protocol (BIND score) [18].

Chronic bilirubin encephalopathy (kernicterus) — Chronic bilirubin encephalopathy (CBE), previously referred to as kernicterus, is the chronic and permanent neurologic sequelae of bilirubin-induced neurologic toxicity. Population-based studies report the incidence ranges from 1.2 to 2.3 per 100,000 live births per year in Denmark, Sweden, and Canada [12,19,20]. The incidence is lower in the United States (0.44 per 100,000 live births) and has decreased after publication of the

2004 AAP guideline recommendations [21].

In a cohort of 525,409 live births from a large Northern California health maintenance organization (HMO) born between 1995 and 2011, the risk for cerebral palsy (CP) consistent with kernicterus was retrospectively reported to occur in 0.57 per 100,000 births and only in infants whose TB levels exceeded the American Academy of Pediatrics (AAP) guideline exchange transfusion thresholds by more than 5 mg/dL [22]. The overall risk of CP in infants who had TB above the 2004 AAP exchange transfusion threshold (ETT) was 0.4 percent compared with 0.1 percent in those having TB below the ETT (RR 4.7, 95% CI 2.2-10.0). A subsequent analysis of infants with TB >30 mg/dL (513 micromol/L) found glucose-6-phosphate dehydrogenase (G6PD) deficiency was the primary etiology when an underlying cause was identified [11].

There still remains a significant risk for death in infants with kernicterus [23,24]. In the United States, 31 deaths associated with kernicterus were reported during the period between 1979 and 2006 resulting in an estimated incidence of 0.28 deaths per million live births [23].

RISK FACTORS

Severe to extreme hyperbilirubinemia — In the 2004 American Academy of Pediatrics (AAP) Practice Guideline, the following major risk factors were noted for severe hyperbilirubinemia and bilirubin neurotoxicity [1] (table 1):

- Predischarge total serum or plasma bilirubin (TB) or transcutaneous bilirubin (TcB) in the high-risk zone defined as >95th percentile for age using the hour-specific TB nomogram (figure 1). The risk for developing severe hyperbilirubinemia and the threshold for intervention based upon the hour-specific TB value may be determined using the newborn hyperbilirubinemia assessment calculator (calculator 1). (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Total serum or plasma bilirubin (TB)' and "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Transcutaneous bilirubin (TcB)'.)

- Jaundice within the first 24 hours of life [25].

- Hemolytic disease due to isoimmune-mediated hemolysis from blood group incompatibility or inherited red blood cell enzymatic deficiencies or membrane defects (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency) [11,14,17]. Evidence of hemolysis is a major risk factor for severe hyperbilirubinemia (eg, elevated end-tidal carbon monoxide [CO], corrected for inhaled CO [ETCOc] levels). (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Increased production'.)

- Gestational age (GA) less than 36 weeks [26-28]. (See "Late preterm infants" and "Unconjugated hyperbilirubinemia in the preterm infant (less than 35 weeks gestation)".)

- Sibling who previously received phototherapy [27,29].
- Cephalohematoma or significant bruising from birth trauma [26].
- Exclusive but suboptimal breastfeeding when nursing is not going well and weight loss is excessive (>10 percent of birth weight [BW]) [26,27,30].
- East Asian race [14]. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Benign neonatal hyperbilirubinemia'.)

Minor risk factors included [1] (table 1):

- TB in a high intermediate range (>75th and ≤95th percentile for age-in-hours)
- Jaundice observed before discharge [27]
- Macrosomic infant of a diabetic mother [31,32]
- Polycythemia
- Male gender [26]
- Maternal age ≥25 years [27]

Factors that reduce bilirubin-albumin binding, thereby increasing the amount of unbound (free) bilirubin, also increase the risk of developing BIND (figure 2). These include certain drugs (eg, sulfisoxazole, moxalactam, and ceftriaxone) and conditions associated with metabolic acidosis. In addition, hypercarbia and hyperosmolality increase the permeability of the blood-brain barrier, allowing bilirubin to enter the brain [33].

Factors associated with decreased risk of severe hyperbilirubinemia include [1] (table 1):

- GA ≥41 to 42 weeks [26].
- Exclusive bottle-feeding [26,27].
- Neonatal discharge from the hospital after 72 hours [27,34].
- African American ethnicity – Overall, these infants have lower TB levels, but there appears to be a subgroup of African American males with G6PD deficiency who remain at risk [35].

These risk factors are used to assess the likelihood of developing clinically significant hyperbilirubinemia. The risk assessment and the age of the infant at the time of discharge from the hospital are used to determine the timing of appropriate follow-up. Both risk assessment and the approach to follow-up for neonatal hyperbilirubinemia are discussed separately. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Risk assessment' and "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Follow-up'.)

A population-based study using data from the Swedish Medical Birth Right Register of term infants (≥37 weeks GA) born from 1999 to 2012 identified the following as risk factors for developing a TB

>20 mg/dL (342 micromol/L) (before 2008) and 20.6 mg/dL (352 micromol/L))from 2008 and after): GA between 37 and 38 weeks, failed or successful vacuum extraction, macrosomic infants, obese mother, and being small for gestational age (SGA) [36]. In this cohort, planned cesarean delivery was associated with a reduced risk of hyperbilirubinemia.

Genetic factors — Although inherited mutations of proteins involved with hepatic conjugation of bilirubin capacity were not included in the AAP guidelines or assessed in the Swedish study as risk factors, genetic predisposition may play a contributing role in severe to extreme hyperbilirubinemia, especially in Gilbert syndrome, which affects 9 percent of the general population [37,38]. The clinical scenario typically presents as persistent jaundice and prolonged (unconjugated) hyperbilirubinemia at age 10 to 14 days. This may in part explain why family history is a predictive risk factor for hyperbilirubinemia. The underlying decrease in bilirubin clearance of infants with Gilbert syndrome in combination with other factor(s) that increases TB (eg, hemolytic disease) can result in severe to extreme hyperbilirubinemia [38,39]. As an example, breastfed infants with Gilbert syndrome have a three- to fourfold increased risk for developing TB >20 mg/dL (342 micromol/L) compared with breastfed infants without Gilbert syndrome [40]. A common mutation in the gene that encodes UGT1A1, which catalyzes the conjugation of bilirubin with glucuronic acid, leads to decreased bilirubin clearance and is more common in infants born to mothers who are East Asian. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Gilbert syndrome' and "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Crigler-Najjar syndrome'.)

In addition, inherited red blood cell enzymatic deficiencies or membrane defects (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency) are risk factors for severe and hazardous hyperbilirubinemia (TB >30 mg/dL [513 micromol/L]) [22].

Readmission — Risk factors for readmission for hyperbilirubinemia for term infants based on data from a large population-based Australian study included [41]:

- Early birth hospital discharge (≤2 days after birth).
- GA <39 weeks.
- Mother from an Asian country.
- Vaginal birth.
- First-time mother.
- Breastfeeding at the time of birth hospital discharge. Of note, the study does not differentiate between suboptimal or successful initiation of breastfeeding at the time of discharge.

In a study from the Pilot Kernicterus Registry, additional factors for readmission included G6PD deficiency, urosepsis, and unrecognized causes of hemolysis [24].

Bilirubin-induced neurologic dysfunction (BIND) — Observational studies report the risk of acute and chronic BIND ranges from 10 to 30 percent for term and late preterm infants with TB ≥30 mg/dL [11,17,42,43].

In a report of 125 patients from the Pilot Kernicterus Registry who had been readmitted for severe hyperbilirubinemia, the following were the major contributing causes of hyperbilirubinemia that resulted in kernicterus [24]:

- No underlying risk factor identified (idiopathic) – 53 patients
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency – 26 patients
- Hemolysis – 25 patients
- Bruising from birth trauma – 18 patients
- Infection – 18 patients (concurrent with other causes)
- Crigler-Najjar Syndrome or galactosemia – 3 patients
- Lactation failure – In this cohort, 122 of 125 infants with kernicterus were breastfed. Twenty-one infants had lost >10 percent of their BW at the time of hospital readmission, suggesting inadequate fluid and caloric intake due to lactation (breastfeeding) failure. (See "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology" and "Unconjugated hyperbilirubinemia in the newborn: Pathogenesis and etiology", section on 'Lactation failure jaundice'.)

CLINICAL MANIFESTATIONS

The clinical manifestations of hyperbilirubinemia are due to bilirubin deposition in the skin, conjunctiva (as visualized on the sclerae), and/or the brain (resulting in the spectrum of bilirubin-induced neurologic dysfunction [BIND]).

Jaundice — Jaundice is the yellow color produced by the deposition of bilirubin in the skin and subcutaneous tissues. However, the presence or absence of jaundice is not a reliable method to assess total serum or plasma bilirubin (TB) concentration or identify infants at risk for rapidly rising bilirubin, especially in those with dark skin [44-46]. Based on available data, in our practice, TB or transcutaneous bilirubin (TcB) levels are measured in any infant with jaundice below the umbilicus or with conjunctival icterus. If there is uncertainty regarding the presence or extent of jaundice, a TB or TcB measurement is performed. In some units, TcB measurements are performed daily on all infants. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Onset and progression of jaundice'.)

The examination for jaundice should be performed with adequate ambient light or under daylight

fluorescent light. Pressing on the skin with a finger reduces local skin perfusion and facilitates detection of jaundice. Jaundice usually progresses in a cephalocaudal direction, appearing first in the face with TB levels of 4 to 8 mg/dL (68 to 137 micromol/L). The entire body, including palms and soles, can appear jaundiced at TB >15 mg/dL (257 micromol/L) [47].

Conjunctival icterus — Conjunctival icterus is due to bilirubin deposition in the conjunctiva and observed on the sclerae. The presence or absence of conjunctival icterus may be useful to help decide which infants may need further assessment as illustrated by the following:

- In an observational study of 240 term or late preterm neonates, most infants with conjunctival icterus had TB ≥15 mg/dL (257 micromol/L) and all infants with this finding had TB levels >75th percentile (primarily greater than the 95th percentile) on the hour-specific Bhutani nomogram (figure 1) [48]. Seven of the 76 infants with conjunctival icterus had a TB in the 10 to 14.9 mg/dL (171 to 255 micromol/L) range.

- In another study of 689 infants between 3 and 10 days of age seen in the follow-up after discharge from the nursery, conjunctival icterus did not correlate with significant hyperbilirubinemia, as 60 percent of those infants with icterus had a TcB measurement of <13 mg/dL (222 micromol/L) [49]. However, the absence of conjunctival icterus was associated with a low probability of significant hyperbilirubinemia.

Differences in the results of these studies may be due to the use of TcB in the second study, which typically underestimates TB, and differences in the study population. (See "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening", section on 'Limitations of TcB'.)

Other physical findings — Other findings on physical examination may suggest an underlying condition associated with an increased risk for hyperbilirubinemia. These include pallor (anemia due to hemolysis), enclosed hemorrhage (eg, cephalohematoma), bruising, and hepatosplenomegaly.

Bilirubin-induced neurologic dysfunction (BIND) — Term and late preterm infants who are at risk for developing BIND are those with TB concentrations ≥30 mg/dL (500 micromol/L) (see 'Bilirubin-induced neurologic dysfunction (BIND)' above). In general, at this threshold, unconjugated bilirubin that is not bound to albumin (also referred to as "free" or "unbound" bilirubin) enters the brain and cause cell death by apoptosis (programmed cell death) and/or necrosis (figure 2) [50-52]. BIND is a spectrum of subtle neurologic findings and sequelae [2], which can manifest as disorders in vision [4], hearing [5], gait [6], and speech, cognition, and language [7].

Acute bilirubin encephalopathy (ABE) may be reversible, or if not addressed, may result in permanent irreversible neurologic dysfunction: chronic bilirubin encephalopathy (CBE, previously referred to as kernicterus). The brain regions most often affected include the basal ganglia and the brainstem nuclei for oculomotor and auditory function, accounting for the clinical features seen in infants with BIND [53].

Acute bilirubin encephalopathy — ABE typically progresses through three phases with persistent severe hyperbilirubinemia [53]:

- Early – In the early phase, the clinical signs may be subtle. The infant is sleepy but arousable, and when aroused has mild to moderate hypotonia and a high-pitched cry. It is challenging to diagnosis ABE during this phase [42].

- Intermediate – If there is no intervention, the intermediate phase evolves with progression and persistence of hyperbilirubinemia. The infant can be febrile and lethargic with a poor suck or irritable and jittery with a strong suck. The cry can be shrill and the infant is difficult to console. Mild to moderate hypertonia develops, beginning with backward arching of the neck (retrocollis) and trunk (opisthotonos) with stimulation. An emergent exchange transfusion at this stage might prevent permanent BIND.

- Advanced – The advanced phase is characterized by apnea, inability to feed, fever, seizures, and a semicomatose state that progresses to coma. Hypertonicity presents as persistent retrocollis and opisthotonos with bicycling or twitching of the hands and feet. The cry is inconsolable, or may be weak or absent. Death is due to respiratory failure or intractable seizures.

Clinical signs associated with ABE can be divided into three domains (mental status, tone, and cry pattern) and be used to determine the severity of ABE in neonates without any other identifiable cause of neurologic impairment (table 2). Brainstem auditory-evoked responses (BAER) can also be used to detect the acute neurologic effects of hyperbilirubinemia and confirm the presence of BIND [54-56]. In one study, increased TB correlated with prolonged brainstem conduction time [55]. These abnormalities resolve as TB values decline. Changes in BAER also have been associated with elevated unbound bilirubin levels [57].

Chronic bilirubin encephalopathy (kernicterus) — Chronic bilirubin encephalopathy (CBE), previously referred to as kernicterus, develops during the first year after birth [53,58].

In general, cognitive function is relatively spared. The major neurologic features of CBE are reflective of the classic affected areas of the brain (basal ganglia and the brainstem nuclei for oculomotor and auditory function) and findings based on magnetic resonance imaging detected in the cerebellum, hippocampus, and brainstem [59,60].

- Choreoathetoid cerebral palsy (CP; chorea, ballismus, tremor, and dystonia). (See "Hyperkinetic movement disorders in children".)

- Sensorineural hearing loss due to auditory neuropathy (abnormal BAER with normal OAE) [61,62]. (See "Hearing loss in children: Etiology", section on 'Hyperbilirubinemia'.)

- Gaze abnormalities, especially limitation of upward gaze.

- Dental enamel hypoplasia, which is a long-term sequelae of severe to extreme hyperbilirubinemia seen in patients with CBE.

Most infants who develop CBE have manifested some or all of the findings associated with ABE [44]. However, there are reported cases of infants who developed CBE with high TB, but without or with only a few signs of ABE [63,64].

Hyperbilirubinemia and autism — It remains uncertain whether hyperbilirubinemia may be associated with autism spectrum disorders as noted by the following:

- A retrospective nested case-control study from a health maintenance organization (HMO) of term newborns born between 1995 and 1998 and followed for more than two years after birth compared maximal TB levels of 338 children (age four to seven years) with the autism diagnosis with 1817 randomly selected matched children without autism [65]. No differences were observed for maximal TB >20 mg/dL (342 micromol/L) between the autism and control groups (2.1 percent versus 2.5 percent). In this cohort, infants with any degree of TB elevation were not at increased risk of autism spectrum disorders after adjustment for gender, birth facility, maternal age, maternal race/ethnicity, maternal education, and gestational age. Phototherapy was also not associated with autism spectrum disorders.

  A previously reported case-cohort study from this HMO also did not find an association between autism spectrum disorders and TB levels of 15 to 19.9 mg/dL (257 to 340 micromol/L), 20 to 24.9 mg/dL (342 to 426 micromol/L), or ≥25 mg/dL (≥428 micromol/L) [66].

- In contrast, a population-based study of 733,826 infants born alive in Denmark between 1994 and 2004 reported that neonatal hyperbilirubinemia was associated with an increased risk of psychological development disorders, including infantile autism [67]. In this study, the presence of jaundice and the diagnoses of psychological disorders were determined based on diagnostic coding from data retrieved from four national registries.

- In a population-based study of 61,238 infants born between 1994 and 2000 from Nova Scotia, there were no differences in the composite outcome of cerebral palsy, developmental delay, hearing and vision losses, autism, and attention deficit hyperactivity disorder (ADHD) between infants without hyperbilirubinemia (n = 52,240) and the 3431 infants with a TB of 13.5 to 19 mg/dL (231 to 325 micromol/L), or the 348 infants with a TB >19 mg/dL (325 micromol/L) [68]. In analyses for each outcome, only developmental delay was increased in those with a TB of 13.5 to 19 mg/dL (231 to 325 micromol/L) (adjusted RR 1.6, 95% CI 1.3-2.0) and ADHD in those with a TB >19 mg/dL (325 micromol/L) (adjusted RR 1.9, 95% CI 1.1-3.3) compared with infants without hyperbilirubinemia. Although not statistically significant, there appeared to be a trend of increased likelihood of autism in infants with hyperbilirubinemia compared with those without hyperbilirubinemia (adjusted RR 1.6, 95% CI 1.0-2.5).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around

the world are provided separately. (See "Society guideline links: Neonatal jaundice".)

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.)

- Basics topics (see "Patient education: Jaundice in babies (The Basics)")
- Beyond the Basics topics (see "Patient education: Jaundice in newborn infants (Beyond the Basics)")

SUMMARY

- Total serum or plasma bilirubin (TB) levels >1 mg/dL (17.1 micromol/L) occur in almost all newborn infants and may present as jaundice. Infants with TB >25 mg/dL [428 micromol/L] are at risk for developing bilirubin-induced neurologic dysfunction (BIND), presenting acutely as acute bilirubin encephalopathy (ABE), and if inadequately treated, long-term neurologic sequelae chronic bilirubin encephalopathy (CBE, previously referred to as kernicterus). (See 'Consequences of severe hyperbilirubinemia' above and 'Bilirubin-induced neurologic dysfunction (BIND)' above.)
- The estimated incidence of severe (defined as TB >25 mg/dL [428 mmol/L]) and extreme hyperbilirubinemia (defined as TB >30 mg/dL [513 mmol/L) varies globally. This variation may be due to differences in racial composition and prevalence of genetic factors that affect bilirubin production and metabolism, breastfeeding practices and use of different definitions to describe the severity of hyperbilirubinemia. (See 'Total serum or plasma bilirubin (TB)' above.)
- CBE is rare, with reported incidence that ranges from 0.4 to 2.3 per 100,000 live births per year. (See 'Chronic bilirubin encephalopathy (kernicterus)' above.)
- The incidence of ABE is unknown. However, the reported risk of ABE is greatest in infants with TB >30 mg/dL [500 micromol/L]). (See 'Acute bilirubin encephalopathy' above.)

- The following major risk factors identify infants at risk for severe hyperbilirubinemia and BIND (table 1) (see 'Risk factors' above):
  - Predischarge TB or transcutaneous bilirubin (TcB) >95th percentile for age (figure 1)
  - Jaundice within the first 24 hours of life
  - Hemolytic disease
  - Gestational age (GA) <37 weeks
  - Sibling who previously received phototherapy
  - Cephalohematoma or significant bruising with extravascular hemolysis [26]
  - Suboptimal breastfeeding
  - East Asian race
- Clinical manifestations are due to bilirubin deposition in the skin, conjunctiva, and the brain. (See 'Clinical manifestations' above.)
  - Jaundice is the yellow color produced by the deposition of bilirubin in the skin and subcutaneous tissues. Although an important and time-honored clinical sign, the presence of jaundice is not a reliable method for assessing the actual TB concentration or for identifying infants at risk for a rapidly rising bilirubin, especially in those with dark skin. If jaundice extends below the level of the umbilicus or if there is uncertainty regarding the presence or extent of jaundice, a TB or TcB measurement should be performed. (See 'Jaundice' above and "Unconjugated hyperbilirubinemia in term and late preterm infants: Screening".)
  - Conjunctival icterus is due to bilirubin deposition in the conjunctiva (as visualized on the sclerae). The absence of conjunctival icterus is associated with a low probability of significant hyperbilirubinemia. (See 'Conjunctival icterus' above.)
  - BIND can occur in otherwise healthy term infants when TB concentrations exceed 25 mg/dL (428 micromol/L) and is manifested as ABE that can be reversible or result in kernicterus or CBE, a chronic permanent condition. (See 'Bilirubin-induced neurologic dysfunction (BIND)' above.)

    ABE typically progresses through three phases. In the early phase, clinical findings are subtle (sleepiness, mild hypotonia, and high-pitched cry) and without intervention progresses to an intermediate phase (fever, lethargy, irritability, shrill cry, and moderate hypertonia), and to an advanced stage (apnea, fever, seizures, severe hypertonia marked by persistent retrocollis and opisthotonus, and semicomatose state that progresses to coma) (table 2). (See 'Acute bilirubin encephalopathy' above.)
  - The major neurologic findings of CBE include choreoathetoid cerebral palsy, sensorineural hearing loss, and gaze abnormalities. (See 'Chronic bilirubin encephalopathy (kernicterus)' above.)

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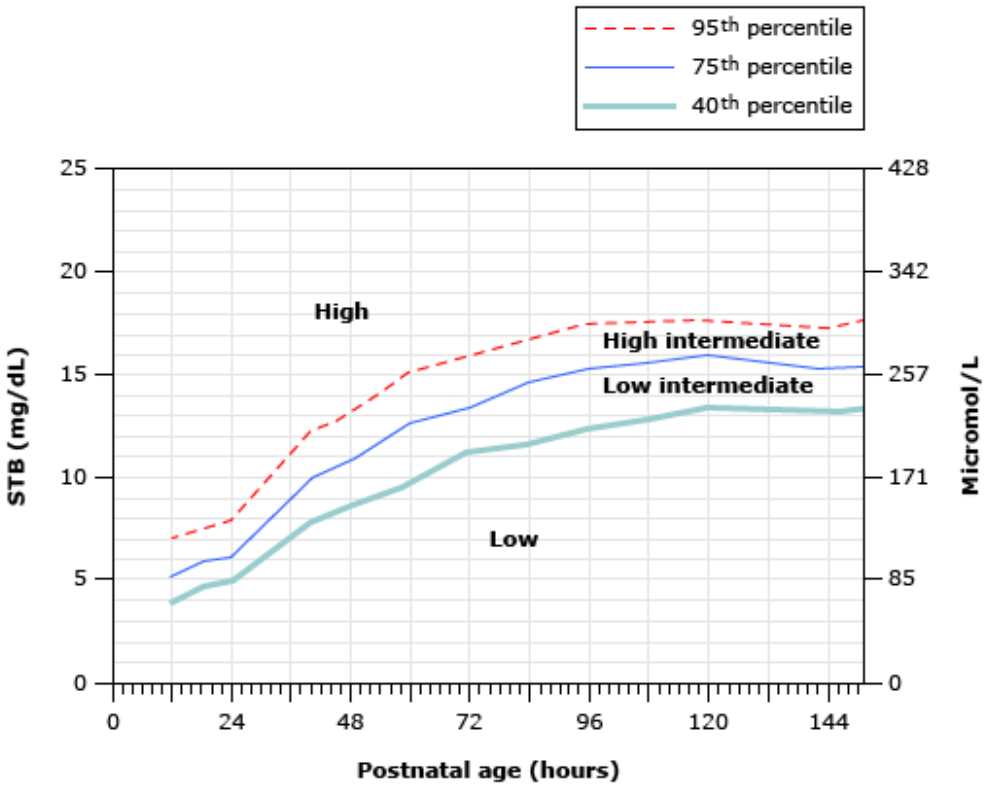
Topic 4994 Version 52.0

GRAPHICS

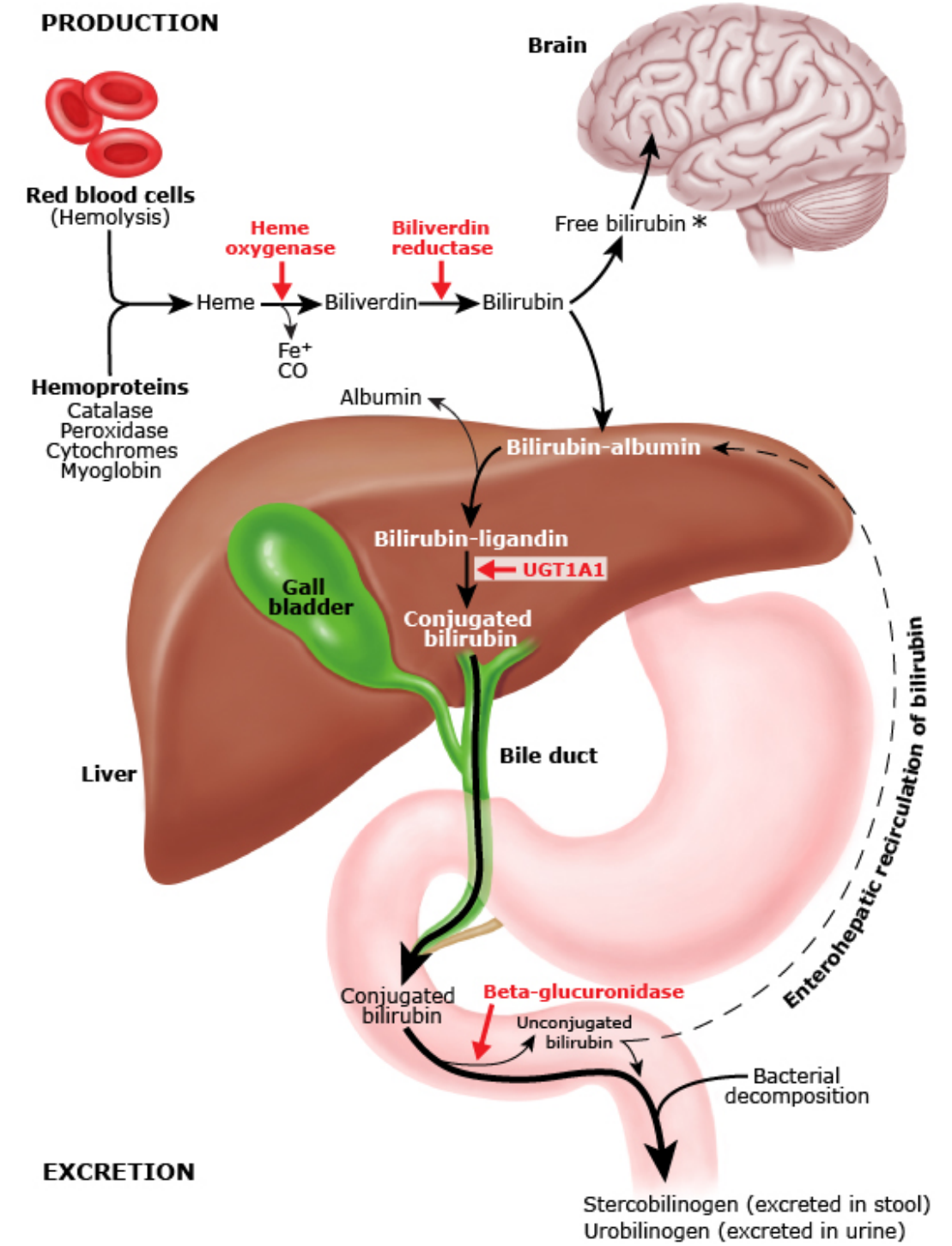
Nomogram of hour-specific serum or plasma total bilirubin (TB) concentration in healthy term and near-term newborns



Risk zones are designated according to percentile: high (TB ≥95th), high intermediate (95th >TB ≥75th), low intermediate (75th >TB ≥40th), and low (TB <40th). Infants with values in the high risk zone are at increased risk for the development of clinically significant hyperbilirubinemia requiring intervention.

Graphic 70863 Version 17.0

Bilirubin production, metabolism, and excretion



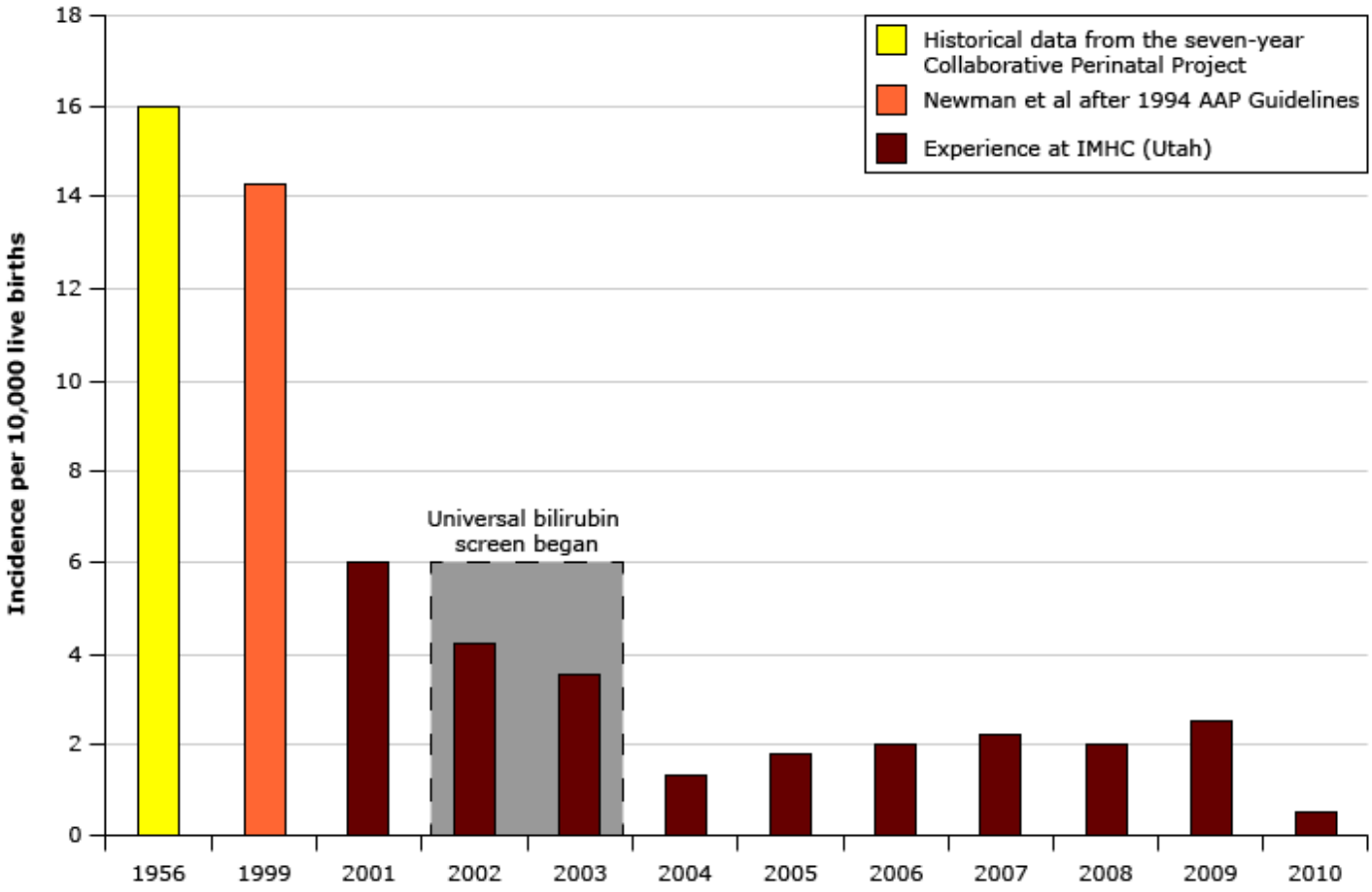
Schematic diagram demonstrating the production, metabolism, and excretion of bilirubin.

*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

Changes in the incidence of extreme hyperbilirubinemia in the United States



Comparison of the incidence of extreme hyperbilirubinemia (total serum bilirubin >25 mg/dL) for 302,399 infants born at one of the Intermountain Healthcare (IMHC) facilities from 2001 to 2010, historical data from the seven-year Collaborative Perinatal Project of 41,324 singleton white and black births with birth weights >2.5 kg initiated in 1959 (prior to availability of phototherapy and most [85 percent] infants with total bilirubin >20 mg/dL were treated with an exchange transfusion), and from Northern California population (Newman et al) managed soon after the implementation of 1994 American Academy of Pediatrics (AAP) Guidelines.

Graphic 101082 Version 1.0

Risk factors for development of severe hyperbilirubinemia in infants of 35 or more weeks gestation (in approximate order of importance)

Major risk factors
Predischarge TB or TcB level in the high-risk zone
Jaundice observed in the first 24 hours
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated ETCOc
Gestational age 35 to 36 weeks
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race*
Minor risk factors
Predischarge TB or TcB level in the high intermediate-risk zone
Gestational age 37 to 38 weeks
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥25 years
Male gender
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TB or TcB level in the low-risk zone
Gestational age ≥41 weeks
Exclusive bottle feeding
Black race*
Discharge from hospital after 72 hours

TB: total serum or plasma bilirubin; TcB: transcutaneous bilirubin; G6PD: glucose-6-phosphate dehydrogenase; ETCOc: end-tidal carbon monoxide concentration.
* Race as defined by mother's description.

Graphic 64584 Version 21.0

Bilirubin-induced neurologic dysfunction (BIND) assessment (score) for term and late preterm infants

Clinical signs	Score
Mental status	
Normal	0
Sleepy but arousable, decreased feeding	1
Lethargic, poor suck, irritable, and/or jittery	2
Semicomatose to comatose, unable to feed, seizures	3
Muscle tone	
Normal	0
Persistent mild to moderate hypotonia	1
Mild to moderate hypertonia alternating with hypotonia	2
Persistent retrocollis and opisthotonos	3
Cry pattern	
Normal	0
High pitched when aroused	1
Shrill, difficult to console	2
Inconsolable crying or weak/absent cry	3
Total BIND score	

Total scores for BIND determine the presence and severity of acute bilirubin encephalopathy (ABE) for infants without other identifiable causes for neurologic dysfunction:

- Scores between 7 and 9: Advanced ABE, requiring emergency intervention (exchange transfusion) to prevent further brain injury and potentially reverse acute brain damage.
- Scores between 4 and 6: Moderate ABE, requiring urgent intervention (intensive phototherapy and potentially exchange transfusion) to possibly (based on timing of intervention) prevent and reverse brain injury.
- Scores between 1 and 3: Consistent with subtle signs of ABE, requiring intervention (phototherapy) depending on total bilirubin. In these patients, auditory brainstem response testing is helpful, as an abnormal result would confirm the presence of moderate ABE.

Graphic 122620 Version 1.0

Contributor 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: Fresenius Kabi [Parenteral nutrition-associated liver disease]. Consultant/Advisory Boards: MilkPep [Childhood nutrition]. **Melanie S Kim, MD** Nothing to disclose

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.

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