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 biliru
also referred to as "physiologic jaundice."

- **Significant hyperbilirubinemia** in infants ≥35 weeks gestational age (GA) is defi
nomogram (figure 2) [1].

- **Severe neonatal hyperbilirubinemia** is defined as a TB >25 mg/dL (428 micromo
bilirubin-induced neurologic dysfunction (BIND).

- **Extreme hyperbilirubinemia** is defined as a TB >30 mg/dL (513 micromol/L). It is
induced neurologic dysfunction (BIND).

- **Bilirubin-induced neurologic dysfunction (BIND)** is due to brain damage from f
to brain tissue, as evidenced by both molecular and cytological injuries of brain ce
and late preterm infants: Epidemiology and clinical manifestations", section on 'Cl

  - **Acute bilirubin encephalopathy (ABE)** is used to describe the acute manifes
hyperbilirubinemia in term and late preterm infants: Epidemiology and clinica
encephalopathy'.)

  - **Chronic bilirubin encephalopathy (CBE)**, previously referred to as kernicteru
of bilirubin neurotoxicity. (See "Unconjugated hyperbilirubinemia in term and
manifestations", section on 'Chronic bilirubin encephalopathy (kernicterus)'.)

OVERVIEW

An association between severe hyperbilirubinemia (total serum or plasma bilirubin [TB
encephalopathy (CBE), previously referred to as kernicterus, the chronic and permane
(BIND), was first identified in infants with extreme hyperbilirubinemia due to erythrob

As a result, prevention of CBE has been focused on eliminating severe neonatal hyperb

- Prevention of significant hyperbilirubinemia (TB >95th percentile on the hour-spec

transfusion'.)

The indications for when to intervene and for which intervention to use are discussed
American Academy of Pediatrics (AAP) guideline [8]. Details regarding phototherapy a
"Unconjugated hyperbilirubinemia in the newborn: Interventions", section on 'Photot
newborn: Interventions", section on 'Exchange transfusion'.)

ASSESSMENT OF RISK SEVERITY

The decision of when to initiate therapy and the choice of intervention are based on a
hyperbilirubinemia (defined as total serum or plasma bilirubin [TB] >25 mg/dL [428 m
TB values and the presence or absence of additional risk factors (including gestational
bilirubin-induced neurologic dysfunction (BIND) (figure 3 and figure 4 and algorithm 1
hyperbilirubinemia include isoimmune hemolytic disease (eg, glucose-6-phosphate de
temperature instability, sepsis, acidosis, hypoalbuminemia (albumin <3 g/dL), East Asi
weight loss (table 1) [5]. This approach of assessing risk severity is consistent with the
Pediatrics (AAP) [1] and the United Kingdom's National Institute for Health and Clinica
national guidelines have also been developed in Norway, which are based on TB value
hyperbilirubinemia in term and late preterm infants: Screening", section on 'Risk asses
late preterm infants: Screening", section on 'Additional evaluation'.)

The risk for severe hyperbilirubinemia and the threshold for intervention either with p
using the newborn hyperbilirubinemia assessment calculator based on TB values and

The bilirubin/albumin (B/A) molar ratio can be used as an additional factor in determi
used alone, but in conjunction with TB values [1,10]. In term neonates, a B/A molar rat
bilirubin binding sites on albumin are occupied. Any further increases in bilirubin can
blood-barrier result in a higher (unmeasured) risk of neurotoxicity (figure 1) [11]. In pr
ability of albumin to bind bilirubin, making it more challenging to predict their bilirubi
hyperbilirubinemia in term and late preterm infants: Screening", section on 'Additiona
preterm infant (less than 35 weeks gestation)", section on 'Other tests'.)

CRITERIA FOR INTERVENTION BASED ON RISK SEVERITY ASSESSMENT

Term infants without risk factors

Term infants with risk factors or late preterm infants without risk factors

- Phototherapy indications – For term infants (≥38 weeks GA) with risk factors for hy
6/7 weeks GA) without risk factors, phototherapy is started at the following TB val

  - 24 hours of age – >10 mg/dL (171 micromol/L)
  - 48 hours of age – >13 mg/dL (222 micromol/L)
  - 72 hours of age – >15 mg/dL (257 micromol/L)

  The threshold for intervention may be lowered for infants closer to 35 weeks GA a

- Exchange transfusion indications – For term infants (≥38 weeks GA) with risk facto
(35 to 37 6/7 weeks GA) without risk factors, exchange transfusion is indicated at t

  - 24 hours of age – >16.5 mg/dL (282 micromol/L)
  - 48 hours of age – >19 mg/dL (325 micromol/L)
  - ≥72 hours of age – >21 mg/dL (359 micromol/L)

  The threshold for intervention may be lowered for infants closer to 35 weeks GA a

  In our practice, neonates with TB >17 mg/dL (291 micromol/L; 95th percentile) sho
hours if their serum albumin is <3 g/dL and have failed to respond adequately to i
used, B/A molar ratio >7 to 8 mg/g/dL in conjunction with TB values may guide a d
"Unconjugated hyperbilirubinemia in term and late preterm infants: Screening" an
preterm infants: Screening", section on 'Additional evaluation' and "Unconjugated
on 'Intensive phototherapy ("crash-cart" phototherapy)'.)

  Term infants with risk factors or late preterm infants who are readmitted with TB
neurologic findings (eg, using BIND scores [13]). In these patients, an exchange tr
("crash-cart") phototherapy or they become symptomatic. (See 'Exchange transfus
"Unconjugated hyperbilirubinemia in the newborn: Interventions", section on 'Int
"Unconjugated hyperbilirubinemia in the newborn: Interventions", section on 'Exc

Late preterm infants with risk factors

- Phototherapy indications – For late preterm infants (35 to <38 weeks GA) with risk
values based on the age of the patient:

vascular access. Intensive phototherapy should be provided in the interim time period
preterm infants: Epidemiology and clinical manifestations", section on 'Acute bilirubin
the newborn: Interventions", section on 'Exchange transfusion'.)

Rhesus isoimmune hemolytic disease refractory to phototherapy — In infants with
of intravenous immune globulin (IVIG; dose 0.5 to 1 g/kg over two hours) is suggested
or 3 mg/dL (34 to 51 micromol/L) of the threshold for exchange transfusion [1,14]. The
'Intravenous immune globulin (IVIG)' below.)

Infants greater than one week of age with acute rise of TB — Infants who have acu
levels (>0.2 mg/dL/hour, [3.42 micromol/L/hour]) who are greater than one week of ag
deficiency causing hemolysis or other intrinsic hemolytic diseases (see "Overview of h
anemias'). These infants require more urgent and aggressive interventions and are be
neurologic signs (eg, using BIND scores) [13], intensive ("crash-cart") phototherapy, an
critical, as delay in intervention may have deleterious effects. (See "Diagnosis and man
deficiency", section on 'Treatment of neonatal jaundice and chronic hemolysis' and "D
dehydrogenase (G6PD) deficiency", section on 'Treatment of acute hemolytic episodes

Subthreshold (prophylactic) phototherapy — There is no indication to use subthresh
phototherapy). Clinicians have initiated phototherapy at subthreshold levels of TB duri
readmission. Although the use of subthreshold phototherapy may reduce the risk of re
phototherapy, impede infant-maternal bonding, and prolong birth hospitalization [15]
preterm infants: Screening", section on 'Follow-up'). As a result, we suggest subthresh
newborns when good follow-up is arranged, as it unnecessarily exposes many infants
birth hospitalization, and increases hospital costs.

INTERVENTIONS USED TO PREVENT AND TREAT SEVERE HYPERBILIRU

Phototherapy — Phototherapy is the most commonly used intervention to treat and p
intervention to lower total serum or plasma bilirubin (TB) and has been considered a s
infants and only infrequent reports of significant adverse effects and long-term neuro

The efficacy, dosing (including selection of light sources and devices), and adverse effe
discontinuation of therapy, are discussed in detail separately. (See "Unconjugated hyp
'Phototherapy'.)

Exchange transfusion — Although exchange transfusion is an increasingly rare, expe

- Ursodeoxycholic acid **(UCDA)** – UDCA enables the emulsification of bile in the bilia and helps to lower TB levels [16]. It is useful in the treatment of cholestatic jaundi infants with combined unconjugated and conjugated hyperbilirubinemia in additi hyperbilirubinemia alone. (See "Causes of cholestasis in neonates and young infa

- Phenobarbital – Phenobarbital increases the conjugation and excretion of bilirubi women or infants. However, prenatal administration of phenobarbital may advers As a result, we do **not** recommend phenobarbital be used routinely used to treat clinically significant adverse effects.

- **Metalloporphyrins** – There is evidence suggesting suggest synthetic metalloporp production by competitive inhibition of heme oxygenase [19-27]. However, SnMP hyperbilirubinemia and is not available for general use.

- **Clofibrate** – Clofibrate is a peroxisome proliferator-activated receptor alpha agon incompatibility, its efficacy and safety have not been proven [28,29]. As a result, it hyperbilirubinemia.

OUTCOME

When infants with hyperbilirubinemia are identified and treated appropriately, the out adverse neurodevelopmental sequelae [30-32].

This was best illustrated in a prospective study of 140 infants with total serum or plasm including 10 infants with TB ≥30 mg/dL (513 micromol/L) identified from a cohort of 1 phototherapy in 136 cases and exchange transfusions in five cases. The hyperbilirubin proportion of infants who were born <38 weeks gestational age (GA), Asian, and exclu follow-up, results were as follows:

- There were no reports of kernicterus in either the severely hyperbilirubinemic or

- Formal cognitive testing was performed in 82 children with neonatal severe hyper of age. There was no difference between patients with severe hyperbilirubinemia behavioral problems, and frequency of parental concerns.

- On physical examination, patients with extreme hyperbilirubinemia (TB ≥25 mg/d lower prevalence of abnormal neurologic findings (14 versus 29 percent). The deg

These results support the American Academy of Pediatrics (AAP) guideline for the mar
infants, especially the use of lower threshold values for intervention in infants with a p

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and re
"Society guideline links: Neonatal jaundice".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond th
plain language, at the 5th to 6th grade reading level, and they answer the four or five k
These articles are best for patients who want a general overview and who prefer short
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

Here are the patient education articles that are relevant to this topic. We encourage yo
also locate patient education articles on a variety of subjects by searching on "patient

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

A list of frequently asked questions and answers for parents is available through the A
www.healthychildren.org/English/ages-stages/baby/Pages/Jaundice.aspx

SUMMARY AND RECOMMENDATIONS

- The prevention of kernicterus (chronic and permanent sequelae of bilirubin-induc
severe hyperbilirubinemia defined as a total serum or plasma bilirubin (TB) >25 m
hyperbilirubinemia (figure 2), and reducing TB in infants with hyperbilirubinemia.
hyperbilirubinemia in term and late preterm infants: Screening", section on 'Scree
- Prevention of hyperbilirubinemia is based on identifying at-risk infants, and using
to initiate therapy and the choice of intervention are based on assessment of the

despite intensive phototherapy (**Grade 1B**). We suggest exchange transfusion for
upon the guideline developed by the American Academy of Pediatrics (AAP) (infan
intensive phototherapy (figure 4) (**Grade 2C**). (See 'Symptomatic patients' above a
hyperbilirubinemia in the newborn: Interventions", section on 'Exchange transfus

- We suggest not to use prophylactic phototherapy (subthreshold therapy) in the ro
subthreshold levels of TB during the birth hospitalization (**Grade 2B**). Although su
unnecessarily exposes many infants to phototherapy (and its potential adverse ef
(prophylactic) phototherapy' above.)

- We suggest administering intravenous immunoglobulin (IVIG) to newborn infants
'Rhesus isoimmune hemolytic disease refractory to phototherapy' above.)

- Unproven or unavailable therapies include phenobarbital and metalloporphyrins.
management of neonates with cholestasis. (See 'Unproven pharmacologic agents

- When infants with hyperbilirubinemia can be identified and treated appropriately,
for adverse neurodevelopmental sequelae. (See 'Outcome' above.)

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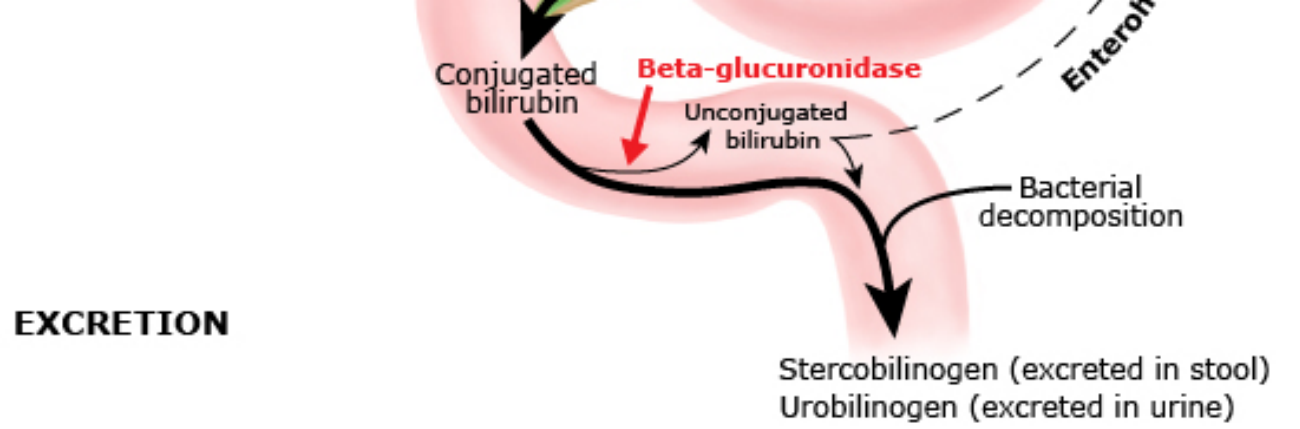

Schematic diagram demonstrating the production, metabolism, and excretion of bilirubin.

*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

This algorithm is based on the clinical practice of universal bilirubin screening for term and late preterm provided by the authors of the UpToDate content on the screening and management of unconjugated hyperbilirubinemia in term and late preterm infants.

TB: total plasma/serum bilirubin; TcB: transcutaneous bilirubin; ROR: rate of rise.
* Exchange transfusion is indicated for any symptomatic infant due to bilirubin-induced neurotoxicity. While setting up for the exchange transfusion, intensive phototherapy is initiated.
¶ TB and TcB values are plotted on the age-specific (hourly), percentile-based Bhutani nomogram. A confirmatory TB value is obtained when TcB measurement exceeds the 95th percentile on the TcB nomogram or 75th percentile on the TB nomogram.
Δ Clinical assessment for risk factors for severe hyperbilirubinemia (TB >20 mg/dL [342 micromol/L]) entails documenting the presence of jaundice, evidence of hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), evidence of significant bruising (cephalohematoma), gestational age 35 to <37 weeks, previous sibling having received phototherapy, exclusive breastfeeding with excessive weight loss, and East Asian ethnicity.
◊ The risk for severe hyperbilirubinemia and the threshold for intervention (phototherapy and exchange transfusion) can be determined using the newborn hyperbilirubinemia assessment calculator based on TB and the presence of concomitant risk factors. The newborn hyperbilirubinemia assessment calculator provides information when the threshold has been reached for either phototherapy or exchange transfusion. Risk categories for asymptomatic newborns include: term infants without risk factors, term infants with risk factors, late preterm infants without risk factors, and late preterm infants with risk factors.
§ Criteria for intervention are determined by TB and the presence of concomitant risk factors. Exchange transfusion is reserved for infants with signs of bilirubin-induced neurologic dysfunction (BIND) and when intensive phototherapy fails to prevent severe hyperbilirubinemia. The threshold for intervention is discussed in the UpToDate topic on the management of unconjugated hyperbilirubinemia in term and late preterm infants.

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Graphic 56490 Version 23.0

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Graphic 64584 Version 21.0

direct reacting or conjugated bilirubin. If infant is well and 35 to 37 6/7 weeks (medium risk) can individualize TB levels for exchange based on actual gestational age. Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the TB rises to these levels despite intensive phototherapy. For readmitted infants, if the TB level is above the exchange level, repeat TB measurement every two to three hours and consider exchange if the TB remains above the levels indicated after intensive phototherapy for six hours.

TB: total serum or plasma bilirubin; G6PD: glucose-6-phosphate dehydrogenase; B/A: bilirubin/albumin.

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