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This Just In Editor

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Hyperbilirubinemia in Neonates: Prevention, Early Identification, and Treatment

Neonatal hyperbilirubinemia can have serious consequences, including bililrubin encephalopathy and kernicterus.[1] Bilirubin encephalopathy can be reversed, whereas kernicterus is permanent. Elevated levels of bilirubin lead to the accumulation of unconjugated bilirubin within the brain, which can result in encephalopathy. The consequences of encephalopathy include disability due to deafness, gaze paresis, decreased intelligence, and choreoathetoid cerebral palsy, and rarely, death.[2]

A newborn produces up to 10 mg/kg/day of bilirubin, most of which is created from the destruction of hemoglobin from red blood cells. Approximately 35 mg of unconjugated, or indirect, bilirubin is formed from each gram of hemoglobin. Bilirubin production is elevated in neonates during the first 24 to 48 hours of life because of their relatively higher hematocrit and more rapid turnover of red blood cells. Conjugation of bilirubin is delayed in newborns during the first hours after birth but increases by about 24 hours of age in the term newborn, reaching adult levels by about 4 days of age. Elimination of bilirubin is further delayed in the preterm infant. An excess of unconjugated bilirubin can result in hyperbilirubinemia.[3]

Approximately 50% of term infants — those 38 weeks gestation or greater — will develop increased serum total bilirubin levels and visible signs of jaundice in the first 3 to 4 days of life, dissipating by the 6th day. Physiologic jaundice/hyperbilirubinemia is defined as a serum total bilirubin level of <13 mg/dl or a rise of less than 0.5 mg/dl/hour.[3]

The incidence of kernicterus peaked in the 1950s and 1960s. Subsequently, kernicterus essentially vanished until the 1990s, when a sudden a rise was again noted. Factors leading to the reappearance of kernicterus are thought to be early discharge, an increase in home births, and an increase in exclusive breast-feeding.[4-6]

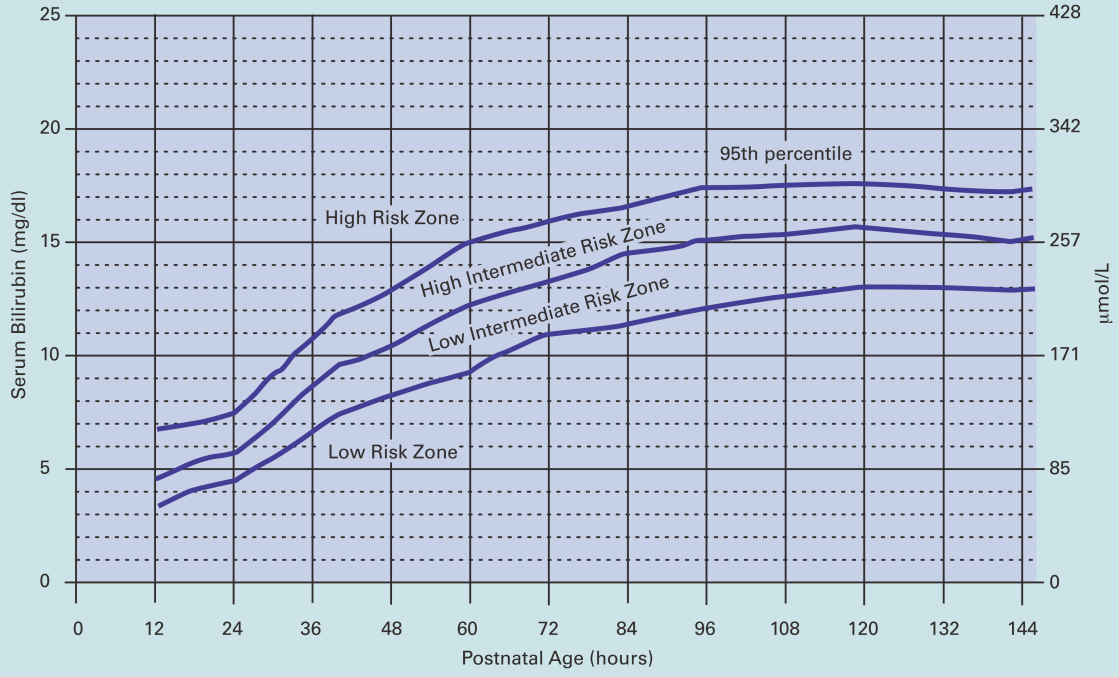
Because hyperbilirubinemia can lead to permanent brain damage, in

Table 1: Risk Factors for the Development of Severe Hyperbilirubinemia

Risk	Factor
Major Risk Factor (Bullets in bold are the most major risk factors)	• **Jaundice in first 24 hours** • **Gestational age 35 to 36 weeks** • **Previous sibling received phototherapy** • **Exclusive breastfeeding (especially if weight loss excessive)** • Predischarge TSB or TcB level high risk as noted on nomogram in Figure 1 • Blood group incompatibility and positive direct antiglobulin test, hemolytic disease such as glucose-6-phosphate dehydrogenase (G6PD), elevated end-tidal carbon dioxide • Cephalohematoma or significant bruising • East Asian ethnicity
Minor Risk Factor	• Jaundice before discharge • Gestational age 37 to 38 weeks • Previous sibling with jaundice • Predischarge TSB or TcB level in high intermediate-risk as noted on nomogram • Macrosomic infant of a diabetic mother • Maternal age ≥ 25 years old • Male
Decreased Risk Factor (listed in order of decreasing importance)	• TSB or TcB level in low risk as noted on nomogram in Figure 1 • Gestational age ≥ 41 weeks • Exclusive bottle feeding • Black race • Discharge from hospital after 72 hours

Adapted from "Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation," by Subcommittee on Hyperbilirubinemia, 2004, Pediatrics, 114, p. 301.

Figure 1: Nomogram of Jaundice in Newborn



Nomogram for designation of risk in 2,840 well newborns at 36 or more weeks gestational age with birth weight of 2,000 g or more or 35 or more weeks gestational age and birth weight of 2,500 g or more based on the hour-specific bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone).

Adapted from "Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation," by Subcommittee on Hyperbilirubinemia, 2004, Pediatrics, 114, p. 301.

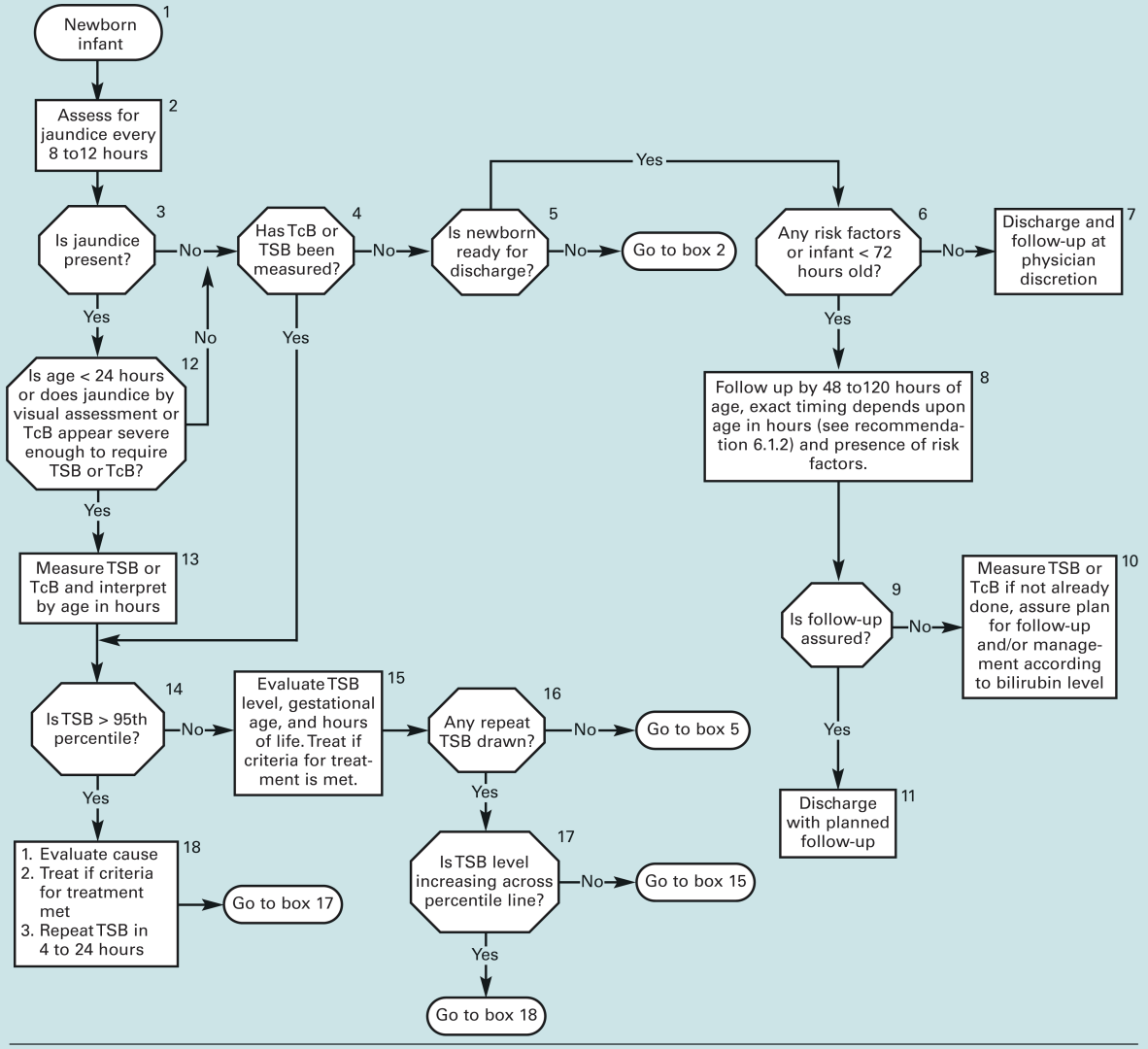
2001 the Centers for Disease Control (CDC) urged more stringent identification and management of hyperbilirubinemia in newborns,[6] In response to that challenge, in 2004 the American Academy of Pediatrics (AAP) developed its Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation.[1] The guideline has not been officially updated since its 2004 release; however, as the guideline has been used and new research has become available, recommendations for updating or clarifying the guideline have surfaced. The two works that add to the knowledge base of the guideline include the 2009 US Preventive Services Task Force (USPSTF) guideline, Screening of Infants for Hyperbilirubinemia to Prevent Chronic Bilirubin Encephalopathy,[2] and the 2010 work by Maisels, Screening and Early Postnatal Management Strategies to Prevent Hazardous Hyperbilirubinemia in Newborns of 35 or More Weeks of Gestation.[4]

The 2004 AAP guideline contains four key recommendations for reducing the risk of severe hyperbilirubinemia. The recommendations are aimed not only at reducing the incidence of hyperbilirubinemia but also at minimizing maternal anxiety through education and support; encouraging breast-feeding; and decreasing unnecessary costs and treatment through appropriate identification, follow-up, and therapy.

The four recommendations include:

- Promote and support breast-feeding.
- Develop nursery protocols to identify hyperbilirubinemia.
  - Measure total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on newborns who become jaundiced within the first 24 hours following birth and interpret the level according to the newborn's age in hours (Figure 2).
  - Visual determination of jaundice is unreliable.
  - Complete a thorough assessment of the newborn before discharge to identify risk factors of hyperbilirubinemia (Table 1).

Figure 2: Management of Jaundice in the Newborn Nursery



Adapted from "Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation," by Subcommittee on Hyperbilirubinemia, 2004, Pediatrics, 114, p. 301.

  - Direct special attention to newborns less than 38 weeks gestation, especially if exclusively breast-fed, because these infants are at greater risk for developing hyperbilirubinemia.
  - Educate parents about newborn jaundice.
- Initial follow-up, after discharge, is determined by risk of hyperbilirubinemia.
- Phototherapy or exchange transfusions are indicated for treatment of newborns with hyperbilirubinemia to prevent severe hyperbilirubinemia and possibly bilirubin encephalopathy (kernicterus).

Breast-feeding

A seeming contradiction of the guideline is seen in the recommendation to promote and support breast-feeding. Exclusive breast-feeding has been identified as potentially one of the major risk factors in the development of hyperbilirubinemia. Although a biologically natural act, breast-feeding requires time for both the mother and the infant to adjust so that the mother supplies sufficient calories and nutrients and the infant ingests enough milk to re-

Table 2: Visual Jaundice and Potential TSB (Total Serum Bilirubin) Values[5]

Zone	Body area that appears jaundiced	Potential TSB Value
1	Head through neck to level of clavicle	5 mg/dl
2	Clavicle to umbilicus	6-8 mg/dl
3	Umbilicus to knees	9-12 mg/dl
4	Knees to ankles	13-15 mg/dl
5	Palms and soles	> 15 mg/dl

ceive adequate calories and nutrients.[4] Therefore, breast-feeding is a risk factor because of insufficient caloric and nutrient intake in the newborn.

Other concerns with breast-feeding include formation of stools that contain less bilirubin when compared to stools of formula-fed infants, as well as smaller cumulative stool output and decreased formation of urobilin in the gastrointestinal tract. Breast-fed infants also demonstrate increased intestinal fat absorption, which permits uptake of bilirubin by adipose cells. In addition, activity of B-glucuronidase is increased in breast milk, which may lead to more rapid absorption of unconjugated bilirubin from the intestine. All of these situations can elevate total serum bilirubin levels.[5]

To promote and support breast-feeding while at the same time reducing the risk of hyperbilirubinemia associated with breast feeding, mothers should be encouraged to feed 8 to 12 times a day for the first 48 to 72 hours. Although no randomized, controlled trial exists, there appears to be enough supporting evidence to suggest this practice, because increasing the number of feeding times encourages caloric and fluid intake as well as weight gain. Maisels notes that in the kernicterus registry, 123 of the 125 infants who developed kernicterus were exclusively breast-fed.[4]

Nursery Protocols

In order to manage hyperbilirubinemia, the condition must first be identified. As can be seen in the recommendations of the 2004 AAP guideline, screening by total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level is suggested because visual identification of jaundice is not considered reliable.[1] The newer USPSTF guideline, "concludes, that there is not enough evidence to recommend screening; risk-factor assessment, measurement of bilirubin level either TcB or TSB, or a combination, of hyperbilirubinemia in order to prevent chronic bilirubin encephalopathy." This rather bold statement is based on an extensive review of the literature, conducted from September 2001 through August 2007, that found screening evidence insufficient in four domains: burden of suffering from the condition, potential of harm from the intervention, cost, and current practice.[2] These statements should be kept in mind when caregivers develop protocols to enhance and improve patient outcomes.

Nursing protocols that enable the bedside nurse to think critically and intervene when necessary will ensure that the patient experiences the best care and outcome. For hyperbilirubinemia, it is suggested that part of the nursery protocol include standing orders that authorize the nurse to order a TSB when hyperbilirubinemia is suspected either by visual observation or by TcB.[4] As stated in the recommendations by the 2004 guideline, visual determination of jaundice is neither a refined nor an accurate skill and therefore cannot be used as the sole means for detecting hyperbilirubinemia.[1,4] However, research has provided a scale that can be used to objectify and quantify visual jaundice.[3] Jaundice appears as bilirubin levels increase, beginning cephalically and moving caudally; or literally, moving from head to toe.

As jaundice progresses cephalocaudally, association with TSB values has been made and can be noted in Table 2.[4] A clinical pearl may be that if jaundice is not seen below the nipple line, it is unlikely that the TSB is >12 mg/dl, and if jaundice does not extend below the umbilicus it is unlikely that the TSB is >14.6 mg/dl.[4]

If jaundice is noted on visual inspection before obtaining a TSB level, which is an invasive procedure, the nurse should obtain a TcB if the facility provides this mode of evaluation. TcB measurements can be performed not only in an inpatient setting but also in outpatient settings because of their noninvasiveness and ease of use. Evidence supports the use of TcB in estimating TSB values, but not as a substitute for obtaining TSB values. TcB measures the yellow color of blanched skin and subcutaneous tissues, and thus can be used only to estimate the TSB value and to determine whether a TSB should be drawn. TcB measurements are plotted on the same nomogram as TSB measurements, noting the value of the measurement and the infant's age in hours.[4]

It should be noted that screening by TSB or TcB is a billable event and thus has the potential to increase insurance premiums, as well

Table 3: Strategies for Prevention of Hyperbilirubinemia in the Newborn

Primary Prevention

1.0: Encourage breastfeeding 8 to 12 or more times a day for the first several days after birth **(C)**

1.1: Supplementation with water or dextrose water is not recommended in nondehydrated breastfed newborns **(B-C)**
Comments
- Inadequate calories or fluid from inadequate breastfeeding may contribute to hyperbilirubinemia
- Water and/or dextrose water does not prevent hyperbilirubinemia or decrease TSB levels

Secondary Prevention

2.0: Perform ongoing assessments during the neonatal stage to determine risk assessment for developing severe hyperbilirubinemia **(B)**

2.1: Test pregnant women for ABO and Rh (D) blood typing, including screening for isoimmune antibodies. **(B)**

2.1.1: If not blood typed, or mom Rh-negative, a direct antibody test or Coombs' test, blood typing, and Rh (D) should be done on the newborn's cord blood. **(B)**

2.1.2: If maternal blood is "O" or Rh +, the newborn's cord blood can be tested for blood type, direct antibody or Coomb's. This testing is not required if "appropriate surveillance, risk assessment prior to discharge from the nursery, and appropriate follow-up" can be carried out. **(C)**

2.2: Assess jaundice in the newborn a minimum of every 8 to 12 hours. **(D)**
Comments
- Jaundice may be observed by blanching the skin by a window with daylight, or in that absence, a well-lit room. Generally jaundice is first identified on the face and progressed caudally. However, visual/blanching is not devoid of human error, especially in light of darker skin newborns and should not be used as a replacement for bilirubin levels.
- Repeat measurements will depend upon the initial levels.

3.0: If an infant demonstrates jaundice in the first 24 hours of life, a TcB and/or TSB should be done. **(C)**

3.1: Obtain a TcB and/or TSB if jaundice appears excessive for age. **(C)**

3.2: Interpret bilirubin levels according to newborn's age in hours. **(D)**

4.1: Determine cause of jaundice, if possible. **(C)**

4.1.1: If bilirubin levels elevated, obtain urinalysis and urine culture, sepsis work-up if indicated. **(C)**

4.1.2: Sick newborns and newborns who are jaundiced at 3 weeks of age or greater should be checked for cholestasis by total and direct or conjugated bilirubin levels, thyroid, and galactosemia. **(D)**

4.1.3: If measurements under 4.1.2 elevated, investigate cause of cholestasis **(C)**

4.1.4: Measure G6PD in newborns receiving phototherapy for jaundice whose family history, ethnic background, geographical origin suggests risk, or in whom phototherapy response is less than expected. **(C)**
Comments
- G6PD is more common in Mediterranean, Middle East, Arabian peninsula, Southeast Asia, and Africa. Immigration and intermarriage has made this a global concern. Occurs in 11% to 13% of African-Americans. And may be responsible for over 30% of newborns who develop kernicterus.
- See 5.1.1 and Table: Risk Factors for Severe Hyperbilirubinemia.

5.1: Before discharge from nursery, assess all newborns, according to established nursery protocol, risk of developing severe hyperbilirubinemia. **(C)**

5.1.1: Assessment for carrying out 5.1 should include TSB or TcB levels plotted on nomogram. **(D)**

6.1: Give written and verbal instructions to parents regarding how to monitor and identify jaundice and what to do if observed. **(C)**

6.1.1: Follow-up after discharge should be done early. **(C)**

6.1.2: Recommended follow-up:

Discharged:	See at:
< 24 hours	72 hours
> 24, < 48 hours	96 hours
48 to 72 hours	120 hours

Consider two early follow-ups in those discharged before 48 hours, one at 24 to 72 hours and one at 72 to 120 hours. **(D)**

6.1.3: If appropriate follow-up is not ensured, consider delaying discharge (72 to 96 hours) in high risk newborns. **(C)**

6.1.4: During follow-up, assess weight, percent change in weight from birth weight, adequacy of intake, voiding and stooling, presence/absence of jaundice. **(C)**
Comments
- Highest risk is in the newborn period of ≤ 96 hours.
- In newborns where doubt exists regarding presence of jaundice, the TSB or TcB level should be obtained.

Treatment

7.1: Treatment recommendations are found in algorithm. **(C)**

7.1.1: Do not subtract direct-reacting (or conjugated) bilirubin level from total bilirubin when using treatment guideline. **(D)**
Comments
- If direct bilirubin is ≥ 50% of total, consult with a specialist.

7.1.2: If exchange transfusion or intensive phototherapy is recommended, based on TSB level, emergently admit newborn to neonatal/pediatric service, do not send to the emergency department which can delay initiation of treatment. **(C)**

7.1.3: Exchange transfusions are to be performed by trained personnel only in a neonatal ICU where intensive monitoring and resuscitation personnel and equipment are available. **(D)**

7.1.4: For isoimmune hemolytic disease, administer intravenous γ-globulin (0.5-1.0 g/kg over 2 hours) and repeat in 12 hours if needed, if TSB rising despite intensive phototherapy or when the TSB level is 2 to 3 mg/dL of the exchange level. **(B)**
Comments
- Reduces the need for exchange transfusion in Rh and ABO hemolytic disease.

7.1.5: A serum albumin level of < 3.0 g/dL may be used as an option for a risk factor to lower the threshold of phototherapy. **(D)**

7.1.6: If planning on performing exchange transfusion, measure serum albumin level, bilirubin/albumin ratio, along with TSB. **(D)**

7.1.7: State exchange transfusions should be carried out on any newborn who is jaundiced and displays intermediate to advanced stages of acute bilirubin encephalopathy. **(D)**
Comments
- Bilirubin encephalopathy red flags include hypertonia, arching, retrocollis, opisthotonos, fever, and/or high-pitched cry.

7.2: All institutions that care for newborns should have the equipment to carry out intensive phototherapy. **(C)**

7.3: It is recommended that breast feeding be continued in newborns who have been breast fed and require phototherapy. **(C)**
Comments
- Using formula during phototherapy is an option and may further enhance phototherapy and bilirubin level reduction.

*Level of evidence: A = beneficial, B = benefits exceed harms, C = benefits exceed harms, D = benefits versus harms exceptional.

Adapted from "Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation," by Subcommittee on Hyperbilirubinemia, 2004, Pediatrics, 114, p. 299.

as place increased financial burden on the parents.

Prior to discharge, the newborn should be assessed for risk factors for the development of hyperbilirubinemia, especially if the infant is being discharged less than 72 hours after birth. Major risk factors include exclusively breast-feeding, a family history of neonatal jaundice, bruising of the neonate during birth, presence of cephalohematoma, East Asian ethnicity, maternal age >25 years, male gender, glucose-6-phosphate dehydrogenase deficiency, and a gestational age less than 38 weeks.[1,4,5] Even though East Asian ethnicity is considered a major risk factor, almost 60% of infants who develop hyperbilirubinemia in the United States are Caucasian.[5] Additional risk factors are presented in Table 1.

Before the infant is discharged, parents should be given both written and verbal information about jaundice, including risk factors, identification, and treatment. Preprinted educational materials are readily available. The American Academy of Pediatrics offers a kit covering breast-feeding and jaundice, Sate and Healthy Beginnings, which can be found at http://www.aap.org/bookstore. Stanford Medical University has a web-based tool, the BiliTool, which can be found at www.bilitool.org. The CDC has also developed a teaching home page for families of newborns with kernicterus. The information can be found at http://www.cdc.gov/ncbddd/jaundice/index.html.

Follow-up After Discharge

Re-evaluation of the newborn is, in large part, determined by when the patient was discharged from the hospital. Recommendations include the infant's first outpatient office visit two days after discharge, if the infant was discharged 72 hours or sooner after birth.[4] However, this first visit can be later if the infant is not at risk for hyperbilirubinemia (Table 1) and no other concerns related to birth or discharge have been identified.[1,4] At the initial outpatient evaluation, the caregiver should reiterate to the parents the information regarding jaundice and hyperbilirubinemia and answer any questions the parents may have.

Treatment

The USPSTF found that even though early treatment of hyperbilrubinemia reduces bilirubin levels, there is inadequate evidence that treatment subsequently reduces bilirubin encephalopathy and kernicterus.[2] Evidence for definitive harm associated with phototherapy is also incomplete. Potential side effects of phototherapy includes weight loss, gastrointestinal problems, interference with feeding and bonding, and potential development of melanocytic nevi.[2] Because of the invasiveness of exchange transfusions, considerable risks to the infant can occur and even though the increased morbidity affects only 5% of patients, even that small a risk in a newborn is too high. Severe side effects include apnea, bradycardia, vasospasm, thrombosis, and necrotizing enterocolitis.[3]

Cautions and Prospects

It should be recognized that hyperbilirubinemia is not a standalone factor for the development of kernicterus. Not all infants with high serum bilirubin levels develop bilirubin encephalopathy or kenicterus. Harm may occur with frequent bilirubin determination include pain from venipuncture or heel sticks, interference with routines of eating and bonding, and increased parental anxiety, as well as the potential for weight loss, gastrointestinal concerns, and possible development of melanocytic nevi.

The USPSTF found significant variations in current methods and practice of screening across the United States and that is why the committee concluded that current evidence does not support universal screening.[2] Therefore treatment must be individualized. Initiation-of-treatment considerations include risk factors, TSB levels, and potential for harm from treatment cost.

A pharmaceutical agent for the prevention of hyperbilirubinemia is currently being investigated. The agent, tin mesoporphyrin, is a potent inhibitor of heme oxygenase which can effectively reduce TSB levels. At this time, its costs, side effects, and burden of proof vs. harm have yet to be realized.[4]

Summary

Severe sequelae from hyperbilirubinemia, bilirubin encephalopathy, and kernicterus, although rare, when they occur lead to morbidity and mortality in neonates. Recent research has modified how the 2004 guidelines are practiced in an effort to continue to reduce the potential for harm, while we await an official guideline update. NP

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