Screening of Infants for Hyperbilirubinemia to Prevent Chronic Bilirubin Encephalopathy: US Preventive Services Task Force Recommendation Statement

abstract

DESCRIPTION: Recommendation on screening newborn infants, based on a recent supplemental review of a 2003 Agency for Healthcare Research and Quality evidence report on the effectiveness of various screening strategies for preventing the development of chronic bilirubin encephalopathy, performed at the request of the US Preventive Services Task Force (USPSTF). This topic has not been previously considered by the USPSTF.

METHODS: The USPSTF reviewed experimental and observational studies that included comparison groups. For harms associated with phototherapy, case reports or case series were also included.

CONCLUSION: The evidence is insufficient to assess the balance of benefits and harms of screening for hyperbilirubinemia to prevent chronic bilirubin encephalopathy (I statement). *Pediatrics* 2009;124: 1172–1177

AUTHORS: US Preventive Services Task Force

KEY WORDS

encephalopathy, hyperbilirubinemia, infants, prevention, screening

ABBREVIATIONS

USPSTF—US Preventive Services Task Force
TcB—transcutaneous bilirubin
TSB—total serum bilirubin

The USPSTF makes recommendations about preventive care services for patients without recognized signs or symptoms of the target condition. It bases its recommendations on a systematic review of the evidence of the benefits and harms and an assessment of the net benefit of the service.

The USPSTF recognizes that clinical or policy decisions involve more considerations than this body of evidence alone. Clinicians and policy makers should understand the evidence but individualize decision-making to the specific patient or situation.

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SCREENING OF INFANTS FOR HYPERBILIRUBINEMIA TO PREVENT CHRONIC BILIRUBIN ENCEPHALOPATHY
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Healthy Newborn Infants ≥35 weeks gestational age
I Statement: Insufficient Evidence	No recommendation due to insufficient evidence

Risk Assessment	Risk factors for hyperbilirubinemia include family history of neonatal jaundice, exclusive breastfeeding, bruising, cephalohematoma, ethnicity (Asian, black), maternal age >25 years, male gender, G6PD deficiency, and gestational age <36 weeks. The specific contribution of these risk factors to chronic bilirubin encephalopathy in healthy children is not well understood.
Importance	Chronic bilirubin encephalopathy is a rare but devastating condition. Not all children with chronic bilirubin encepahalopathy have a history of hyperbilirubinemia.
Rationale for No Recommendation	Evidence about the benefits and harms of screening is lacking. Therefore, the USPSTF could not determine the balance of benefits and harms of screening newborns for hyperbilirubinemia to prevent chronic bilirubin encephalopathy.
Considerations for Practice	In deciding whether to screen, clinicians should consider the following: ▪ Potential preventable burden. Bilirubin encephalopathy is a relatively rare disorder. Hyperbilirubinemia alone does not account for the neurologic condition of chronic bilirubin encephalopathy. There is no known screening test that will reliably identify all infants at risk of developing chronic bilirubin encephalopathy. ▪ Potential harms. Potential harms of screening are unmeasured but may be important. Evidence about the potential harms of phototherapy is lacking. Harms of treatment by exchange transfusion may include apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis, and, rarely, death. ▪ Current practice. Universal screening is widespread in the United States.
Screening tests	Screening may consist of risk factor assessment, measurement of bilirubin level either in serum or by transcutaneous estimation, or a combination of methods.
Interventions	Phototherapy is commonly used to treat hyperbilirubinemia. Exchange transfusion is used to treat extreme hyperbilirubinemia.
Relevant USPSTF Recommendations	USPSTF recommendations on screening newborns for hearing loss, congenital hypothyroidism, hemoglobinopathies, and phenylketonuria (PKU) can be found at http://www.preventiveservices.ahrq.gov.

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents please go to http://www.preventiveservices.ahrq.gov.

FIGURE 1

SUMMARY OF RECOMMENDATION AND EVIDENCE

The US Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy (I statement) (see "Clinical Considerations" below for additional information). See Figure 1 for a summary of this recommendation and suggestions for clinical practice; Table 1 for a description of the USPSTF grades; and Table 2 for a description of the USPSTF classification of levels of certainty about net benefit.

RATIONALE

Importance

The exact incidence of chronic bilirubin encephalopathy is not known but is very low; in 1 study, 90 cases were documented in term and near-term infants in 21 states over a period of 17 years.[1] In a recent prospective study in the United Kingdom and Ireland, the incidence of chronic bilirubin encephalopathy was estimated at 0.9 per 100 000 live births.[2] Efforts have been made by clinicians to eliminate this rare but devastating condition by instituting system-level measures to screen for hyperbilirubinemia and by aggressively managing high bilirubin levels.

Detection

There is adequate evidence that screening using risk factors and/or hour-specific bilirubin measurement can identify infants at risk of developing hyperbilirubinemia. However, not all children with chronic bilirubin encephalopathy have a history of hyperbilirubinemia, and there is no known screening test that will reliably identify all infants who are at risk of developing chronic bilirubin encephalopathy.

TABLE 1 What the USPSTF Grades Mean and Suggestions for Practice

Grade	Grade Definitions	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.	Offer/provide this service only if there are other considerations in support of the offering/providing the service to an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read "Clinical Considerations" in the USPSTF recommendation statement. If offered, patients should understand the uncertainty about the balance of benefits and harms.

TABLE 2 USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; or lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings not generalizable to routine primary care practice; or a lack of information on important health outcomes More information may allow an estimation of effects on health outcomes.

Definition: The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.

Benefits of Detection and Early Intervention

Early treatment can decrease the number of infants with elevated serum bilirubin levels. However, the USPSTF found inadequate evidence that treating elevated bilirubin levels in term or near-term infants to prevent severe hyperbilirubinemia resulted in the prevention of chronic bilirubin encephalopathy.

Harms of Detection and Early Treatment

Hyperbilirubinemia is commonly treated with phototherapy, and severe hyperbilirubinemia may be treated with exchange blood transfusion. The USPSTF found inadequate evidence regarding the harms of phototherapy. Potential harms of phototherapy include weight loss, gastrointestinal problems, interruption of breastfeeding and disruption of the maternal-infant relationship, and possibly growth of melanocytic nevi. Significant morbidity (apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis) occurs in as many as 5% of patients who undergo exchange transfusion.[3]

USPSTF Assessment

The USPSTF concludes that evidence about the benefits and harms of screening is lacking. Thus, the USPSTF could not determine the balance of benefits and harms of screening newborn infants to prevent chronic bilirubin encephalopathy.

CLINICAL CONSIDERATIONS

Considerations for Practice When Evidence Is Insufficient

- Potential preventable burden: Severe neonatal hyperbilirubinemia is

associated with kernicterus, the yellow staining of specific areas of brain tissue in the neonate caused by accumulation of unconjugated bilirubin. Chronic bilirubin encephalopathy describes the clinical neurologic sequelae associated with severe hyperbilirubinemia, including choreoathetoid cerebral palsy, sensorineural hearing loss, gaze paresis, and intellectual deficits. However, hyperbilirubinemia alone is not sufficient to account for these neurologic findings. Infants with extremely high levels of serum bilirubin but no apparent sequelae have been reported, and infants without documented high serum levels of bilirubin have been found to have kernicterus. As mentioned earlier, the UK incidence of bilirubin encephalopathy is estimated at 0.9 in 100 000 live births.[2]

- Potential harms: Potential harms caused by interference with breastfeeding, disruption of maternal-infant bonding, pain caused by heel stick or venipuncture, weight loss, gastrointestinal problems, possible growth of melanocytic nevi, and labeling of infants that have elevated bilirubin levels are unmeasured but may be important.
- Costs: The monetary cost to provide universal screening would be very large, particularly if serum or transcutaneous bilirubin (TcB) measurement is adopted as a universal screening tool.
- Current practice: Universal screening with a variety of methods is widespread in the United States.

Patient Population Under Consideration

This USPSTF recommendation addresses screening for hyperbilirubinemia to reduce the incidence of chronic bilirubin encephalopathy in healthy term or near-term infants (≥35 weeks' gestational age).

Assessment of Risk

Risk factors for hyperbilirubinemia include exclusive breastfeeding, family history of neonatal jaundice, bruising, cephalohematoma, ethnicity (Asian, black), maternal age (>25 years), male gender, glucose-6-phosphate dehydrogenase deficiency, and gestational age of <38 weeks. The contribution of these risk factors to chronic bilirubin encephalopathy in otherwise healthy children is not well understood.

Screening Tests

Screening for hyperbilirubinemia may consist of risk-factor assessment, measurement of bilirubin level (either in serum or by transcutaneous estimation), or a combination of methods.

Treatment

Phototherapy is commonly used to treat hyperbilirubinemia. A previous systematic review reported that one needs to treat 6 to 10 otherwise healthy jaundiced neonates with total serum bilirubin (TSB) levels of ≥15 mg/dL with phototherapy to prevent the TSB level in 1 additional infant from rising above 20 mg/dL.[4]

Exchange transfusion is used to treat extreme hyperbilirubinemia. Although death as a complication of exchange transfusion is rare, significant morbidity (apnea, bradycardia, cyanosis, vasospasm, thrombosis, or necrotizing enterocolitis) occurs in as many as 5% of exchange transfusions, and the risks associated with the use of blood products must always be considered. Hypoxic-ischemic encephalopathy and AIDS have occurred in otherwise healthy infants receiving exchange transfusions.

OTHER CONSIDERATIONS

Research Needs and Gaps

Further understanding is needed of the natural history of chronic bilirubin encephalopathy. Population-based surveillance for kernicterus and chronic bilirubin encephalopathy is necessary for an understanding of the incidence of the disease and of its risk factors. Such surveillance could also demonstrate whether the current efforts to systematically screen neonates to prevent severe hyperbilirubinemia is temporally associated with a reduction in chronic bilirubin encephalopathy. A better understanding of the harms from phototherapy is also needed. For example, data from prospective and controlled studies would be helpful in clarifying the relationship between exposure to neonatal phototherapy and the development of melanocytic nevi.

DISCUSSION

Burden of Disease

The true incidence of kernicterus or chronic bilirubin encephalopathy is unknown and difficult to determine. Clinically recognizable jaundice occurs in many newborns. Severe neonatal hyperbilirubinemia is associated with kernicterus, a rare condition traditionally diagnosed at autopsy. The clinical presentation of chronic bilirubin encephalopathy may include athetoid cerebral palsy, gaze abnormalities, deafness or hearing loss, and cognitive problems. However, although bilirubin is neurotoxic, no definite causal pathway between hyperbilirubinemia and kernicterus has been demonstrated to exist in every case.

Scope of Review

This topic has not been previously considered by the USPSTF. In a 2003 evidence report, the Agency for Healthcare Research and Quality reviewed the effects of elevated bilirubin on neu-

rodevelopmental outcomes, the efficacy of phototherapy, and the accuracy of various screening tests in predicting hyperbilirubinemia.[4] In 2007, the USPSTF commissioned a supplemental review to examine the effectiveness of screening to prevent the development of chronic bilirubin encephalopathy, as well as the benefits and harms of phototherapy.[5]

Accuracy of Screening Tests

No studies have directly addressed whether screening with risk-factor assessments or bilirubin testing reduced the incidence of chronic bilirubin encephalopathy. Available studies have only evaluated the effectiveness of using risk-factor assessment or bilirubin testing to identify infants for treatment intended to reduce the incidence of various levels of elevated bilirubin (eg, TSB level of ≥20 mg/dL or ≥25 mg/dL).

Four fair-quality studies demonstrated that using risk-factor assessments can be effective in predicting later significant hyperbilirubinemia (defined as a postdischarge TSB level of >95th percentile on the hour-specific bilirubin nomogram or as a TSB level of ≥25 mg/dL during the first 30 days after birth). These 4 studies used 1 of 2 screening instruments. Only 2 risk factors were common to both assessment instruments: exclusive breastfeeding and younger gestational age. Neither instrument has been independently validated in diverse populations.[5]

There were no studies that directly addressed whether bilirubin testing identified infants who may benefit from phototherapy. Authors of the supplemental review approached the key question by examining whether bilirubin testing identifies infants who will develop an increased TSB after discharge that requires phototherapy. Six studies were identified by using this approach: 4 studies used early TSB measurements, and 2 studies used TcB measurements.[5]

Three fair-quality studies[6–8] and 1 poor-quality study[9] indicated similar diagnostic abilities of early TSB measurements to predict late increased TSB measurements. In 3 of the studies, the reference standard was a postdischarge measurement above the hour-specific 95th percentile. In the fourth study, the reference standard was a TSB level of >20 mg/dL (>95th percentile at ≥48 hours). Two poor-quality studies examined the ability of TcB measurements to identify increased TSB measurements "requiring phototherapy" (as defined in the study protocol and using diverse definitions). TSB cutoffs predicting the need for phototherapy were defined differently. TcB measurements less than the 75th hour-specific percentile in 1 study and the 90th hour-specific percentile in the other study suggested TSB measurements not requiring phototherapy.

A fair-quality study that compared the ability of different screening strategies to predict later hyperbilirubinemia (TSB level of ≥20 mg/dL at ≥48 hours after birth) showed that the combination of the modified risk index with early TSB levels significantly improved prediction compared with using risk factors alone.[7]

Effectiveness of Early Detection and/or Treatment

In a 2003 review, the Agency for Healthcare Research and Quality reported that from 6 to 10 otherwise healthy jaundiced neonates with a TSB level of ≥15 mg/dL needed to be treated by phototherapy to prevent 1 neonate from developing a TSB level of >20 mg/dL.[4] No studies in the 2003 report or the current update evaluated the effectiveness of phototherapy in reducing the occurrence of chronic bilirubin encephalopathy.[10]

Potential Harms of Screening and/or Treatment

No studies were found that addressed the harms of screening, including pain caused by heel stick or venipuncture and the labeling of the infants. There is little specific evidence of harms of phototherapy. Potential harms of phototherapy include weight loss, gastrointestinal problems, interruption of breastfeeding, disruption of the maternal-infant relationship, and possibly growth of melanocytic nevi.[5,11] Exchange transfusions may result in apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis, and, rarely, death.

Estimate of Magnitude of Net Benefit

Evidence to estimate the benefits and harms of screening neonates for hyperbilirubinemia to prevent chronic bilirubin encephalopathy is lacking. Thus, the USPSTF could not determine the balance between benefits and harms. As a result of this significant evidence gap, the USPSTF concluded that the evidence is insufficient to make a recommendation about screening neonates for hyperbilirubinemia to prevent chronic bilirubin encephalopathy.

How Does Evidence Fit With Biological Understanding?

The extreme rarity of chronic bilirubin encephalopathy makes it nearly impossible to design and conduct a study that could directly evaluate the effectiveness of an intervention to reduce the incidence of this condition. As a result, intermediate outcomes such as bilirubin levels are used.

RECOMMENDATIONS OF OTHERS

In 2004, the American Academy of Pediatrics published clinical prac-

tice guidelines on the management of hyperbilirubinemia in infants of at least 35 weeks' gestation.[3] The guidelines recommend risk evaluation by using predischarge measurement of the bilirubin level (TSB or TcB) individually or in combination with clinical risk-factor assessment, close follow-up of infants at risk, and the use of phototherapy and exchange transfusion to decrease the level of bilirubin.

The Canadian Paediatric Society recently (2007) published guidelines for the detection, management, and prevention of hyperbilirubinemia in term and late-preterm newborn infants.[12] The group recommended that TSB or TcB be measured in all infants during the first 72 hours of life with individualized follow-up based on risk assessment.

MEMBERS OF THE USPSTF

The members of the USPSTF at the time that this recommendation was finalized were Ned Calonge, MD, MPH, Chair, USPSTF (Colorado Department of Public Health and Environment, Denver, CO), Diana B. Petitti, MD, MPH, Vice-chair, USPSTF (Arizona State University, Phoenix, AZ), Thomas G. DeWitt, MD (Children's Hospital Medical Center, Cincinnati, OH), Allen J. Dietrich, MD (Dartmouth Medical School, Lebanon, NH), Kimberly D. Gregory, MD, MPH (Cedars-Sinai Medical Center, Los Angeles, CA), Russell Harris, MD, MPH (University of North Carolina School of Medicine, Chapel Hill, NC), George J. Isham, MD, MS (HealthPartners, Minneapolis, MN), Michael L. LeFevre, MD, MSPH (University of Missouri School of Medicine, Columbia, MO), Rosanne M. Leipzig, MD, PhD (Mount Sinai School of Medicine, New York, NY), Carol Loveland-Cherry, PhD, RN (University of Michigan School of Nursing, Ann Arbor, MI), Lucy N. Marion, PhD, RN (School of Nursing, Medical College of Georgia, Augusta, GA), Bernadette Melnyk, PhD, RN (Arizona State University College of Nursing & Health Innovation, Phoenix, AZ), Virginia A. Moyer, MD, MPH (Baylor College of Medicine, Houston, TX), Judith K. Ockene, PhD (University of Massachusetts Medical School, Worcester, MA), George F. Sawaya, MD (University of California, San Francisco, CA), and Barbara P. Yawn, MD, MSPH, MSc (Olmsted Medical Center, Rochester, MN). For a list of current USPSTF members, go to www.ahrq.gov/clinic/uspstfab.htm.

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