Tips from Other Journals

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Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

▶ See related U.S. Preventive Services Task Force Recommendation Statement on page 408 and related Putting Prevention into Practice on page 411.

▶ See related editorial on page 336.

Systematic Review of Screening for Newborn Bilirubin Encephalopathy

Background: Severe neonatal hyperbilirubinemia is associated with chronic bilirubin encephalopathy, or kernicterus, which is a rare disorder characterized by spasticity, hearing and vision abnormalities, and sometimes mental retardation. Reportedly occurring at a rate of 0.9 instances per 100,000 live births, kernicterus has a mortality rate of at least 10 percent and a morbidity rate of at least 70 percent. Severe hyperbilirubinemia has been used as a surrogate marker because no studies have directly measured kernicterus as an outcome. Screening, by risk factor and bilirubin measurement, and treatment of elevated bilirubin levels have become widespread to try to prevent kernicterus.

In 2007, the Center on Primary Care, Prevention and Clinical Partnerships at the Agency for Healthcare Research and Quality, on behalf of the U.S. Preventive Services Task Force (USPSTF), asked the Tufts Evidence-Based Practice Center to update its 2003 evidence report on hyperbilirubinemia. The USPSTF uses those findings in its screening recommendations for bilirubin encephalopathy in neonates. Trikalinos and colleagues summarized the key findings from the systematic review that examined the effects of screening for hyperbilirubinemia on the incidence of acute and chronic bilirubin encephalopathy.

The Study: The study addressed four key questions: (1) Does screening using risk-factor assessment and bilirubin testing reduce the incidence of acute or chronic bilirubin encephalopathy?; (2) Does risk-factor assessment correctly identify infants who may benefit from bilirubin testing?; (3) Does bilirubin testing correctly identify infants who may benefit from phototherapy?; and (4) What are the adverse effects of screening?

In the previous evidence report, investigators reviewed studies through August 2001; eligible studies for this review were identified by searching Medline for all English-language studies from September 2001 through August 2007 and included additional relevant articles obtained from the reference lists of the identified articles. Studies on healthy infants born at 35 weeks of gestation or later were eligible if they addressed screening by risk-factor scores, transcutaneous or serum bilirubin testing, or a combination of these. Each study was assigned a quality rating of good, fair, or poor based on USPSTF criteria and the presence or absence of flaws in the way the study was conducted. The identified studies were too dissimilar to allow a meta-analysis, so sensitivity and specificity pairs and positive and negative likelihood ratios were calculated for each study.

Results: Of the 742 abstracts and 96 articles reviewed, nine were eligible for the systematic review. None of the studies directly evaluated the effects of screening on bilirubin encephalopathy, but used hyperbilirubinemia as a surrogate outcome. The four studies that reviewed two risk-assessment tools were considered to be of fair quality and showed comparable predictive ability to determine which infants would be at risk of significant hyperbilirubinemia. Studies of transcutaneous and serum bilirubin measurements were analyzed separately. Four studies reviewed early serum bilirubin testing; three were deemed fair and one poor for methodologic quality. All four showed comparable ability to predict postdischarge elevated bilirubin levels. The two studies on transcutaneous bilirubin measurement were of poor quality. None of the studies addressed the adverse effects of screening.

Screening by risk factors, bilirubin testing, or a combination is effective in predicting high bilirubin levels. In addition, noncontrolled studies suggest that early detection reduces the rate of readmission for hyperbilirubinemia. However, the literature assumes that high bilirubin levels are a valid marker for bilirubin encephalopathy, and that treating high bilirubin levels can prevent

bilirubin encephalopathy. The small number of eligible studies, none of good methodologic quality, limited the ability to determine definitive answers to the study questions.

Conclusion: The authors conclude that high-quality evidence is lacking to determine the actual value of screening for hyperbilirubinemia to prevent chronic bilirubin encephalopathy.

AMY CRAWFORD-FAUCHER, MD

Source: Trikalinos TA, et al. Systematic review of screening for bilirubin encephalopathy in neonates. *Pediatrics.* October 2009;124(4):1162-1171.

Transcutaneous Bilirubin Nomogram Can Predict Significant Hyperbilirubinemia

Background: For healthy newborns discharged before 72 hours of life, neonatal hyperbilirubinemia is the most common cause of readmission to the hospital. Predischarge serum bilirubin levels require blood draws that can be invasive, time-consuming, and stressful. Hospitals are increasingly using transcutaneous bilirubin (TcB) values because the measurement devices are noninvasive and save time. However, there are limited data on the predictive value of TcB measurements. Varvarigou and colleagues developed a predictive nomogram using TcB measurements for the evaluation of neonatal hyperbilirubinemia.

The Study: This prospective study involved healthy infants born at 35 weeks of gestation and older, and weighing at least 2,000 g (4 lb, 7 oz), who were admitted to the well-infant nursery at a hospital in Greece from late 2005 through 2007. Exclusion criteria included admission to the intensive care unit, positive direct Coombs testing, jaundice requiring intervention within 24 hours of birth, and glucose-6-phosphate dehydrogenase deficiency.

Infants had TcB testing at 12, 18, 24, 36, 48, 60, and 72 hours of life (± 2 hours at each measurement), with a final measurement between 96 and 120 hours. All infants stayed for at least 72 hours, and had outpatient follow-up within 48 hours after discharge. Results were plotted against hour-specific bilirubin nomograms proposed by the American Academy of Pediatrics (AAP),

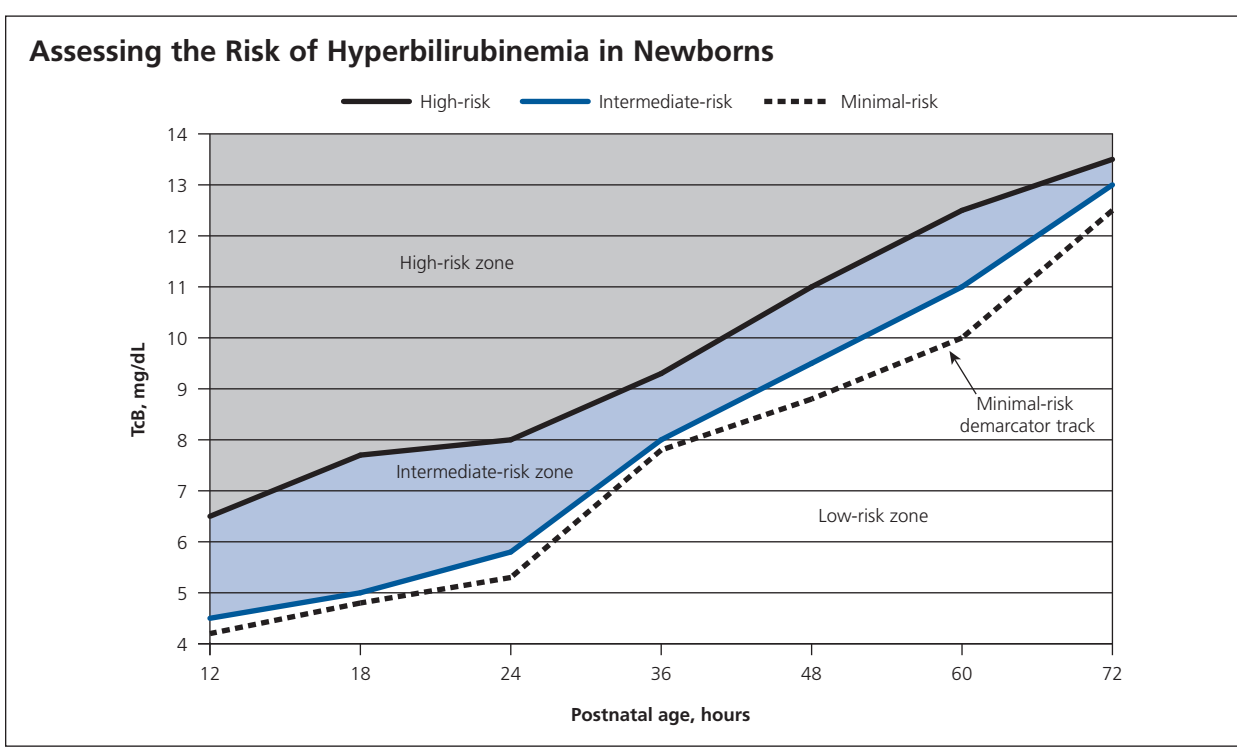

Figure. TcB nomogram for assessing the risk of subsequent significant hyperbilirubinemia in healthy term and near-term newborns. The high-risk zone is defined by the track of TcB values with a positive LR of greater than 10 and the low-risk zone by the track of TcB values with a negative LR of less than 0.1. The minimal-risk demarcator track (negative LR of 0) is also presented *(dotted line).* The nomogram was developed by using a total of 10,382 TcB measurements from 2,039 neonates with a gestational age of 35 weeks or older and a birth weight of 2,000 g (4 lb, 7 oz) or more. (LR = likelihood ratio; TcB = transcutaneous bilirubin.)

Reprinted with permission from Varvarigou A, Fouzas S, Skylogianni E, Mantagou L, Bougioukou D, Mantagos S. Transcutaneous bilirubin nomogram for prediction of significant neonatal hyperbilirubinemia. Pediatrics. *2009;124(4):1056.*

and total serum bilirubin (TSB) testing was performed immediately if the TcB level was more than 15 mg per dL (256.56 μmol per L) or if the TcB level was 15 mg per dL or less but exceeded or was within 2 mg per dL (34.21 μmol per L) of the phototherapy guidelines of the AAP.

Results: Of the 2,745 infants born during the study, 2,039 met inclusion criteria and completed the follow-up process, resulting in 10,382 TcB measurements and 3,249 TSB measurements. Significant hyperbilirubinemia was documented in 122 infants (6 percent). The authors constructed a TcB nomogram *(see accompanying figure)* based on likelihood ratios (LR) because they are not dependent on disease prevalence and can predict disease probability more reliably than percentiles. Consequently, LRs were used to determine the high-, intermediate-, and low-risk cutoffs for each time point. A positive LR of greater than 10 indicates a high likelihood of disease, whereas a negative LR of less than 0.1 indicates a low likelihood. The high-risk zone of the nomogram had a positive LR for significant hyperbilirubinemia of 12.1 (73.9 percent sensitivity) at 24 hours of life, and a positive LR of 12.1 (90 percent sensitivity) at 48 hours of life. The TcB levels for the high-risk zone were 8 mg per dL (136.83 μmol per L) or higher at 24 hours of life and 11 mg per dL (188.14 μmol per L) or higher at 48 hours of life. The low-risk zone of the nomogram had a negative LR of 0.04 (97.7 percent sensitivity) at 24 hours of life, and a negative LR of 0.02 (98.8 percent sensitivity) at 48 hours of life. The TcB levels for the low-risk zone were 5.8 mg per dL (99.20 μmol per L) or lower at 24 hours of life and 9.5 mg per dL (162.49 μmol per L) or lower at 48 hours of life. Comparing the TcB and TSB results showed similar predictive value for the risk of significant hyperbilirubinemia. This study may be limited by the relatively homogeneous patient population, a cesarean delivery rate of 38 percent, and the hospital protocol requiring that nursery stays last a minimum of 72 hours.

Conclusion: The authors conclude that using TcB measurements between 12 and 72 hours of life can predict significant neonatal hyperbilirubinemia.

AMY CRAWFORD-FAUCHER, MD

Source: Varvarigou A, et al. Transcutaneous bilirubin nomogram for prediction of significant neonatal hyperbilirubinemia. *Pediatrics.* October 2009;124(4):1052-1059.

Single Transcutaneous Bilirubin Value Adequate to Predict Hyperbilirubinemia

Background: Infants in many areas of the world are being discharged from the hospital before the age at which significant hyperbilirubinemia typically develops. As a result, phototherapy is one of the most commonly reported reasons for neonatal readmission to the hospital. The American Academy of Pediatrics recommends plotting bilirubin measurements on an hour-specific nomogram to help identify infants at risk of hyperbilirubinemia. Dalal and colleagues postulated that a single value could better predict subsequent hyperbilirubinemia than determining the change between two bilirubin measurements taken within the first 48 hours of life.

The Study: This prospective cohort study was conducted between October 2006 and April 2007 at a hospital in New Delhi, India. Infants who were born at 35 weeks of gestation or later, lived within 100 km (62.5 miles) of the hospital, and able to return for follow-up were eligible for inclusion. Neonates who received phototherapy before 48 hours of age, had Rh isoimmunization, and required neonatal intensive care unit admission for longer than 24 hours, or had major congenital malformations were excluded. All mothers were encouraged by hospital staff to breastfeed exclusively.

Each infant enrolled in the study had two transcutaneous bilirubin (TcB) levels measured, one at 24 ± 6 hours and another at least 12 hours later, but within the first 48 hours of age. Each value was plotted on the hour-specific nomogram. The difference between the two values was calculated for each participant and percentiles of change were determined. The primary outcome was hyperbilirubinemia requiring phototherapy. Neonates were assessed clinically for jaundice twice a day by a team blinded to the TcB findings, and were subsequently discharged according to hospital policy. Parents of enrolled newborns were instructed to return on the fifth day of life for follow-up or earlier if they recognized worsening jaundice. Follow-up included clinical assessment for jaundice, with serum bilirubin testing as indicated.

Results: Of the 972 term and near-term infants born during the study, 358 met inclusion criteria. Ninety percent of participants finished the study, and 15 percent required phototherapy. For measurements taken 24 hours or less apart, the magnitude of change between measurements was not affected by the time interval between them (0.14 ± 0.08 mg per dL [2.39 ± 1.37 μmol per L] per hour at 12 to 18 hours between the two TcB measurements, and 0.14 ± 0.07 mg per dL [2.39 ± 1.20 μmol per L] per hour at 18 to 24 hours between them). However, if more than 24 hours elapsed between the first and second readings, the change between them was smaller (0.10 ± 0.5 mg per dL [1.71 ± 8.55 μmol per L] per hour). In general, TcB readings increased at an average rate of 0.14 mg per dL per hour in the first 48 hours of life, ▶

with the exceptions of a greater change between the two readings in neonates who subsequently required phototherapy than in neonates who did not, and late-preterm neonates versus full-term neonates.

Single TcB readings at 30 to 48 hours of life were more predictive of future hyperbilirubinemia than the readings taken between 18 and 30 hours of age. The positive likelihood ratios were equivalent for the second TcB reading and the change in readings, and were higher than the positive likelihood ratio for the first TcB measurement.

Conclusion: The authors conclude that a single TcB reading at 30 to 48 hours of age can reasonably predict subsequent hyperbilirubinemia in the neonate and is as accurate as calculating the change between two readings.

AMY CRAWFORD-FAUCHER, MD

Source: Dalal SS, et al. Does measuring the changes in TcB value offer better prediction of hyperbilirubinemia in healthy neonates? *Pediatrics.* November 2009;124(5):e851-e857.

Universal Screening Effective in Identifying Severe Hyperbilirubinemia

Background: In a 2004 guideline, the American Academy of Pediatrics (AAP) recommended that every newborn be evaluated for the risk of developing severe hyperbilirubinemia before discharge using total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) levels, or by clinical risk assessment. It is unclear what effect universal screening has had on the rates of severe hyperbilirubinemia and phototherapy use. The Northern California Kaiser Permanente Medical Care Program (NC-KPMCP) instituted universal screening with TSB or TcB levels in 11 hospitals starting in September 2005. Kuzniewicz and colleagues studied the impact of universal screening on the incidence of severe hyperbilirubinemia, defined as TSB levels above the AAP level for exchange transfusion.

The Study: The historical cohort design was used to compare severe hyperbilirubinemia and phototherapy rates before and after universal screening. All live-born infants born between January 1, 1995, and June 30, 2007, at the NC-KPMCP hospitals at 35 weeks of gestation or later and weighing at least 2,000 g (4 lb, 7 oz) were included in the analysis. The authors reviewed all TSB measurements from each infant's first month of life, excluding any in which direct bilirubin accounted for 20 percent or more of the total. Direct Coombs tests were also recorded if performed, and hospitalizations for phototherapy were recorded. TcB readings of 15 mg per dL (256.56 μmol per L) or more (or if the TcB level plus 3 mg per dL [51.31 μmol per L] was above the phototherapy treatment line) were confirmed with a follow-up TSB measurement, per hospital policy.

In 1998, NC-KPMCP refined its newborn management to include a follow-up visit within 48 hours of discharge. Each TSB value was plotted against 2004 AAP treatment curves for phototherapy and exchange transfusion, and infants were risk-stratified based on gestational age and direct antiglobulin test results. Missed phototherapy was defined as any TSB values above the levels at which the AAP recommends phototherapy for a given risk group and time point but that did not result in phototherapy. Phototherapy performed when no TSB values exceeded the AAP cutoff values was defined as subthreshold phototherapy. Characteristics of babies born before and after implementation of universal screening were compared.

Results: The cohort included 319,904 infants; 38,182 were born after universal screening was implemented. The two groups were similar except that the post-implementation group included a higher proportion of Asian infants and more infants in the AAP medium-risk group. The mean number of bilirubin tests increased notably from 0.8 ± 1.7 tests per infant to 1.9 ± 2.0 after implementation. Overall, the mean length of birth hospitalization increased by 2.2 hours after implementation, although among infants receiving phototherapy, the mean length of stay decreased by 28.5 hours. As the proportion of infants undergoing TSB measurements increased during the study, the proportion with a TSB level of 25 mg per dL (427.60 μmol per L) or higher decreased, although the incidence of maximum TSB levels between 15 and 19.9 mg per dL (256.56 and 340.37 μmol per L) increased. There was a 62 percent reduction of TSB values above the exchange guideline, from 0.45 percent before to 0.17 percent after universal screening was implemented. The use of subthreshold phototherapy increased dramatically after 2003, but leveled off with the implementation of universal screening. After 2005, the proportion of infants receiving appropriate phototherapy increased.

Conclusion: The authors conclude that implementing universal screening decreases the incidence of severe hyperbilirubinemia, and results in increased phototherapy rates, often at TSB levels lower than recommended previously by the AAP.

AMY CRAWFORD-FAUCHER, MD

Source: Kuzniewicz MW, et al. Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use. *Pediatrics.* October 2009;124(4):1031-1039. ■