Screening for Hyperbilirubinemia

Report prepared for the U.K. Screening Committee
Thomas B. Newman, MD, MPH
M. Jeffrey Maisels, MB,BCh
November 1, 2006

1. The condition should be an important health problem

1. What is the "condition"? Defining hyperbilirubinemia:
    a.) Conjugated, Unconjugated and Total Bilirubin

Hyperbilirubinemia is an excess of bilirubin in the blood. Bilirubin, a breakdown product from heme from red blood cells, is yellow, and hyperbilirubinemia causes jaundice, a yellow coloration of the skin and whites of the eyes. Hyperbilirubinemia can be either *conjugated or unconjugated* (or both); a simple and inexpensive test often done at the same time as the bilirubin level can distinguish between the two, and is generally recommended as a first step in evaluating either severe or prolonged hyperbilirubinemia.

Conjugated hyperbilirubinemia suggests a problem with the liver or biliary tract, is much less common than unconjugated hyperbilirubinemia, and is significant primarily as a sign of other illnesses. These illnesses include hypothyroidism, infections, and biliary atresia, for all of which there is an advantage to early detection. However, because there are commonly other signs of illness in infants with conjugated hyperbilirubinemia (e.g., fever, hypotonia, light stools, or dark urine), because conjugated hyperbilirubinemia is less commonly associated with kernicterus (defined below), and because it is much less common, it will not be discussed further here. However, it should be kept in mind that a screening program for hyperbilirubinemia has the potential to identify some previously undiagnosed cases of conjugated hyperbilirubinemia, with resulting medical benefits, and to detect some false-positive elevations of conjugated hyperbilirubinemia, which might lead to additional unnecessary laboratory evaluation.(1)

Unconjugated hyperbilirubinemia can either be a result of an increase in bilirubin production, a decrease in the conjugation of bilirubin, an increase in reabsorption of bilirubin from the intestine, or some combination of the three. The decrease in conjugation may be due to delay in the maturation of the activity of the enzyme that conjugates bilirubin (UDP Glucuronosyl transferase), as is commonly seen in preterm infants, or to genetic variation in the activity of that enzyme, which leads to racial differences in the frequency of unconjugated hyperbilirubinemia. An increase in bilirubin production is most often due to hemolysis (increased red cell destruction), either because of maternal-infant blood type incompatibility or other causes, including a common inherited deficiency of the enzyme Glucose-6-Phosphate Dehydrogenase (G6PD). Because in most newborns almost all bilirubin is unconjugated and because most of the research and guidelines relate to total bilirubin, in this report we will focus on total bilirubin levels with the understanding that in cases of significant or prolonged elevation of bilirubin levels, the bilirubin should be fractionated to rule out conjugated hyperbilirubinemia, and conjugated hyperbilirubinemia should trigger additional evaluation.

b.) The definition of hyperbilirubinemia and purpose of screening vary with the age of the infant

As is the case with other health conditions measured on a continuous scale, such as blood pressure or serum cholesterol, in considering how to define hyperbilirubinemia, the higher the level chosen, the fewer the number of affected people and the greater the level of concern in each one. However, unlike other entities for which the UK may have considered screening in the past, the task of defining hyperbilirubinemia has the additional challenge that normal bilirubin levels increase rapidly after birth, as do levels at which different treatments are recommended. Thus interpretation of any bilirubin level must take into account the infant's age in hours.(2)

Furthermore, the short-term goal of screening for hyperbilirubinemia may vary with the age of the infant. (The long term goal is always preventing kernicterus.) During the first 24-48 hours after birth, the main short-term goal is to assist with *risk assessment*, identifying bilirubin levels that, while not high enough to warrant treatment, would warrant closer follow-up or future bilirubin tests (or, at least, a lower threshold for performing these.) Screening at this early age may also identify bilirubin levels that would warrant immediate treatment. Most such newborns would be expected to be jaundiced in the first 24 hours after birth, but because in the first 24 hours treatment is indicated at much lower levels (e.g., the American Academy of Pediatrics recommends phototherapy for a total serum bilirubin level of only about 125 μMol/L {7.5 mg/dL} at 12 hours of age in a 37-week gestation infant) significant jaundice may not be present or may be missed.[*]

As the age of the baby increases beyond about 48 hours, the main goal moves from risk assessment to identifying levels already high enough to warrant treatment, because bilirubin levels typically peak 3 to 5 days after birth. However as newborns get older and the bilirubin levels at which treatment is indicated rise, the ability to identify infants needing bilirubin testing by physical examination for jaundice increases. If screening is defined as: "the application of a test to detect a potential disease or condition in people with no known signs or symptoms of that disease or condition"(3), the goal of screening these older infants is to identify significant hyperbilirubinemia that is in some sense occult -- i.e., that is not accompanied by a level of jaundice that would otherwise have triggered a bilirubin measurement.

2. Public health significance

The significance of hyperbilirubinemia derives primarily from its potential to cause **kernicterus**, a form of brain damage that can cause death or long term sequelae including cerebral palsy and hearing loss. The incidence of kernicterus appears to vary geographically, with much higher rates reported in Africa and India than in North America or Europe. A recent report from The British Paediatric Surveillance Unit estimated the incidence at about 1 per 100,000 live births in the United Kingdom.(4) (Hyperbilirubinemia may also have some significance as a predictor of outcome in very premature infants(5-7), however this area is still under active investigation and will not be covered in this review.)

[*] The example is for illustrative purposes only – recent experience of one of the authors of this report (MJM) suggests that phototherapy may not always be necessary at the levels currently recommended by the AAP for infants less than 24 hours old, as bilirubin levels sometimes rise steeply for 12 hours and then level off rapidly.

Less serious than kernicterus, but more common, and therefore also of public health significance, is treatment for hyperbilirubinemia, either with exchange transfusion (which has significant morbidity and mortality)(8-10) or with phototherapy, which while apparently safe, leads to expense, separation of mother and infant, and carries with it the remote possibility of as yet unidentified or unconfirmed adverse effects.(11) Population-based data on the frequency of exchange transfusion are not available. Anecdotally, there has been a significant decline in use of exchange transfusions, but there also has been wide variation across institutions. Surveys of pediatricians indicate significant variability in the bilirubin levels at which exchange transfusion and phototherapy are endorsed.(12-14)

Finally, jaundice in newborns has public health significance, because it can be a source of concern to parents and other family members.(15, 16) A screening program for hyperbilirubinemia might lead to reassurance of some families that otherwise might have excessive levels of concern about jaundice. On the other hand, as discussed below, it might lead to an increase in parent and provider concern.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

This item makes the most sense for the current discussion if we consider the "condition" to be kernicterus, and the detectable risk factor to be hyperbilirubinemia. Then the question is: how well is the development of kernicterus from hyperbilirubinemia understood? The best data relate to who is *not* at significant risk of kernicterus. Among term infants without hemolysis in the US and Western Europe, the risk of kernicterus is extremely low if the bilirubin remains below 428 μMol/L (25 mg/dL), (17-21) and is also quite low (none observed out of 130 infants) if the bilirubin is 428 to 513 μMol/L (25-30 mg/dL) and promptly treated.(22). Most cases of kernicterus in these newborns occur at bilirubin levels above 513 μMol/L, but the actual risk in these infants has not been well quantified and many escape with no apparent sequelae if promptly treated.(22-25)

Other newborns, including premature newborns, those with hemolysis from isoimmunization or G6PD deficiency, those with other illnesses (such as infections) and those born in other countries are at higher risk, but the magnitude of the increase in risk and the biologic mechanisms are generally not clear.(26-28)

There are no recent studies of the natural history of significant hyperbilirubinemia, in particular none in which levels approaching those at which kernicterus has been reported have been left untreated. Thus, for example, the number-needed-to-treat to prevent one case of kernicterus at differing levels of hyperbilirubinemia is not known.

If the condition for which we are screening is hyperbilirubinemia warranting *treatment* that would otherwise not have been detected, i.e., hyperbilirubinemia not associated with jaundice sufficiently concerning to trigger a bilirubin level, then less is known about the epidemiology or natural history. There are case reports of newborns who were known to be jaundiced but did not have bilirubin levels tested and subsequently developed kernicterus.(29, 30) It is thought that if their bilirubin had been measured at an earlier time, intervention might have prevented their kernicterus.

However, other cases of kernicterus have occurred despite treatment of known hyperbilirubinemia; these presumably would not be impacted by a screening program.

3. All cost effective primary prevention interventions should have been implemented as far as practicable.

The major program for primary prevention of jaundice and kernicterus is identifying Rhesus-negative women during pregnancy, and treating them with Rh immune globulin (Rhogam) to prevent sensitization to the Rh(D) antigen. This treatment has been dramatically successful and has been widely implemented. Pharmaceutical treatment to inhibit bilirubin production is another primary prevention strategy, likely to be quite effective,(31-33) however safety and cost-efficacy are not yet known. Because such treatment would be given to large numbers of infants to prevent a rare outcome, even a very rare serious adverse effect might lead to an unfavorable risk:benefit ratio. This issue was nicely illustrated by the concerns raised about 15 years ago about adverse effects of prophylactic Vitamin K in newborns.(34)

Encouraging and supporting breast feeding may be helpful, since more frequent breastfeeding is associated with lower TSB levels in observational studies.(35-37) Although a randomized trial failed to confirm a benefit,(38) there was a trend towards lower TSB levels in the frequent feeding group (-0.6 mg/dL; P=0.1) and the efficacy may have been underestimated because TSB levels were measured relatively early, at a median age of 53 hours. In any case, support of lactation is likely to be cost effective for other reasons.

4. Does screening identify carriers of a mutation?

While screening for hyperbilirubinemia does not itself identify carriers of a mutation, it might identify people in whom additional testing for G6PD deficiency (or possibly other mutations) would be indicated.

5. There should be a simple, safe, precise and validated screening test

Screening for hyperbilirubinemia can include physical examination for jaundice, or measurement of bilirubin in the skin (transcutaneous bilirubin or TcB) or in the serum (total serum bilirubin or TSB). Physical examination for jaundice can utilize the progression of jaundice from the face to the extremities as bilirubin levels rise.(39) Correlations between bilirubin levels estimated from physical examination by observers at various levels of training and TSB levels have been fair (0.4 to 0.70),(40, 41) but these studies have included mostly newborns with TSB levels of 200 μMol/L or less, thus not directly addressing how commonly TSB levels high enough to warrant treatment would be missed. Several studies suggest that the vast majority (> 95%) of newborns with levels of 200 μMol/L or more will have jaundice below the level of the nipples, although many infants with lower TSB levels will, too.(39-42)

Studies of TcB measurements with various devices have found them to correlate closely with TSB levels, generally within 35 – 50 μMol/L.(43-48) However, again, most of the infants in these studies had only moderate elevations of bilirubin levels, and there is some evidence that the

transcutaneous instruments are less accurate at higher bilirubin levels. The Minolta JM-103 is easiest to use, but tends to overestimate bilirubin levels in dark-skinned infants.(46)

The "gold standard" in most of these studies has been a TSB level measured in a clinical laboratory, but even these may not be accurate -- significant interlaboratory variability in TSB measurements, with coefficients of variation across laboratories of 10-15% has been reported.(49, 50) However, more recent studies using a more appropriate standard show promise in reducing this variability.(51, 52) Certainly before embarking upon any screening program for hyperbilirubinemia, it would be important to optimize and document the accuracy of TSB measurements in clinical laboratories.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

As previously mentioned, interpretation of bilirubin levels is complicated by their rapid rise over the first few days after birth, as well as the fact that treatment thresholds vary depending upon the gestational age and other illnesses of the baby. If the goal of screening is to identify newborns in need of immediate treatment, it would be fairly straightforward for the NSC or its designates to review and either endorse or modify the treatment guideline suggested by the AAP, which provides bilirubin levels at each age and in three different risk strata at which phototherapy and exchange transfusion are recommended.

On the other hand, if the goal is risk assessment, more work would need to be done to agree upon what alterations in management would be indicated in newborns with different bilirubin levels, taking into account clinical risk factors for jaundice (especially gestational age).(53) A good place to start would be plotting the bilirubin on the "Bhutani Nomogram,"(54) which has been shown in several studies to be a good predictor of risk of significantly increasing TSB levels.(47, 53-55) However, the percentile labels on this nomogram are not valid even in the population from which they were derived,(2) and may be far from the mark in other populations. For example, the 95th percentile for TcB levels in a recent study from Michigan was between the 40th and 75th percentiles in the Bhutani nomogram.(56)

7. The test should be acceptable to the population

Measurement of bilirubin transcutaneously will likely be very acceptable to the population, as the test is painless and takes only a minute or two to do. Measurement of total serum bilirubin is likely to be more acceptable if combined with a blood draw for routine screening. Measurement of blood levels after that is likely to be acceptable if the newborn is significantly jaundiced and/or if a transcutaneous measurement suggests the need for a serum bilirubin level. Universal TSB testing in outpatients is likely to be met with resistance because it will require a blood test (with resulting pain to the infant and inconvenience to the family and provider) and providers and parents may appropriately doubt that it is necessary if the infant is not jaundiced or the jaundice is clearly minimal or improving.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test and on the choices available to those individuals

This is partly discussed under #6 above. Policies would need to be developed with regard to what levels of TSB would warrant additional diagnostic evaluation, including G6PD screening, blood type and direct anti-globulin (Coombs') testing, hemoglobin levels, etc.

9. If the test is for mutations are all possible mutations being screened for?

Not applicable; see above.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

There is considerable evidence that phototherapy can lower bilirubin levels and/or keep them from rising.(21, 57) Although there is not direct evidence that this treatment reduces the risk of kernicterus, there is strong evidence that kernicterus is caused by extreme elevations in bilirubin levels, thus it seems very likely that phototherapy is effective at preventing kernicterus and that the major issue is not lack of efficacy but (depending upon the treatment threshold) a potentially high number-needed-to-treat because of the rarity of the outcome and generally benign natural history of jaundice.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and appropriate treatment to be offered

Which individuals should be offered treatment is discussed under #6 above; the treatment to be offered is discussed under #15 below.

12. Clinical management of the condition and patient outcomes should be optimized in all health care providers prior to participation in a screening programme

We have not seen studies of how hyperbilirubinemia is managed by practitioners in the UK. As mentioned previously (see #1), there appears to be wide variation in practice elsewhere. Although an effort could be made to develop a new guideline or adapt the AAP guideline, one obstacle to any type of heavy-handed effort to secure adherence to the guideline is that it will be based primarily on expert opinion.(27)

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective at reducing mortality or morbidity

No randomized trials of bilirubin screening have had morbidity or mortality outcomes. A recent time-series study found a decrease in readmissions for hyperbilirubinemia following institution of universal screening,(58) but this may be due to an increase in phototherapy during the birth hospitalization.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable to health professionals and the public

We know of no studies directly addressing this question. Because of the tragic and devastating consequences of kernicterus and the seeming ease of preventing it, we suspect that at least the public might have greater difficulty accepting the status quo than a screening program.

15. The benefit from the screening programme should outweigh any potential physical and psychological harm

The risk of greatest physical harm would be if the screening program led to an increase in the use of exchange transfusions, but given the narrow indications for the procedure and the likelihood that earlier detection of hyperbilirubinemia would lead to more timely phototherapy, a *decrease* in exchange transfusion seems more likely. There also is a risk that phototherapy (or interruption of nursing, which is another treatment for jaundice that is included as an option by the AAP)(27) might interfere with breastfeeding in some cases, with resulting loss of health benefits of breast milk and avoidance of cow's milk formula. Although phototherapy appears to be safe, there have been no studies with sufficient follow-up periods or large enough sample sizes to rule out clinically significant but rare and/or late adverse effects. Furthermore, earlier studies and long-term experience are with doses of phototherapy considerably less than the currently recommended "intensive phototherapy." As an example of a clinically significant adverse effect that might have escaped previous detection, phototherapy treatment was associated with later insulin-dependent diabetes (OR=3.79; 95% CI 3.13-4.59) in a recent Swedish study.(11)

There is also a significant potential for psychological harm, since jaundice is so common, if large numbers of families become concerned about the risk of overt or subtle brain damage from jaundice. Any screening program would need to strike a balance between raising awareness of the potential for jaundice to be dangerous and unnecessarily alarming parents.

16. The opportunity cost of the screening programme should be economically balanced in relation to other medical care

This will likely require subjective judgments. One concern is that a public or physician education campaign related to the dangers of neonatal jaundice might lead to significant concern about jaundice among parents of newborns, which might in turn require healthcare providers to spend more time on reassuring about this particular topic, with the possible opportunity cost that other pertinent issues (for example, infant sleep position or parental smoking) might get short shrift as a result. On the other hand, we suspect that there are other healthcare expenditures that are much less cost-effective than counseling about jaundice and feeding in newborns.

17. There should be a plan for managing and monitoring the screening programme

A plan for managing and monitoring would need to be developed. Such a plan might include centralized reporting of elevated bilirubin levels in order to track progress on reducing the

frequency of dangerously high (e.g., > 450 - 500 μMol/L in a term baby) levels, audits to indicate level of adherence to screening and guidelines, periodic surveys of breast feeding, and possibly surveys about knowledge and level of anxiety about neonatal jaundice.

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available

The staffing and facilities needed would be those needed to facilitate monitoring of TSB levels and treating those that are elevated. For example, availability of TcB instruments to home health visitors, and in out- and inpatient settings would be very helpful. Hospitals should have equipment necessary to do intensive phototherapy.

19. All other options for managing the condition should have been considered

As noted above, an alternative to screening for hyperbilirubinemia would be an attempt to optimize decisions based upon the history and physical examination (perhaps by educating providers about risk factors for hyperbilirubinemia and physical examination technique and limitations), perhaps with education leading to a lower threshold for bilirubin testing.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment should be made available.

It is worth distinguishing between making information available, which is likely to be beneficial, and distributing it widely to new parents, which could have unintended consequences. New parents can absorb and retain only a finite amount of information; as mentioned under #20 it would be unfortunate if too much information about neonatal jaundice crowded out other information that night be more important for many families.

21. Public pressure for widening the eligibility criteria, etc, should be anticipated

This is an important point. Whatever guidelines are adopted, even if they prevent most cases of kernicterus, they are unlikely to be 100% effective, and one should anticipate families coming forward with powerful stories(59, 60) that might lead to a tendency to diagnose and treat hyperbilirubinemia more aggressively than would be optimal.

22. Mutation screening should be acceptable …

N/A

Reviewer's conclusions

Although rare, kernicterus is devastating and worth preventing. We suspect that most cases could be prevented without screening by educating practitioners about risk factors for severe hyperbilirubinemia and developing and promoting adherence to guidelines for treatment of recognized hyperbilirubinemia. An analysis of the cases reported by the British Paediatric Surveillance Unit (BPSU) would provide helpful information in this regard – how many of the cases were associated with risk factors, known jaundice, and/or early symptoms being ignored (as was the case with "Olivia"), versus how many would likely have required a screening program to have been prevented?

A step that should be taken as soon as practical is ensuring that TSB measurements throughout the UK are adequately standardized. It would be very helpful to develop the capability to monitor the extent of hyperbilirubinemia by mandating reporting by clinical laboratories of very high (e.g., > 500 μMol/L) levels to a central authority.

Another step that might be helpful even without a universal screening program would be to facilitate access to bilirubin measurements, either through distribution of a large number of TcB instruments or streamlining the process for obtaining TSB measurements in hospital and outpatients. TcB levels are probably best used as an adjunct to physical examination to identify infants who should have a TSB measured.

Screening with the purpose of identifying newborns who already have bilirubin levels high enough to warrant treatment during the birth hospitalization would be relatively straightforward. The yield would probably be low, but the ease of providing immediate treatment, if needed, would be high. It would make sense also to use this screening for risk assessment as well, but specific guidelines would need to be developed specifying how the results would be used to inform timing of follow-up visits and subsequent bilirubin testing. Screening all outpatients with a blood test for TSB would be more difficult logistically and likely less acceptable, whereas making TcB measurements readily available in outpatient settings, with TSB confirmation for elevated values, would likely be more acceptable and efficient.

Summary: We suggest that a decision on universal bilirubin screening be deferred until:

1. Adequate standardization of TSB measurements has been accomplished
2. The cases reported to the BPSU have been analyzed (e.g., with a "root cause" analysis)
3. A system of mandatory reporting of elevated bilirubin levels is in place to quantify the extent of the problem at baseline and monitor progress
4. Ready access to TcB and TSB measurements among in- and outpatients has been assured

REFERENCES:

1. Newman TB, Hope S, Stevenson DK. Direct bilirubin measurements in jaundiced term newborns. A reevaluation. Am J Dis Child 1991;145(11):1305-9
2. Maisels MJ, Newman TB. Predicting hyperbilirubinemia in newborns: the importance of timing. Pediatrics 1999;103(2):493-5.
3. Eddy D. Common screening tests. Philadelphia, PA: American College of Physicians; 1991.
4. On the state of the public health: Annual report of the Chief Medical Officer 2005. Chapter 4: Taking No Chances., 2006. (Accessed 11/1/06, 2006, at http://www.dh.gov.uk/assetRoot/04/13/73/71/04137371.pdf.)
5. Oh W, Tyson JE, Fanaroff AA, et al. Association between peak serum bilirubin and neurodevelopmental outcomes in extremely low birth weight infants. Pediatrics 2003;112(4):773-9.
6. van de Bor M, Ens-Dokkum M, Schreuder AM, Veen S, Brand R, Verloove-Vanhorick SP. Hyperbilirubinemia in low birth weight infants and outcome at 5 years of age Pediatrics 1992;89(3):359-64.
7. van de Bor M, van Zeben-van der Aa TM, Verloove-Vanhorick SP, Brand R, Ruys JH. Hyperbilirubinemia in preterm infants and neurodevelopmental outcome at 2 years of age: results of a national collaborative survey. Pediatrics 1989;83(6):915-20.
8. Jackson J. Adverse events associated with exchange transfusion in healthy and ill newborn. Pediatrics 1997;99:e7.
9. Sanpavat S. Exchange transfusion and its morbidity in ten-year period at King Chulalongkorn Hospital. J Med Assoc Thai 2005;88(5):588-92.
10. Patra K, Storfer-Isser A, Siner B, Moore J, Hack M. Adverse events associated with neonatal exchange transfusion in the 1990s. J Pediatr 2004;144(5):626-31.
11. Dahlquist G, Kallen B. Indications that phototherapy is a risk factor for insulin-dependent diabetes. Diabetes Care 2003;26(1):247-8.
12. Hansen T. Therapeutic approaches to neonatal jaundice: An international survey. Clinical Pediatrics 1996;June:309-16.
13. Gartner L. Practice patterns in neonatal hyperbilirubinemia. Pediatrics 1998;101:25-31.
14. Petrova A, Mehta R, Birchwood G, Ostfeld B, Hegyi T. Management of neonatal hyperbilirubinemia: pediatricians' practices and educational needs. BMC Pediatr 2006;6:6.
15. Kemper K, Forsyth B, McCarthy P. Jaundice, terminating breast-feeding, and the vulnerable child. Pediatrics 1989;84(5):773-8.
16. Kemper KJ, Forsyth BW, McCarthy PL. Persistent perceptions of vulnerability following neonatal jaundice. Am J Dis Child 1990;144(2):238-41.
17. Newman TB, Maisels MJ. The bilirubin debate. Pediatrics 1992;90(1 Pt 1):132.
18. Newman TB, Maisels MJ. Evaluation and treatment of jaundice in the term newborn: a kinder, gentler approach. Pediatrics 1992;89:809-18.
19. Newman TB, Klebanoff MA. Neonatal hyperbilirubinemia and long-term outcome: another look at the Collaborative Perinatal Project. Pediatrics 1993;92(5):651-7.
20. Newman TB, Maisels MJ. Does hyperbilirubinemia damage the brain of healthy full-term infants? Clin Perinatol 1990;17(2):331-58
21. Ip S, Chung M, Kulig J, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114(1):e130-53.

22. Newman TB, Liljestrand P, Jeremy RJ, et al. Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. N Engl J Med 2006;354(18):1889-900.
23. Hansen TW. Acute management of extreme neonatal jaundice--the potential benefits of intensified phototherapy and interruption of enterohepatic bilirubin circulation. Acta Paediatrica 1997;86(8):843-6.
24. Harris MC, Bernbaum JC, Polin JR, Zimmerman R, Polin RA. Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia. Pediatrics 2001;107(5):1075-80.
25. Newman T, Liljestrand P, Escobar G. Infants with bilirubin levels of 30 mg/dl or more in a large managed care organization. Pediatrics 2003;111(6):1303-11.
26. Ip S, Glicken S, Kulig J, O'Brien R, Sege R. Management of neonatal hyperbilirubinemia. Evidence report/technology assessment No. 65 (Prepared by Tufts-new England Medical Center Evidence-based Practice Center under Contract No. 290-97-0019); 2003.
27. Maisels MJ, Baltz RD, Bhutani VK, et al. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114(1):297-316.
28. Maisels M. Jaundice. In: MacDonald M, Seshia M, Mullett M, eds. Neonatology: Pathophysiology and Management of the Newborn. 6th ed ed. Philadelphia: JB Lippincott; 2005:768-846.
29. Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breast-fed term newborns. Pediatrics 1995;96(4 Pt 1):730-3.
30. Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr 2002;140(4):396-403.
31. Kappas A, Drummond GS, Valaes T. A single dose of Sn-mesoporphyrin prevents development of severe hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns. Pediatrics 2001;108(1):25-30.
32. Drummond GS, Kappas A. Chemoprevention of severe neonatal hyperbilirubinemia. Semin Perinatol 2004;28(5):365-8.
33. Kappas A. A method for interdicting the development of severe jaundice in newborns by inhibiting the production of bilirubin. Pediatrics 2004;113(1 Pt 1):119-23.
34. Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. Bmj 1992;305(6849):341-6.
35. Yamauchi Y, Yamanouchi I. Breast-feeding frequency during the first 24 hours after birth in full-term neonates. Pediatrics 1990;86(2):171-5.
36. Varimo P, Simila S, Wendt L, Kolvisto M. Frequency of breast-feeding and hyperbilirubinemia. Clin Pediatr (Phila) 1986;25(2):112.
37. De Carvalho M, Klaus MH, Merkatz RB. Frequency of breast-feeding and serum bilirubin concentration. Am J Dis Child 1982;136(8):737-8.
38. Maisels MJ, Vain N, Acquavita AM, de Blanco NV, Cohen A, DiGregorio J. The effect of breast-feeding frequency on serum bilirubin levels. Am J Obstet Gynecol 1994;170(3):880-3.
39. Kramer LI. Advancement of dermal icterus in the jaundiced newborn. Am J Dis Child 1969;118(3):454-8.
40. Recognition of the presence and severity of newborn jaundice by parents, nurses, physicians, and icterometer. 1997. (Accessed 9/23/02, 100, at http://www.pediatrics.org/cgi/content/full/100/3/e3.)
41. Moyer VA, Ahn C, Sneed S. Accuracy of clinical judgment in neonatal jaundice. Arch Pediatr Adolesc Med 2000;154(4):391-4.

42. Ebbesen F. The relationship between the cephalo-pedal progress of clinical icterus and the serum bilirubin concentration in newborn infants without blood type sensitization. Acta Obstet Gynecol Scand 1975;54(4):329-32.
43. Carbonell X, Botet F, Figueras J, Riu-Godo A. Prediction of hyperbilirubinaemia in the healthy term newborn. Acta Paediatr 2001;90(2):166-70.
44. Engle WD, Jackson GL, Sendelbach D, Manning D, Frawley WH. Assessment of a transcutaneous device in the evaluation of neonatal hyperbilirubinemia in a primarily Hispanic population. Pediatrics 2002;110(1 Pt 1):61-7.
45. Janjindamai W, Tansantiwong T. Accuracy of transcutaneous bilirubinometer estimates using BiliCheck in Thai neonates. J Med Assoc Thai 2005;88(2):187-90.
46. Maisels JM, Ostrea EM, Cepeda E, al e. Evaluation of the the Minolta Model 103 transcutaneous bilirubinometer. Pediatric Research 2002;51:341A.
47. Bhutani VK, Gourley GR, Adler S, Kreamer B, Dalin C, Johnson LH. Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. Pediatrics 2000;106(2):E17.
48. Tayaba R, Gribetz D, Gribetz I, Holzman IR. Noninvasive estimation of serum bilirubin. Pediatrics 1998;102(3):E28.
49. Vreman HJ, Verter J, Oh W, et al. Interlaboratory variability of bilirubin measurements. Clin Chem 1996;42(6 Pt 1):869-73.
50. Schreiner R, Glick M. Interlaboratory bilirubin variability. Pediatrics 1982;69:277-81.
51. Lo SF, Doumas BT, Ashwood ER. Bilirubin proficiency testing using specimens containing unconjugated bilirubin and human serum: results of a College of American Pathologists study. Arch Pathol Lab Med 2004;128(11):1219-23.
52. Lo SF, Doumas BT, Ashwood ER. Performance of bilirubin determinations in US laboratories--revisited. Clin Chem 2004;50(1):190-4.
53. Newman TB, Liljestrand P, Escobar GJ. Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns. Arch Pediatr Adolesc Med 2005;159(2):113-9.
54. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103(1):6-14.
55. Stevenson DK, Fanaroff AA, Maisels MJ, et al. Prediction of hyperbilirubinemia in near-term and term infants. Pediatrics 2001;108(1):31-9.
56. Maisels MJ, Kring E. Transcutaneous bilirubin levels in the first 96 hours in a normal newborn population of > or = 35 weeks' gestation. Pediatrics 2006;117(4):1169-73.
57. Maisels MJ. Jaundice. In: Effective care of the newborn infant. Oxford, UK: Oxford University Press; 1992:507-61.
58. Eggert LD, Wiedmeier SE, Wilson J, Christensen RD. The effect of instituting a prehospital-discharge newborn bilirubin screening program in an 18-hospital health system. Pediatrics 2006;117(5):e855-62.
59. Newman TB, Maisels MJ. Less aggressive treatment of neonatal jaundice and reports of kernicterus: lessons about practice guidelines. Pediatrics 2000;105:242-5.
60. Newman TB. The power of stories over statistics. BMJ 2003;327(7429):1424-7.