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Screening for Bilirubin Encephalopathy

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Structured Abstract

Background: Kernicterus or chronic bilirubin encephalopathy is a devastating disease. Thus, it is important to examine strategies to prevent the development of kernicterus.

Purpose: To systematically review evidence for the effectiveness of strategies to prevent chronic bilirubin encephalopathy. This is an update of our previous evidence report.

Data Sources: We searched Medline for articles from September, 2001 to August, 2007 using the MeSH terms and keywords, such as "jaundice," "bilirubin," "hyperbilirubinemia," and "kernicterus." For additional studies, we examined the bibliographies in existing studies and also consulted the lead experts from USPSTF.

Study Selection: We identified 18 articles that met our inclusion/exclusion criteria. Three studies in two publications addressed key question 2 (Does risk factor assessment accurately identify infants who may benefit from bilirubin testing?), nine studies addressed key question 3 (Does bilirubin testing accurately identify infants who may benefit from phototherapy?), and nine studies addressed key question 6 (What are the harms of treatment with phototherapy?). Of the 11 studies that addressed key questions 2 and 3, five were of fair quality; six were of poor quality according to US Preventive Services Task Force (USPSTF) criteria. We did not grade the methodological quality for the nine studies that addressed key question 6.

Data Extraction: Data elements were abstracted on to standardized forms and included information about the study setting, population, control, description of screening strategy, definitions of bilirubin encephalopathy and elevated bilirubin, and methods of analyses. Any adverse events or other effects from screening or phototherapy were also extracted. We also assessed the internal validity of the studies according to USPSTF criteria.

Data Synthesis (Results): There was no study that directly addressed the effectiveness of using risk factor assessment and/or bilirubin testing to reduce the incidence of kernicterus. Three fair quality studies (two nested case-control studies and a large retrospective cohort) examined the effectiveness of either using a risk score or a risk index to predict significant hyperbilirubinemia. The data suggest comparable predictability of the risk score (newborn and familial jaundice history and clinical characteristics) and the modified risk index (i.e., the risk score without family history of jaundice in a newborn) in predicting later significant hyperbilirubinemia. Three fair quality studies (one prospective and two retrospective cohorts) and one poor quality prospective study suggest comparable diagnostic abilities of early total serum bilirubin (TSB) measurements to predict late high TSB measurements. Results from one fair quality retrospective study comparing the ability of various screening strategies in predicting later hyperbilirubinemia suggest that the combination of using the modified risk index with early TSB levels significantly enhanced prediction than using either one of the strategies alone. None of the studies in this review assessed potential harms of screening. Studies in this review did not evaluate the effectiveness of phototherapy in reducing the risk of bilirubin encephalopathy. Our previous review reported that one needs to treat six to ten otherwise healthy jaundiced neonates with TSB ≥ 15 mg/dL by phototherapy in order to prevent the TSB in one infant from rising above 20

mg/dL. No definitive harm could be attributed to phototherapy. One retrospective study found an association in children between sizes of melanocytic nevi and exposure to neonatal phototherapy.

Conclusions: A study that directly evaluates the effectiveness of different strategies to reduce the incidence of kernicterus is not feasible given the rare occurrence of kernicterus. For practical consideration, studies on the effectiveness of different strategies to reduce the incidence of bilirubin encephalopathy could only rely on a surrogate outcome like serum bilirubin level. Based on retrospective analyses among infants who had both early and late TSB measurements available, the combination of risk factors and early TSB measurement has better diagnostic ability to predict clinically significant hyperbilirubinemia compared to risk factors alone.

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CHAPTER 1. INTRODUCTION

Scope and Purpose

Some degree of jaundice or hyperbilirubinemia occurs in most newborns. Severe neonatal hyperbilirubinemia is associated with kernicterus, a rare condition characterized by athetoid spasticity, gaze and visual abnormalities, and sensori-neural hearing loss in survivors. It may also be associated with mental retardation. A 2003 review concluded that kernicterus has a mortality of at least 10% and a morbidity of at least 70%.[1] The true incidence of kernicterus is unknown because it is not a mandatory reportable disease. However, a 2001 Joint Commission Sentinel Event Alert stated that cases of kernicterus have continued to be reported in recent years.[2] Efforts have been made by clinicians and investigators to eliminate this rare disease by instituting system-level measures to screen for hyperbilirubinemia and prevent the occurrence of kernicterus.[3-5] Most notable among these is a set of clinical practice guideline concerning the management of hyperbilirubinemia in infants of at least 35 weeks gestation published by the American Academy of Pediatrics (AAP) in 2004.[3] The 2004 guideline emphasizes the attention to risk factors associated with hyperbilirubinemia, close followup of at-risk infants, and the use of phototherapy and exchange transfusion to decrease the level of hyperbilirubinemia as appropriate.

Tufts-New England Medical Center Evidence-based Practice Center (Tufts-NEMC EPC) completed a review in 2003 examining the effects of bilirubin on neurodevelopmental outcomes in infants of at least 34 weeks gestation.[1] The report also examined the efficacy of phototherapy, the accuracy of transcutaneous bilirubin (TcB), and the various strategies for predicting hyperbilirubinemia. The Center on Primary Care, Prevention and Clinical Partnerships at the Agency for Healthcare Quality and Research (AHRQ), on behalf of the US Preventive Services Task Force (USPSTF), has now requested an update evidence report on the effectiveness of various screening strategies to prevent the development of kernicterus. This topic has not been previously considered by the USPSTF.

In the literature, the term “kernicterus” has been used interchangeably with both the acute and chronic findings of bilirubin encephalopathy. To avoid confusion as has been advocated by the AAP Subcommittee on Hyperbilirubinemia,[3] we use the terms acute and chronic bilirubin encephalopathy in this report. The term “kernicterus” is reserved for the chronic form of bilirubin encephalopathy.

This review examines the effectiveness of screening for hyperbilirubinemia to reduce the incidence of acute or chronic bilirubin encephalopathy. It also examines the benefits and harms of phototherapy. Populations of interests are healthy term infants, pre-term infants of at least 35 weeks gestation, and their mothers. Examples of screenings are system approach measures based on risk factors assessment, universal screening for bilirubin level (either serum or transcutaneous), or combinations of both. Outcomes of interest are the rates of acute or chronic bilirubin encephalopathy (if data are available), or surrogate measures (e.g., bilirubin level ≥ 20, 25 mg/dL); and any health outcomes or adverse events related to phototherapy.

To expand on the background behind the present review, the following is a brief summary of the 2003 evidence review.[1]

Brief Summary of the 2003 Evidence Review

Relationship between peak bilirubin levels and/or duration of hyperbilirubinemia and neurodevelopmental outcome:

- A summary of 28 reports of 123 cases of kernicterus in infants of at least 34 weeks gestation that spanned over 30 years affirms the role of elevated bilirubin level in kernicterus. The disease, although infrequent, has significant mortality (at least 10 percent) and long-term morbidity (at least 70 percent). It is important to note that a significant amount of demographic information was missing in these case reports. Thirty-five infants of at least 34 weeks gestation with idiopathic hyperbilirubinemia developed kernicterus with a total serum bilirubin level (TSB) ranging from 22.5 mg/dL to 54 mg/dL. Eighty-eight infants with hyperbilirubinemia and other co-morbid factors (like sepsis and hemolysis) developed kernicterus with TSB ranging from 4 mg/dL to 51 mg/dL.
- The Collaborative Perinatal Project (CPP), with 54,795 live births between 1959 and 1966 from 12 centers in United States has, by far, the largest database for the study of hyperbilirubinemia. Newman and Klebanoff focused only on black and white infants with birth weight ≥ 2,500 grams, and performed a comprehensive analysis of 33,272 subjects on their 7-year-outcomes. All causes of jaundice were included in the analysis. The authors found no consistent association between peak bilirubin level and IQ. Rate of sensorineural hearing loss was not related to bilirubin level. Only the frequency of abnormal or suspicious neurologic examination result was associated with bilirubin.
- Six high quality studies (not counting the CPP) showed significant relationship between abnormalities in brainstem auditory evoked potentials and high bilirubin levels. The majority reported resolution with treatment. Three studies reported hearing impairment associated with elevated bilirubin (>16 mg/dL to > 20 mg/dL).
- Excluding CPP, of the eight studies reporting intelligence outcomes in subjects with hyperbilirubinemia, four were considered high quality. These four studies reported no association between IQ and bilirubin level with followup ranging from 6.5 years to 17 years.
- Again, excluding CPP and the studies looking at IQ, of the nine studies primarily looking at behavioral and neurodevelopmental outcomes in patients, only three studies were of high methodologic quality. One showed a correlation between bilirubin level and decreased scores on newborn behavioral measurements. One found no difference in prevalence of central nervous system abnormalities at age 4 years when bilirubin was below 20 mg/dl, but infants with bilirubin above 20 mg/dl had a higher prevalence of central nervous system abnormalities. Another study that followed infants with bilirubin greater than 16 mg/dl found no relationship between bilirubin and neuro-visual-motor testing at 61 to 82 months of age.
- Given the overall diverse conclusions, except in cases of chronic bilirubin encephalopathy, we concluded that the use of a single total serum bilirubin level (within

the range described in the studies) to predict long-term behavioral or neurodevelopmental outcomes was inadequate and could lead to conflicting results.

Accuracy of various strategies for predicting hyperbilirubinemia:

- Based on the results from a single study, pre-discharge hour-specific bilirubin percentiles yielded very good accuracy for predicting clinically significant neonatal hyperbilirubinemia in the first week of life, as determined by an analysis of the receiver operating characteristic (ROC) curve, with an area-under-the-curve (AUC) of 0.93. There was no study that directly compared one strategy with another.

Efficacy of phototherapy in reducing the peak bilirubin levels and effects on visual and neurodevelopmental outcomes:

- Regardless of different protocols of phototherapy, the Number-Needed-to-Treat (NNT) for prevention of serum bilirubin level exceeding 20 mg/dL ranged from six to 10 in infants of at least 34 weeks gestation. This implies that one needs to treat six to 10 jaundiced neonates with TSB ≥ 15 mg/dL by phototherapy in order to prevent the TSB in one infant from rising above 20 mg/dL. Phototherapy combined with cessation of breastfeeding and substitution with formula was the most efficient treatment protocol for infants of at least 34 weeks gestation with jaundice.
- Eight studies examined the effect of bilirubin reduction on brainstem auditory evoked response (BAER). All consistently showed treatments for neonatal hyperbilirubinemia significantly improved abnormal BAER's in both healthy jaundiced infants and jaundiced infants with hemolytic disease.
- Three studies evaluated the effect of phototherapy on visual outcomes. All showed no short- or long-term (up to 36 months) effect on vision as a result of phototherapy when infants' eyes were properly protected during treatment.
- There was no evidence to suggest that phototherapy for neonatal hyperbilirubinemia has any long-term neurodevelopmental adverse effect in either healthy jaundiced infants or infants with hemolytic disease.

Accuracy of transcutaneous bilirubin measurements:

- The Minolta Airshields Jaundice Meter™, the Ingram Icterometer, and the SpectRx BiliCheck showed a linear correlation to TSB and could be useful as screening devices to detect clinically significant jaundice and decrease the need for determinations of TSB.
- The Minolta Airshields Jaundice Meter™ appeared to perform less well in black infants as compared to white infants, performed best when measurements were made at the sternum, and performed less well when infants had been exposed to phototherapy. This instrument required daily calibrations and each institution must develop its own correlation curves of TcB to TSB. As a screening test, it did not perform consistently across studies as evidenced by the summary ROC curves. The Ingram Icterometer has the added limitation of lacking objectivity of the other methods as it is dependent on observer visualization of depth of yellow color of the skin.
- BiliCheck™ and Colormate III devices that utilize reflectance data from multiple wavelengths appeared to be a significant improvement over the Ingram Icterometer and the Minolta AirShields bilirubinometer. This could be due to these devices' ability to determine correction factors for the effect of melanin and hemoglobin.

CHAPTER 2. METHODS

This report will be used by the USPSTF to make recommendations concerning screening for hyperbilirubinemia in neonates. Tufts-NEMC EPC, the Center on Primary Care, Prevention and Clinical Partnerships at AHRQ, and the USPSTF jointly developed an analytic framework (**Figure 1**) and a set of study inclusion/exclusion criteria that are suitable to meet the USPSTF objectives.

The key questions (KQs) are:

KQ1: Does screening using risk factor assessment and/or bilirubin testing reduce the incidence of acute or chronic bilirubin encephalopathy?

KQ2: Does risk factor assessment accurately identify infants who may benefit from bilirubin testing?

KQ3: Does bilirubin testing accurately identify infants who may benefit from phototherapy?

KQ4: What are the harms of screening?

KQ5: Does treatment reduce the risk of bilirubin encephalopathy in infants identified by screening?

KQ6: What are the harms of treatment with phototherapy?

Approach to Key Questions

This review focuses on the effectiveness of screening for hyperbilirubinemia to reduce the incidence of acute or chronic bilirubin encephalopathy. It also focuses on the benefits and harms of phototherapy. Populations of interests are healthy term or near-term infants (≥35 weeks gestation) and their mothers. Examples of screenings are system approach based on risk factors assessment, universal screening for bilirubin level (transcutaneous and/or serum), or combinations of both. Outcomes of interest are the rates of acute or chronic bilirubin encephalopathy (when data are available), or surrogate measures (e.g., bilirubin level ≥ 20, 25, 30 mg/dL), and any health outcomes or adverse events related to phototherapy.

Study Selection

We included experimental and observational studies with comparison groups (concurrent or historical comparison groups, or before-and-after comparison) in our review. For adverse events or other effects associated with phototherapy, we also included case report or case series. As this is an update of our previous report,[1] our literature search of Medline was restricted to studies

published after September of 2001 (search date of our previous report). Only English language studies published in peer-reviewed journals were included. Review articles, letter to the editors, or comments were excluded.

General inclusion criteria for the studies were:

Study Design: Experimental or observational studies

Population: Healthy term or near-term infants (≥35 weeks gestation) regardless of countries

Intervention: Screening for risk factors or serum bilirubin or transcutaneous bilirubin or combinations; phototherapy or exchange transfusion

Setting: Hospital, primary care office, home (for followup studies).

Comparator: No screening or different risk levels for developing hyperbilirubinemia defined by the screening programs; no phototherapy or exchange transfusion

Outcomes: Rates of acute or chronic bilirubin encephalopathy; rates of serum bilirubin (≥ 20, 25, 30 mg/dL); risk for developing hyperbilirubinemia or undergoing phototherapy; health outcomes and adverse events related to phototherapy

Specific exclusion criteria per key question were:

KQ1: None

KQ2: None

KQ3: Studies on clinical or maternal assessments of jaundice, cord blood bilirubin, end-tidal carbon monoxide (ETCO), or umbilical cord alpha-fetoprotein alone; studies reported correlation coefficients and/or Bland-Altman limit of agreement data only; no data on the timing of measurements; data were insufficient to determine the percentile of TSB

KQ4: None

KQ5: Treatments were not phototherapy

KQ6: Side effects or adverse events were not reported; data on adverse events for exchange transfusion; no usable numerical data

Search Strategy

We searched Medline for studies published from September, 2001 to December, 2006, using the MeSH terms and keywords, such as “jaundice”, “bilirubin”, “hyperbilirubinemia”, and “kernicterus”. For additional studies, we examined the bibliographies in existing studies and also consulted the Lead Experts from USPSTF. We updated our search in August of 2007.

Data Extraction

One reviewer initially screened abstracts for possible inclusion. This initial screening used very broad criteria to ensure that all potentially relevant abstracts were included (i.e., any human studies with any kind of screening or treatment of hyperbilirubinemia were screened in). A second person reviewed all the potentially relevant abstracts using the formal study inclusion/exclusion criteria. The full papers of the eligible abstracts were retrieved and examined in detail. After full article evaluation, data from qualified studies were abstracted (Appendix B). Items of interest extracted were: study setting, population, control, description of screening strategy, definitions of bilirubin encephalopathy and elevated bilirubin, and methods of analyses. Any adverse events or other effects from screening or phototherapy were also extracted.

Quality Assessment

We assessed the quality using criteria developed by the USPSTF.[6] Each paper was assigned a quality rating of "good", "fair", or "poor" by two reviewers. The criteria of quality assessment for primary studies included the randomization techniques, clear definitions of outcomes, and consideration for potential confounders in cohort studies, or intention to-treat analysis for RCTs. A third reviewer reviewed those studies in which the quality rating was discordant between the first two reviewers. Final grade in those studies were reached via consensus. Because of the wide variability in reporting of adverse events or other effects (e.g., temperature changes, sizes of nevi), the findings from those studies were summarized but the quality of those studies was not assessed.

Data Analysis and Presentation

Because of dissimilarities in the identified studies, no quantitative synthesis (meta-analysis) was performed. We assessed the ability of risk factor scores, transcutaneous or early bilirubin testing, or combinations thereof (index tests) to identify infants with high TSB (i.e., above the 95th hour-specific percentile) and infants who may benefit from phototherapy (as defined in the individual studies). To this end, we calculated from each study the corresponding sensitivity and specificity pairs. Multiple sensitivity/specificity pairs may be calculated for studies that report different cutoffs for the index or reference tests.

We also characterized the diagnostic ability of each test using positive and negative likelihood ratios (LR+ and LR-, respectively). These quantities express the information conveyed by the test results. Briefly, LR+ quantifies the increase of the pre-test odds (e.g., identifying high TSB values when the screening test is positive). Conversely, LR- quantifies how much less likely a high TSB value is if the index test result is negative. LR+ and LR- values of 1 imply no diagnostic ability. By convention, LR+>10 and LR-<0.1 imply informative and useful tests.[7] Instead of providing tables of likelihood ratios per study and cutoff used, we integrate the relevant information in the figures.

We recorded and reported the area under the curve (AUC) value from receiver operating characteristic (ROC) curve analyses. AUC values close to 1 imply better diagnostic ability. AUC values of 0.5 mean that the diagnostic ability of a test is no better than chance.

Whenever possible, direct comparisons are made; otherwise we performed qualitative indirect comparisons.

Intercooled Stata 8.2 (Stata Corp., College Station, TX) was used for calculations and graphics.

CHAPTER 3. RESULTS

Our search yielded 742 abstracts, of which 646 were rejected after initial abstract screening using very broad inclusion/exclusion criteria. Ninety-six articles were retrieved for full text examination. Full-text screening using the formal criteria rejected additional 79 articles. The following studies met our inclusion/exclusion criteria: Three studies in two publications addressed key question 2 (Does risk factor assessment accurately identify infants who may benefit from bilirubin testing?),[8,9] nine studies addressed key question 3 (Does bilirubin testing accurately identify infants who may benefit from phototherapy?),[4,8-15] and nine studies addressed key question 6 (What are the harms of treatment with phototherapy?).[16-24] Of the 11 studies that addressed key questions 2 and 3, five were of fair quality; six were of poor quality (**Figure 2**). There was no good quality study. We did not grade the methodological quality for the nine studies that addressed key question 6.

Key Question 1. Does screening using risk factor assessment and/or bilirubin testing reduce the incidence of acute or chronic bilirubin encephalopathy?

There was no study that directly addressed this question. In the United States, acute or chronic bilirubin encephalopathy is not a mandated reportable condition and therefore, the true incidence and prevalence could not be reliably ascertained. Studies could only measure the effectiveness of using risk factor assessment and/or bilirubin testing to reduce the incidence of specific levels of hyperbilirubinemia (e.g., ≥ 20 mg/dL, ≥ 25 mg/dL, ≥ 35 mg/dL) (see answers to questions 2 and 3), but not the incidence of bilirubin encephalopathy as not every infant with hyperbilirubinemia develops bilirubin encephalopathy.

Key Question 2. Does risk factor assessment accurately identify infants who may benefit from bilirubin testing?

One retrospective cohort study,[8] and one nested case-control study and retrospective cohort study published in the same article[9] examined the predictability using risk score or risk index for developing significant hyperbilirubinemia. All three studies were graded fair quality.

Sampling of infants in each study. Keren 2005 retrospectively included all healthy term and near-term infants who participated in the hospital's early discharge followup program and who had both pre- and post-discharge TSBs measured in the study period. Newman 2005 (Study 1) was a nested case-control study. The cases were all term and near-term infants with a maximum TSB ≥25 mg/dL in the first 30 days after birth, and the controls were randomly sampled from the cohort in the study period. Newman 2005 (Study 2) retrospectively included all infants discharged before 48 hours after birth who had a TSB measured before 48 hours in the study period. Infants with a TSB ≥20 mg/dL before 48 hours were excluded.

Significant hyperbilirubinemia - reference standard. In Keren 2005, the outcome of significant hyperbilirubinemia was defined as a post-discharge TSB greater than 95th percentile on the hour-specific bilirubin nomogram, which is nearly identical to the phototherapy threshold curve recommended for "medium risk" infants in the AAP's 2004 clinical practice guideline. In Newman 2005 (Study 1), the outcome of significant hyperbilirubinemia was defined as a TSB ≥25 mg/dL in the first 30 days after birth. In Newman 2005 (Study 2), the outcome of significant hyperbilirubinemia was defined as a TSB ≥20 mg/dL at 48 hours or older after birth.

Risk scores or risk indexes that predict significant hyperbilirubinemia. There were no common risk factors that predict significant hyperbilirubinemia included in the calculation of the risk score or risk index between Keren 2005 and Newman 2005, except for exclusive breastfeeding and gestational age (**Table 1**). Calculation of the risk score from gestational age was handled differently between the two studies. Newman 2005 study aimed to validate a risk index for predicting significant hyperbilirubinemia that they previously developed and published in 2000.[25] The Newman 2000 study has been summarized in our previous report and the detailed results are presented in Appendix F. However, in contrast to the original risk index, family history of jaundice was removed from the list of risk factors used to calculate the risk index in Newman 2005 study (**Table 1**).

Methodological comments. The risk score in Keren 2005 and the modified risk index in Newman 2005 had not yet been independently verified in another population. If a predictive score was derived in the same population that used to assess the predictability (e.g., sensitivity, specificity) for the outcome, the predictive model is almost always optimistically biased. Moreover, diagnostic studies of highly selected cases versus controls often show improved diagnostic ability compared with prospective cohort studies.[26]

Ability of risk factor scores/indexes to predict later significant hyperbilirubinemia. Overall, the data suggest comparable predictability of the risk score developed by Keren et al. and the modified risk index (without family history of jaundice in a newborn) developed by Newman et al. in predicting later significant hyperbilirubinemia (**Table 2**). Keren 2005 reported an AUC value of 0.71 (95% CI: 0.66, 0.76) for their risk score in predicting a post-discharge TSB greater than 95th percentile on the hour-specific bilirubin nomogram. Newman 2005 (Study 2) reported an AUC value of 0.69 (no data for the 95%CI) for their modified risk index in predicting a TSB level ≥20 mg/dL at 48 hours. The original risk index (with family history of jaundice in a newborn) developed in Newman 2000 study had an AUC value of 0.84 (95% CI: 0.79-0.89) in predicting a TSB ≥25 mg/dL in the first 30 days after birth. This risk index had been independently verified in Newman 2005 (Study 1) and showed that eliminating the family history variable had little effect on the prediction. The AUC value declined from the previous reported value of 0.84 to 0.83 (95%CI: 0.77-0.89).

Key Question 3. Does bilirubin testing accurately identify infants who may benefit from phototherapy?

Ability of early TSB measurements to predict high late TSB measurements

Two prospective cohorts from India[11] and Turkey[10] and two retrospective cohorts from the United States[8,9] with relevant data are described in **Table 3.** Three studies were graded fair quality,[8-10] and one was graded poor quality.[11]

Sampling of infants in each study. Argawal 2002 prospectively included healthy infants with gestational age ≥35 weeks who were born in one center over a period of 5 months. Sarici 2004 prospectively included 366 consecutive infants with gestational age between 35 and 42 weeks, but reported data on the diagnostic ability of early TSB measurements only among 146 near-term infants (gestational age between 35 and 37 weeks). Newman 2005 Study 2 described a retrospective cohort of approximately 5,700 infants who were discharged earlier than 48 hours and had a pre-discharge TSB measurement less than 20 mg/dL (data were obtained from an electronic database on approximately 105,000 infants from Kaiser Permanente hospitals). Keren 2005 was a retrospective cohort of near-term and term infants born between 1995 and 1997, for whom both early (mostly pre-discharge – see **Table 3** footnote) and late (mostly post-discharge– see **Table 3** footnote) TSB measurements were available.

Post-discharge TSB measurement - reference standard. In three studies, the reference standard was a post-discharge measurement above the hour-specific 95th percentile,[8,10,11] and in Newman 2005 it was a TSB greater than 20 mg/dL (which is above the 95th percentile at 48 hours or later).[9] The timing of the reference measurement varied between 48 to 150 hours. In Sarici 2004, at least one of four measurements above the 95th percentile during the first week (150 hours) was sufficient for TSB to be characterized as high.

Methodological comments. In Agarwal 2002, the reference standard (TSB at 72 hours) was not applied to infants with TSB less than 10 mg/dL at 72 hours (unclear how this was determined). This study may have underestimated the false negatives (inflating the calculated sensitivity) and overestimated the true negatives (inflating the calculated specificity) as apparently almost one-third of the infants did not get a TSB at 72 hours. Sarici 2004 reported results only among 146 near-term infants out of 366 near-term and term infants (reason was not given); it is unclear if this would have affected the reported findings.

Ability of early (pre-discharge) TSB to identify high late (post-discharge) TSB. The diagnostic ability of early measurements to identify post-discharge TSB above the 95th hour-specific percentile (>20 mg/dL for Newman 2005) is shown in **Figure 3**. Overall, the four studies suggested comparable diagnostic abilities of early TSB measurements to predict late high TSB measurements. Keren 2005 reported an AUC value of 0.83 (95% CI 0.80-0.86). Newman 2005 reported an AUC value of 0.79 (95% CI 0.77- 0.81) for an empirical ROC curve that considered four cutoffs for the early TSB measurement; and an AUC value of 0.83 (95% CI 0.80 0.85) when they considered continuous rather than categorical early hour-specific TSB measurements. Sarici 2004 used measurements at 6 hours and 30 hours to predict post-discharge high TSB. Measurements at 30 hours had better diagnostic ability than the earliest measurements. Agarwal 2002 suggested a negative likelihood ratio of less than 0.1, which showed a good ability to exclude post-discharge high TSB when early TSB was below the 75th hour-specific percentile. However, this study had overt verification bias and therefore, the estimate may be overly optimistic.

Ability of TcB measurements to predict high late TSB measurements

One study from Thailand[12] and one study from China (Hong-Kong)[14] had relevant data; their characteristics are described in **Table 4**. Both studies were graded poor for their methodological quality.

Sampling of infants in each study. Both studies included almost exclusively infants of Asian descent. Ho 2006 examined retrospectively all healthy term or near-term infants born over a period of 6 months that had TcB measurements above the 40th percentile and also had a TSB measurement. Sapnavat 2005 enrolled healthy term infants born with caesarean section.

TSB measurement suggestive of phototherapy - reference standard. Ho 2006 used the American Academy or Pediatrics (AAP) guidelines to define TSB measurements indicating the need for phototherapy. According to the AAP guidelines, three hour-specific boundaries may be set; the lower corresponds to high risk infants (near-term with risk factors) and the highest one to low risk infants (term without risk factors). The middle boundary corresponds to middle risk infants (near-term without other risk factors or term with risk factors) and it roughly follows the hour-specific 95th percentile line in the Bhutani nomogram. Sapnavat 2005 used their own criteria to define TSB values indicating the need for phototherapy. These were at least 10 mg/dL in the second day of life, at least 13 mg/dL in the third and at least 15 mg/dL after the third day of life.

Methodological comments. The study by Ho 2006 analyzed retrospectively only children who had TcB measurements above the 40th hour-specific percentile and had undergone paired TcB and TSB measurements. Approximately 62% of children with TcB measurements above the 40th percentile had paired measurements. Part of the analysis inappropriately used the 40th percentile in TcB as cutoff (although no infants below this cutoff were included), yielding misleading estimates of sensitivity and specificity. The methodological quality of the study was graded poor. Sanpavat 2005 verified approximately 40% of the TcB measurements with TSB (unclear how the infants were selected; the study did mention obtaining TSB when infants were "jaundiced").

Ability of early (pre-discharge) TSB to identify high late (post-discharge) TSB. **Figure 4** summarizes the diagnostic ability of TcB measurements to identify TSB indicative of phototherapy in these two studies. Ho 2006 used three definitions of TSB that suggest the need for phototherapy according to the AAP TSB boundaries for low, medium, and high risk infants. Ho 2006 performed TSB infants with TcB measurements above the 40th hour specific percentile. Using the TSB boundary for medium risk infants as a reference standard (which roughly corresponds to the 95th hour-specific percentile in the Bhutani nomogram) suggests low negative likelihood ratio (LR-<0.1) when the TcB measurements are less than the 75th percentile in the Bhutani nomogram. Using the TSB boundary for high risk infants, TcB measurements have sensitivity and specificity pairs that are not in the regions corresponding to high diagnostic ability (LR+>10 or LR-<0.1). Sanpavat 2005 had low negative LR for most of TcB measurements lower that the 90th hour-specific percentile in the Bhutani nomogram. However, this study had overt verification bias, and therefore its sensitivity and specificity are likely to be inflated.

Outcomes associated with the implementation of TcB screening and the use of hour-specific bilirubin nomogram

Three studies compared the number of newborns received phototherapy and/or readmission rate for hyperbilirubinemia for newborns who were born before to those who were born after the implementation of transcutaneous bilirubin (TcB) screening and the use of the hour-specific bilirubin nomogram in the United States.[4,13,15] Their characteristics and results are summarized in **Table 5**. All studies were of poor methodological quality because the outcomes reported in these studies came from retrospective descriptive analyses without controlling for confounding factors. Specifically, all three studies were retrospective in design, and the information on bilirubin levels in the populations was not obtained in two studies.[4,13] In addition, many factors that could likely affect the prevalence of hyperbilirubinemia (e.g., increase in breastfeeding rate, increase in Asian immigrants, sentinel alert of resurgence in kernicterus[2]) and other potential confounders (e.g., changes in phototherapy procedures or background healthcare policy) were not ascertained. Therefore, the data presented here could only provide indirect evidence of the outcomes associated with the introduction of the implementation of TcB screening and the use of hour-specific bilirubin nomogram.

Bhutani 2006 described the changes in the use of intensive phototherapy and the changes in the readmission rates for intensive phototherapy in term and near-term infants with an incremental implementation of a systems approach that incorporated a hospital policy to (a) authorize nurses to obtain a bilirubin (total serum/transcutaneous) measurement for clinical jaundice, (b) universal pre-discharge total serum bilirubin (at routine metabolic screening), and (c) targeted followup, using the bilirubin nomogram (hour-specific, percentile-based total serum bilirubin/ transcutaneous bilirubin).[4] The data showed that the use of intensive phototherapy increased from 4.49% during 1993 to 1995 (the phase of universal TSB screening without hour-specific bilirubin nomogram) to 5.44% during 1996 to 1998 (the phase of universal TSB screening with hour-specific bilirubin nomogram). After a system-based approach for hyperbilirubinemia screening was implemented, the use of intensive phototherapy had decreased to 2.49% (3.0% in 1999 and 1.98% in 2000) during 1999 and 2000. During the nomogram development phase and the initiation of a system-based program, a steady and significant decline in readmission rate for intensive phototherapy was noted from 14 admitted in 1994 to 5.5 infants per 1000 well babies admitted in 2001 to 2003.

Eggert 2006 described the changes in the proportion of infants with significant hyperbilirubinemia and in the proportion readmitted to the hospital with a diagnosis of hyperbilirubinemia comparing before with after the initiation of universal pre-discharge TSB or TcB screeninge.[15] Only two out of 18 hospitals used a screening jaundice meter for TcB estimation of bilirubin levels. A modified Bhutani's hour-specific bilirubin nomogram was used. The authors stated the reason was that "an inordinately high number of neonates had bilirubin values in the intermediate- and high-risk zones of the Bhutani et al nomogram, particularly when evaluated between 24 and 48 hours of age.". If an infant had a bilirubin level ≥40th percentile on the modified nomogram, the care provider was notified. Appropriate evaluation, intervention, and followup were arranged as necessary. The study reported that the incidence of severe hyperbilirubinemia among term and near-term infants increased significantly; while the proportion of newborns readmitted to the hospital for treatment of hyperbilirubinemia decreased

from 0.55% to 0.43% (P<0.005) comparing before with after the initiation of universal pre-discharge TSB or TcB screening.

Petersen 2005 described the changes in the number of newborns received phototherapy, readmission rates for hyperbilirubinemia, length of stay, and the number of bilirubin measurements comparing before to after the initiation of TcB testing. The decision to start phototherapy or obtain additional bilirubin measurements was made using the hour-specific bilirubin nomogram. The study reported that the proportion of newborns treated with phototherapy in the nursery increased significantly after initiation of TcB (5.9% vs. 7.7% per month before vs. after TcB, respectively). However, the mean number of serum bilirubin per newborn did not change after introduction of TcB testing (1.51 vs. 1.56 TSB per newborn before vs. after TcB, respectively). After initiation of TcB testing, the mean (SD) number of readmission for hyperbilirubinemia decreased from 4.5 (2.8) to 1.8 (1.7) per 1000 births per month (P=0.044).

Combination of the risk index with early TSB levels

Newman 2005 (Study 2) also compared the ability of various screening strategies in predicting a TSB level ≥20 mg/dL at 48 hours or older after birth. The results suggested that the combination of the modified risk index (described in Newman 2005 Study 1) with early TSB levels significantly enhanced prediction. The AUC value for prediction of developing a TSB level of 20 mg/dL or higher at age 48 hours or older improved from 0.69 to 0.86 (95%CI 0.84-0.88) after adding the early TSB z scores (the standard normal deviates for each participants' early hour-specific TSB measurements) to the modified risk index. The AUC value for the combination of the modified risk index with early TSB z scores was also significantly better than that for the early TSB z scores alone (0.86 vs. 0.83, P=0.001).

Key Question 4. What are the harms of screening?

Studies reviewed in this report did not assess the harms of screening.

Key Question 5. Does treatment reduce the risk of bilirubin encephalopathy in infants identified by screening?

No studies in this review evaluated the effectiveness of phototherapy in reducing the risk of bilirubin encephalopathy.

Key Question 6. What are the harms of treatment with phototherapy?

A total of nine studies assessed for potential adverse or other effects of phototherapy.[16-24] One retrospective study compared the number of melanocytic nevi in children who received phototherapy with children who did not receive phototherapy.[19] One study compared polysomnography findings in infants before phototherapy with findings during phototherapy.[16]

Three studies compared temperature before with during phototherapy.[17,20,23] Seven studies compared different aspects of phototherapy (e.g., with versus without white curtain,[18] single versus double,[20] conventional versus fiberoptic,[21] conventional versus LED,[22] far versus near,[23] hospital versus home[24]). Results are summarized in **Table 6**.

Number of subjects in the studies ranged from 10 to 104. Adverse or other effects in infants evaluated included: hypo- or hyperthermia; weight loss; gastrointestinal problems; skin rash or erythema; and changes in cardiopulmonary parameters.

In the study that compared cardiopulmonary parameters in ten term infants before phototherapy with parameters in the same infants during phototherapy, the study reported the respiratory rate decreased from a mean of 54.3 ± 10.3 to 49.1 ± 10.8 ($P < 0.05$) and the heart rate increased from a mean of 125.9 ± 11.7 to 129.7 ± 15.3 ($P<0.05$) in the active sleep phase, but no significant difference was found during the quiet sleep phase.[16] There was a trend towards an increase in the duration of central apnea ($P=0.07$) while under phototherapy. It also reported a significant increase in heart rate ($P<0.02$) in the same group of infants while under phototherapy compared to no phototherapy. No significant effects on oxygen saturation, rate of apnea, or periodic breathing were found.

One study reported that the infants' mean temperature increased from a baseline of 36.43ºC ± 0.21ºC to 36.70ºC ± 0.25ºC after 6 hours of phototherapy ($P<0.05$).[23] Another study reported that 29/81 (36%) infants with initial core temperature of 36.5-37.5ºC increased to >37.5º C after 2 hours of phototherapy.[17] The same study also reported that 2/81 (2.5%) infants with initial core temperature of 36.5-37.5º decreased to <36.5º C after 2 hours of phototherapy. A third study on the exposure of phototherapy with or without white curtain reported no hypo- or hyperthermia in the infants.[18]

One retrospective study examined the presence of melanocytic nevi (a brown to black macule or papule) in 18 children who received phototherapy compared with 40 children who did not receive phototherapy.[19] In the multivariate analysis, an association between phototherapy and nevi sizes were found after adjusting for risk factors (phototherapy, age, skin type I or II, color of skin, eye, and hair, freckles, sun exposure during vacation, and severe sunburn) (2-5 mm, $P<0.001$; ≥ 2 mm, $P=0.003$). This study did not control for the number of melanocytic nevi in parents and it was also unclear how the subjects in the phototherapy group were selected.

One study reported no significant weight loss, no skin or gastrointestinal problems in infants exposed to phototherapy with or without white curtain.[18] Another study reported no significant difference in weight loss, stooling or hyperthermia in infants with single versus double phototherapy.[20] A third study reported transient erythema and watery stool in either the infants who received fiberoptic (1/50; 3/50, respectively) or conventional phototherapy (1/50; 3/50 respectively).[21] A fourth study reported no side effects were noted in infants who received either conventional or LED blue or blue-green phototherapy.[22] A fifth study found no significant difference in terms of rash, hyperthermia, or diarrhea in infants who received home versus hospital phototherapy.[24] Positive findings reported in these studies could not be confidently attributed to the use of phototherapy as none of the studies compared infants exposed to phototherapy with infants who were not exposed to phototherapy.

CHAPTER 4. DISCUSSION

This report is prepared for the USPSTF for use in drafting a set of statements concerning screening for neonatal hyperbilirubinemia. Whether screening for neonatal hyperbilirubinemia should be implemented is not addressed in this report. We only critically examined the evidence concerning the effectiveness of various screening strategies published in the literature.

Key Question 1

A study that directly evaluates the effectiveness of different strategies to reduce the incidence of acute or chronic bilirubin encephalopathy is not feasible given the rare occurrence of kernicterus (one estimate of the prevalence of kernicterus was 1.87 cases per 100,000 live births[27]). One would have to perform a very large (cluster) randomized trial to evaluate the effectiveness of a particular strategy versus standard care in reducing the incidence of kernicterus in the general population. For practical consideration, studies on the effectiveness of different strategies to reduce the incidence of bilirubin encephalopathy could only rely on a surrogate outcome like serum bilirubin level.

Key Question 2

Overall, the data suggest comparable predictability of the risk score developed by Keren et al.[8] and the modified risk index (without family history of jaundice in a newborn) developed by Newman et al.[9] in predicting later significant hyperbilirubinemia. Significant hyperbilirubinemia was defined as a post-discharge TSB greater than 95th percentile on the hour-specific bilirubin nomogram in one study[8] and as a TSB ≥25 mg/dL the first 30 days after birth in the other study.[9] The risk score instruments used in the aforementioned studies predict significant hyperbilirubinemia had only two risk factors in common, namely exclusive breastfeeding and gestational age (gestational age was evaluated differently, as shown in **Table 1**). Therefore, the same infant may receive different risk scores with the two risk assessment instruments. Furthermore, the risk score and risk index (without family history of jaundice in a newborn) had not yet been independently verified in another population.

The original risk index (with family history of jaundice in a newborn) developed by Newman et al. in 2000[25] had been independently verified in their later study and showed that eliminating the family history variable had little effect on the prediction of later significant hyperbilirubinemia.[9]

Key Question 3

Ability of early TSB measurements to predict high late TSB measurements

Three fair quality studies,[8-10] and one poor quality study[11] provided relevant data on the ability of early TSB measurements to predict high late TSB measurements. In three studies, the reference standard was a post-discharge measurement above the hour-specific 95th percentile, and in the other study was a TSB greater than 20 mg/dL (which is above the 95th percentile at 48 hours or later).[9] The timing of the reference measurement varied between 48 to 150 hours. Overall, the four studies suggest comparable diagnostic abilities of early TSB measurements to predict late high TSB measurements.

Ability of TcB measurements to identify TSB indicating need for phototherapy

Two poor quality studies provided relevant data on the ability of TcB measurements to identify TSB indicating the need for phototherapy.[12,14] TSB cutoffs suggesting need for phototherapy were defined quite differently in these two studies. TcB measurements less than specific thresholds (the 75th hour-specific percentile in one study[14] and the 90th in the other[12]) may predict TSB measurements that do not indicate the need for phototherapy. The later study had overt verification bias.[12]

Combination of the risk index with early TSB levels

Results from one fair quality study comparing the ability of various screening strategies in predicting later hyperbilirubinemia suggest that the combination of the modified risk index with early TSB levels significantly enhanced prediction than using either one of the screening strategies alone.[9]

Key Question 4

None of the studies in this review assessed potential harms of screening. Nevertheless, the potential harms of any form of screening should be carefully considered and monitored in any strategy.

Key Question 5

Studies in this review did not evaluate the effectiveness of phototherapy in reducing the risk of bilirubin encephalopathy. Our previous review reported that one needs to treat six to ten otherwise healthy jaundiced neonates with TSB ≥ 15 mg/dL by phototherapy in order to prevent the TSB in one infant from rising above 20 mg/dL.[1]

Key Question 6

This group of studies reporting on adverse or other effects associated with phototherapy had relatively small number (10 to 104) of subjects, compared to the 1974-1976 National Institute of Child Health and Human Development (NICHD) phototherapy trial where 672 infants received phototherapy and 667 infants did not. The NICHD trial found that term-infants who were treated

with phototherapy tended to pass more stools and lose more weight during phototherapy than the control infants.[28] In our review, one study reported changes in cardiopulmonary parameters while under phototherapy, although the clinical significance of these findings is unclear. One retrospective study found an association in children between sizes of melanocytic nevi and exposure to neonatal phototherapy. The study did not control for the number of melanocytic nevi in the parents. Also, how the subjects were selected for the study was not adequately explained. With these limitations in mind, it is difficult to agree with the conclusion proffered by the study authors that "intensive neonatal phototherapy is a strong risk factor for nevus development in childhood". One study reported that one-third of the infants had an increase in core temperature after 2 hours of phototherapy; it also found a small proportion (~2%) of the infants had a decrease in core temperature after 2 hours of phototherapy. These findings emphasized the need to monitor infant's temperature while undergoing phototherapy. One reviewer of this report alerted us to a published letter from Sweden suggesting that a history of phototherapy may be associated with an increased risk of type 1 diabetes.[29] This letter did not provide detailed methodological information and therefore, it was difficult to assess the validity of this finding. Nonetheless, this is a potential harm that bears further investigation, although the mechanism behind the reported association is unknown.

Limitations

First, because this is an update of our previous report, studies published prior to 2001 (search date of the previous report) that may provide potentially useful information were not included. Second, the number of eligible studies that addressed the key questions was limited, and none was graded good methodological quality. Of the included studies, half were of fair quality and half were of poor quality. Finally, because of the small number of studies and the clinical and methodological between study heterogeneity, we did not perform quantitative analyses.

Future Research

In principle, a pragmatic (cluster) randomized controlled trial comparing different strategies would give the most definitive answer on which strategy can identify most infants developing severe hyperbilirubinemia. However, because severe hyperbilirubinemia is a relatively rare event (and because of the clustered design), tens of thousands of infants per arm would be needed to attain statistical power. This poses questions on the feasibility of this task. Alternative options (without the internal validity of a randomized trial) exist. As of this writing, the diagnostic ability of strategies that combine risk factors and early TSB measurements has not been verified in an independent sample. A prospective independent validation study could compare multiple screening strategies (e.g., risk factors only, early TSB only and combination thereof) in the *same infants*. This may inform on the incremental predictive ability of different strategies in an *independent setting*. It will improve the quality of the data in this field if the reporting of acute and chronic bilirubin encephalopathy is made mandatory. Future studies on preventive and screening strategies should actively monitor the potential harms from implementing such strategies in both infants and their family members. Prospective and properly controlled study

will be helpful in clarifying the relationship between exposure to neonatal phototherapy and the development of melanocytic nevi.

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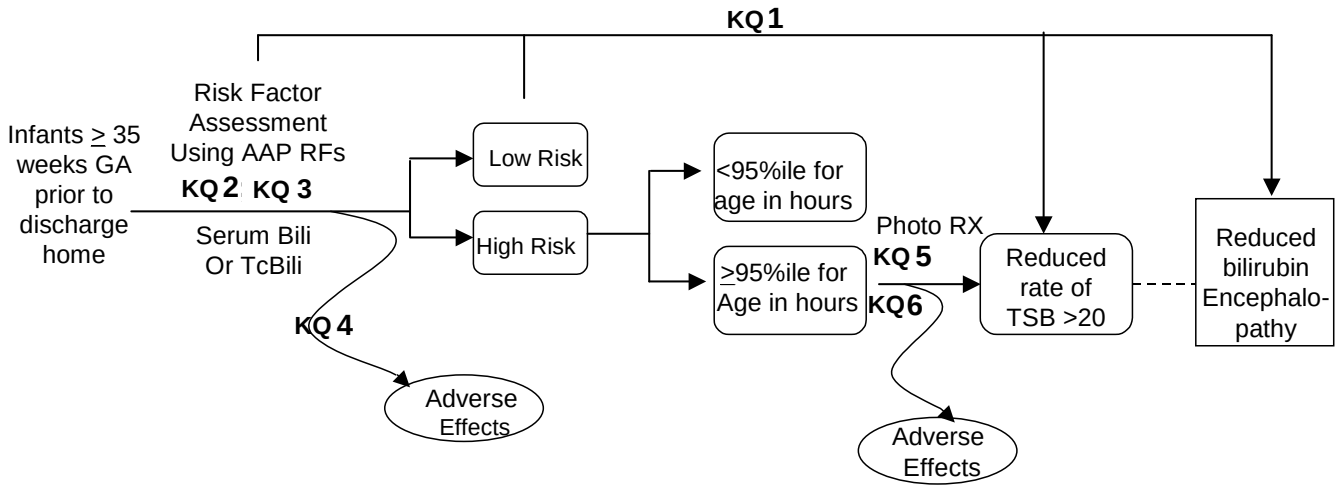
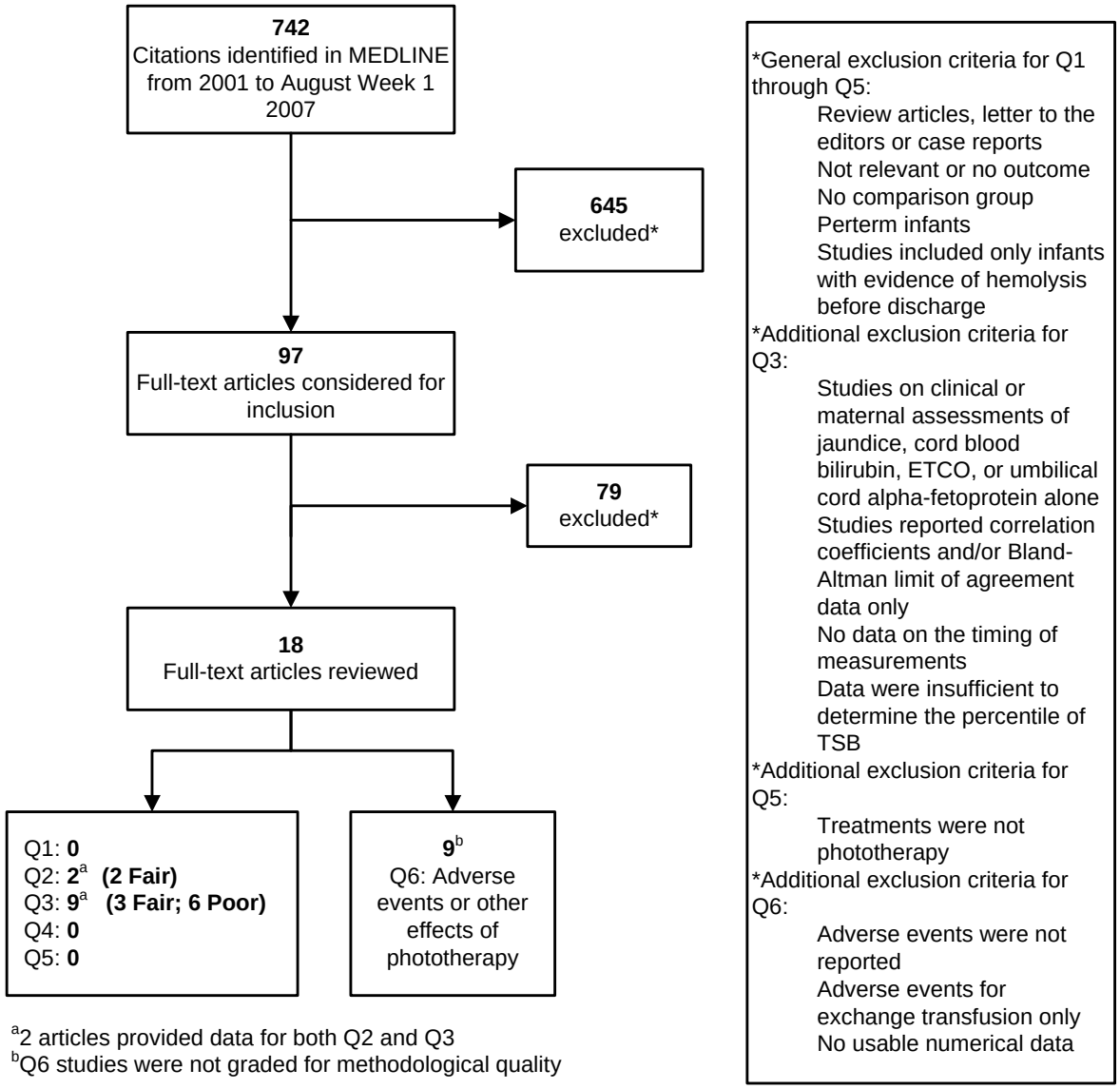
Figure 1. Hyperbilirubinemia Screening Analytic Framework



KQ1: Does screening using risk factor assessment and/or bilirubin testing reduce the incidence of acute or chronic bilirubin encephalopathy?
KQ2: Does risk factor assessment accurately identify infants who may benefit from bilirubin testing?
KQ3: Does bilirubin testing accurately identify infants who may benefit from phototherapy?
KQ4: What are the harms of screening?
KQ5: Does treatment reduce the risk of bilirubin encephalopathy in infants identified by screening?
KQ6: What are the harms of treatment with phototherapy?

Key: GA=Gestational age; AAP=American Academy of Pediatrics; RF=Risk factor; Bili=Bilirubin; TcBili=Transcutaneous bilirubin; %ile=Percentile; TSB=Total serum bilirubin.

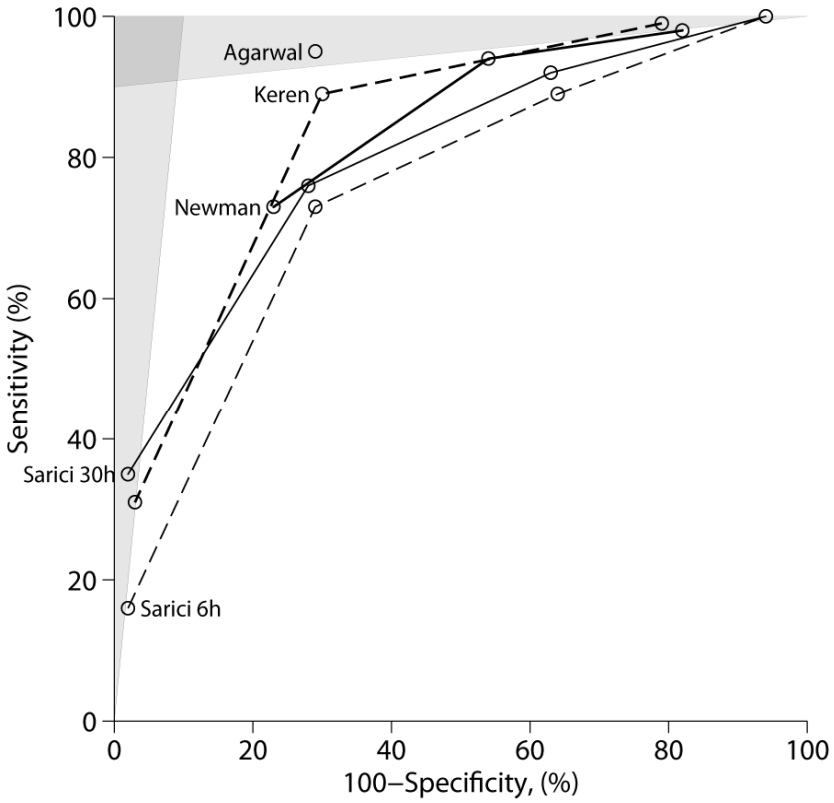
Figure 2. Study Eligibility Flow Chart



[a]2 articles provided data for both Q2 and Q3
[b]Q6 studies were not graded for methodological quality

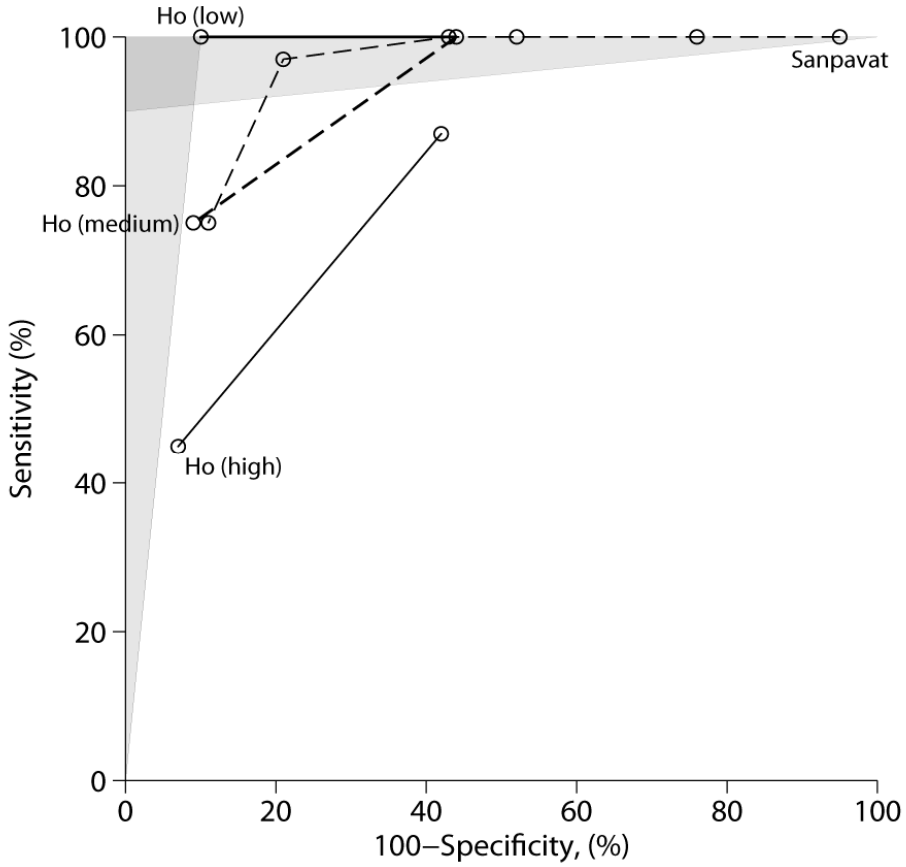
Key: ETCO=End-tidal carbon monoxide; TSB=total serum bilirubin

Figure 3. Diagnostic Ability of Pre-discharge TSB Measurements to Predict Post-discharge Hour-specific TSB >95th Percentile



Sensitivity/specificity pairs from the same study (obtained with different cutoffs for the early TSB measurement) are connected with lines. These lines may not be representative of the ROC curve of the pertinent studies. For example, Newman 2005 report higher AUC value than Keren 2005, something that is not directly evident from this graph (many intermediate cutoffs are not depicted). Studies lying on the left shaded area have a positive likelihood ratio of 10 or more. Studies lying on the top shaded have a negative likelihood ratio of 0.1 or less. Studies lying at the intersection of the grey areas (darker grey polygon) have both LR+>10 and LR-<0.1.

Figure 4. Diagnostic Ability of TcB Measurements to Identify Hour-specific TSB Suggesting the Need for Phototherapy



Sensitivity/specificity pairs from the same study (obtained with different cutoffs for the early TSB measurement) are connected with lines. These lines may not be representative of the ROC curve of the pertinent studies. Studies lying on the left shaded area have a positive likelihood ratio of 10 or more. Studies lying on the top shaded have a negative likelihood ratio of 0.1 or less. Studies lying at the intersection of the grey areas (darker grey polygon) have both LR+>10 and LR-<0.1.

Table 1. Comparisons of the Risk Scores/Indexes Across Studies

Risk Factors	Weighting for Risk Score/Index		
	Keren, 2005	Newman, 2005	Newman, 2000[a]
Exclusive breastfeeding	5	6	6
Breast and bottle feeding	4	-	-
Family history of jaundice in newborn	-	-	6
Bruising	-	4	4
Asian race	-	4	4
Cephalohematoma	-	3	3
Mother age ≥25 years	-	3	3
Male sex	-	1	1
Black race	-	-2	-2
Gestational age in weeks minus 40 weeks	-	2	2
Gestational age <38 wk	5	-	-
3 points per 500 gram above 2000 gram in birth weight[b]	3	-	-
Oxytocin used	4	-	-
Vacuum delivery	4	-	-

[a] Summarized in the previous report (see Appendix F)

[b] Calculation: (Birth weight in grams – 2001)/500, rounding down to the nearest integer

Table 2. Summary of Studies That Used Risk Predictive Instruments to Predict High TSB

Author, Year Country (single/multi center)	Design	N (cases)	Birth weight (g), gestational age (wk)	Risk score	High TSB cutoff (mg/dL)	Verification bias	Independent validation	AUC	RI Cutoff with Best Predictive Values	Quality
Keren, 2005 US (single center)	Retrospective cohort	993	≥2000, ≥36 or ≥2500 if ≥35	Personal history[d]	NA (>95th %tile)	No	No	0.71	≥12	B
Newman, 2005 - Study 2 US (multi center)	Retrospective cohort	5706	>2000, >36	Personal history[b]	20	No	No[f]	0.69	≥10	B
Newman, 2005 - Study 1 US (multi center)	Nested case-control	275 (67)	2000, >36	Personal history[b]	25	No	Yes[c]	0.83	n.d.	B
Newman, 2000 [e] US (multi center)	Nested case-control	496 (73)	>2000, >36	Personal and family history[a]	25	No	No	0.84	≥10	-

GA=gestational age; N=Number analyzed; NA=Not applicable; NICU=neonatal intensive care unit; TSB=total serum bilirubin; RI=risk index; AUC=area under the curve.

[a] Score=6*Exclusive breastfeeding + 6* Family history of jaundice in newborn+4* Bruising + 4* Asian race + 3* Cephalohematoma + 3* Mother age ≥25 years+ 1* Male sex –2 * Black race +2*(Gestational age in weeks - 40)

[b] Modified Score is the same as above, excluding the family history of jaundice in newborn term, i.e., (modified score) =6*Exclusive breastfeeding at discharge + 4* Bruising + 4* Asian race + 3* Cephalohematoma + 3* Mother age ≥25 years+ 1* Male sex –2 * Black race +2*(Gestational age in weeks - 40)

[c] Independent validation of the score developed in Newman 2000. However, the score was "modified", abolishing one of the most influential factors (family history of jaundice in newborn) because it was available only in 10% of infants.

[d] Score= [3 points per 500 g above 2000 g in BW]+5*GA<38 wk + 4* oxytocin used or not + 4 * vacuum delivery + 5*exclusive breastfeeding +4* breast and bottle feeding

[e] Summarized in the previous report (see Appendix F)

[f] Most likely all cases of significant hyperbilirubinemia in Newman 2005 (Study 2) were included in Newman 2005 (Study 1) and Newman 2000

Table 3. Summary of Studies That Used Early TSB to Predict Late High TSB

Author, Year Country (single/multi center)	Design	N_E (N_A)	Birth weight (g), gestational age (wk)	Early TSB		Late TSB		Verification bias	Quality
				Timing (h)	Cutoff	Timing (h)	Cutoff		
Keren, 2005 USA (single center)	Retrospective cohort[g]	996 (899)	≥2000, ≥36 ≥2500, ≥35	Pre-discharge[h]	%tile 40, 75, 95	Post-discharge[h]	%tile 95	No	B
Newman, 2005 - Study 2 USA (multi center)	Retrospective cohort[e]	5711 (5706)	>2000, >36	<48	%tile 40, 75, 95	≥48	>20 mg/dL[f]	No	B
Sarici, 2004 Turkey (Single center)	Prospective cohort	366 (146)[b]	ND, 35 to 42	6 and 30	%tile 5, 30, 60, 95	150[c]	%tile 95[d]	No	B
Agarwal, 2002 India (single center)	Prospective cohort	220 (213)	ND, ≥35	24	6mg/dL [≅%tile 75]	72 (ND)	%tile 95	Yes[a]	C

%tile=percentile(s) in the Bhutani nomogram; h=hours; N_A/N_E=Number analyzed/enrolled; TSB=total serum bilirubin; wk=weeks

[a] Late TSB was measured only among those with ">10mg/dL" (unclear how this was deduced); 69% of infants were verified

[b] 146 near-term and 219 term infants were analyzed, i.e., 365 infants total; however only near-term infants were analyzed (not stated why)

[c] 4 measurements were taken on 4 days; last was on day 7, at 150 h of life

[d] In any measurement during the first week

[e] The paper by Newman 2005 describes a retrospective cohort (shown here) and a nested case-control study

[f] This is above the 95th hour-specific percentile

[g] These infants were included in the Bhutani et al. publication that reports the nomogram for hour-specific TSB values

[h] If there were no post-discharge measurements, the latest pre-discharge measurement was used provided it was after 40 h (n=213); if there were no post-discharge measurements, the earliest post-discharge was used, provided it was <72 h (n=96)

Table 4. Summary of Studies That Used TcB to Identify Infants With TSB Suggesting Phototherapy

Author, Year Country (single/ multi center)	Design	N_E (N_A)	Birth weight (g), gestational age (wk)	Time of measure-ment	TcB				TSB level suggesting photoRx	Verifi-cation bias	Quality
					Device	Site	Cutoff	Δt from TSB			
Ho, 2006 Hong Kong-China (single center)	Retro-spective cohort	1621[a] (997)	ND; >35	Within first 3 days[b]	JM-103[c]	Mid-sternum	%tile 75, 95	30 min	3 different cutoffs [high-, medium-, & low- risk infants][d]	No	C
Sanpavat, 2005 Thailand (single center)	Unclear if pro-spective or not	392 (392)	≥2000; ≥37	ND	Bilicheck[f]	Fore-head	%tile 10, 25, 50, 75, 85, 90, 95	ND	• 25-48h: ≥10 mg/dL • 49-72h: ≥13 mg/dL • >72h ≥15 mg/dL	Yes[g]	C

%tile=percentile(s) in the Bhutani nomogram; Δt=time interval between the two measurements; N_A/N_E=Number analyzed/enrolled; ND=no data; PhotoRx=phototherapy; TcB=transcutaneous bilirubin; TSB=total serum bilirubin; wk=weeks

[a] 1621 term or near-term infants fulfilled eligibility criteria and had TcB measurements above the 40th hour-specific percentile. However, only 997 had paired measurements with TSB

[b] 97% of measurements obtained within the first 3 days of life

[c] Minolta Airshields

[d] Low risk infants: gestational age ≥38 wk and well; medium risk infants: ≥38 wk with risk factors or 35-37 6/7 wk and well; high risk infants 35-37 6/7 wk with risk factors

[e] Because only children with TcB measurement above the 40th hour-specific percentile who had paired measurements were actually analyzed in the study

[f] SpecRx Inc

[g] Only 39% (n=154) of infants received TSB measurements (unclear how these were selected –"jaundice")

Table 5. Outcomes Associated With the Implementation of TcB Screening and the Use of Hour-specific Bilirubin Nomogram in Term and Near-term Infants

Author, Year Country Hospital	Phases of Hyperbili Screening	Years	N	PhotoRx (%)	Exchange Transfusion	Mean LOS (days)	Readmission for Hyperbili /PhotoRx (per 1000 discharges)	Quality
Bhutani, 2006	Universal TSB (pre-nomogram)	1993-1995	7,929	4.5%	6 (1:1,322)	-	14	C
US	Universal TSB with nomogram	1996-1998	8,186	5.4%	5 (1:1,637)	-	11	
Pennsylvania Hospital	Systems-based approach (TSB/TcB+ nomogram)	1999-2000	6,395	2.5%	2 (1:3,198)	-	5.5	
Eggert, 2006	Before universal TSB/TcB (with modified nomogram)	March 1, 2001 to Dec 31, 2002	48,798	-	0	-	5.5	C
US								
Intermountain Health Care, Salt Lake City, Utah	After universal TSB/TcB (with modified nomogram)	Jan 1, 2003 to Dec 31, 2004	52,483	-	0	-	4.3	
Petersen, 2005	Before TcB (with nomogram)	Aug 2002 to March 2003	405 births per mo	5.9% per mo	-	2.2	4.5	C
US								
University of Texas Medical Branch	After TcB (with nomogram)	May 2003 to Dec 2003	421 births per mo	7.7% per mo	-	2.1	1.8	

Hyperbili=hyperbilirubinemia; PhotoRx=phototheray; LOS=length of stay; TSB=total serum bilirubin; TcB=transcutaneous bilirubin; mo=month

Table 6. Adverse or Other Effects Reported in Phototherapy Studies on Term Infants

Study year country	Intervention (N) vs. Control (N)	Dose (time under phototherapy)	Adverse or other effects reported
Randomized studies			
Djokomuljanto 2006 Malyasia	phototherapy with white curtain (n=51) vs. without white curtain (n=49)	Median duration of phototherapy: with white curtain: 12 h; Without white curtain: 34 h	No hypo or hyperthermia; no significant weight loss; no skin or gastrointestinal problems; no detectable abnormalities on neurological exam before discharge
Nuntnarumit 2002 Thailand	single vs. double phototherapy	Single phototherapy: 43.7 h ±17.5; Double phototherapy: 34.9 h ±12.6	1X / 2X / P: wt↓ (%/d) 1.2±0.8 / 1.7±1.3 / 0.25; Stooling (times/d) 2.2±17.5 / 2.8±1.7 / 0.10; Temp >38º C 12.5% / 7.4% / 0.65
Sarici 2001 Turkey	fiberoptic (n=50) vs. conventional phototherapy (n=50)	Conventional 49.4 h ±14.4; Fiberoptic 61 h ±13.1	1 in each group had transient erythema; 3 in each group had mild watery stool; no other complications noted
Seidman 2003 Israel	Open randomized study:Conventional phototherapy (n=57); LED blue (n=25); LED blue-green (n=22)	Conventional 35.4 h (29.8-41.0); LED blue 31.6 h (23.1-40.0); LED blue-green 39.2 h (30.0-48.4)	No adverse or other effects (e.g., erythema) were noted.
Turan 2004 Turkey (1º aim was to compare NO and vascular endothelial growth factor)	phototherapy 15 cm away (15-18 μW/cm^2 /nm) (n=29) vs. 30-45 cm away (10-12 μW/ cm^2/nm) (n=32)	ND	15 cm / 30-45 cm: Baseline temperature 36.43±0.21 / 36.49±0.34; Temperature at 6th h phototherapy 36.70±0.25* / 36.82±0.26*; Baseline heart rate 140.96±13.28 / 142.06±12.21; Heart rate at 6th h phototherapy 146.75±8.14* / 144.62±9.60; Baseline mean blood pressure 61.03±11.29 / 60.12±7.61; Mean blood pressure at 6th h phototherapy 57.65±8.46 / 55.50±8.07*; *P comparing baseline with 6th h:<0.05; All other comparisons:NS

<table>
<tr><td colspan="4">Comparative studies</td></tr>
<tr><td>Bader 2006
Israel</td><td>10 infants evaluated before vs. during phototherapy: cardio-respiratory activity using polysomnography (PSG)</td><td>ND</td><td>
<table>
<tr><th></th><th>Before phototherapy</th><th>During phototherapy</th><th>P</th></tr>
<tr><td colspan="4">Active sleep</td></tr>
<tr><td>Respiratory Rate</td><td>54.3 ± 10.3</td><td>49.1 ± 10.8</td><td><0.05</td></tr>
<tr><td>Heart Rate</td><td>125.9 ± 11.7</td><td>129.7 ± 15.3</td><td><0.05</td></tr>
<tr><td colspan="4">Quiet sleep</td></tr>
<tr><td>Respiratory Rate</td><td>46.0 ± 9.9</td><td>45.7 ± 12.0</td><td>NS</td></tr>
<tr><td>Heart Rate</td><td>123.1 ± 12.5</td><td>127.7 ± 14.4</td><td>NS</td></tr>
<tr><td colspan="4">Mean ratio of breath depth before/after apnea (active sleep)</td></tr>
<tr><td></td><td>1.1 ± 0.2</td><td>1.3 ± 0.3</td><td><0.02</td></tr>
</table>
6 infants had apnea in and out of phototherapy. There was a trend in increase in central apnea duration while under phototherapy (P=0.07). An increased heart rate under phototherapy as compared to no phototherapy (P<0.02) was also noted.</td></tr>
<tr><td>Maitchard 2006
France

Comparative (retrospective collection of phototherapy exposure); subjects were examined for melanocytic nevi</td><td>Group 1 (n=18): received blue light phototherapy during the first few days

Control (n=40): no phototherapy

Excluded children with rarely to never burn skin (Fitzpatrick IV to VI)</td><td>“Results not shown”</td><td>Univariate analysis:
• Mean number of nevi ≥2 mm : 3.5/child (SD 3.05) in phototherapy vs. 1.45/child (SD 1.99) in no phototherapy (P=0.02)
• Mean number of nevi 2-5 mm : 3.17/child (SD 2.67) in phototherapy vs. 1.23/child (SD 1.49) in no phototherapy (P=0.008)
• Association between phototherapy and nevus count for nevi <2mm or >5mm was not significant
Multivariate analysis:
An association between phototherapy and nevi sizes (2-5 mm, P<0.001; ≥ 2 mm, P=0.003) after adjusting for all other risk factors in the model (phototherapy, age, skin type I or II, color of skin, eye, and hair, freckles, sun exposure during vacation, and severe sunburn)</td></tr>
</table>

<table>
<tr><td>Zainab 2004
Malaysia</td><td>Home (n=18) vs. hospital (n=18) phototherapy</td><td>Home: 1.17 d ± 0.73;
Hospital: 1.72 d ± 0.73</td><td><table><tr><td></td><td>home</td><td>hospital</td></tr><tr><td>No complications</td><td>78%</td><td>78%</td></tr><tr><td>rash</td><td>5.5%</td><td>11%</td></tr><tr><td>hyperthermia</td><td>0</td><td>0</td></tr><tr><td>Diarrhea >5x</td><td>16.7%</td><td>11%</td></tr></table>Differences between groups: NS</td></tr>
<tr><td colspan="4">Cohort analysis of an RCT</td></tr>
<tr><td>Boo 2006
Singapore</td><td>Healthy term infants who need phototherapy</td><td>2 h</td><td>After 2 h of phototherapy:
2/81 (2.5%) infants with initial core temperature of 36.5-37.5º decreased to <36.5º C;
29/81 (36%) infants with initial core temperature of 36.5-37.5º increased to >37.5º C</td></tr>
</table>

Appendix A. MEDLINE® Search Strategy

Human and Animal Search
1996 to August Week 1 2007

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1 exp Hyperbilirubinemia/ (3156)
2 exp Hyperbilirubinemia, Hereditary/ (463)
3 exp Bilirubin/ (3958)
4 exp Jaundice, Neonatal/ (936)
5 exp Kernicterus/ (213)
6 (bilirubin or hyperbilirubin$).tw. (8617)
7 kernicterus.tw. (225)
8 jaundice.tw. (6056)
9 exp Hyperbilirubinemia, Neonatal/ (1023)
10 neonat$.tw. (60251)
11 1 or 2 or 3 or 6 or 7 or 8 (15348)
12 limit 11 to newborn infant <birth to 1 month> (2104)
13 (6 or 8) and 10 (1411)
14 4 or 5 or 9 or 12 or 13 (2473)
15 limit 14 to human (2402)
16 limit 15 to english language (2105)
17 "20010925".em. (0)
18 "20010926".em. (0)
19 "20010927".em. (10624)
20 "20010928".em. (0)
21 "20010929".em. (0)
22 "20010930".em. (0)
23 20011$.em. (120344)
24 2002$.em. (507152)
25 2003$.em. (531876)
26 2004$.em. (584306)
27 2005$.em. (595731)
28 2006$.em. (633204)
29 2007$.em. (407921)
30 or/17-29 (3391158)
31 16 and 30 (1251)
32 limit 31 to (guideline or meta analysis or practice guideline or "review") (194)
33 31 not 32 (1057)
34 limit 33 to (addresses or bibliography or biography or case reports or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) (322)
35 33 not 34 (735)
36 limit 35 to yr="2007" (46)
37 from 36 keep 1-46 (46)

Appendix B. Data Abstraction Form

Evidence Table Template, General

Author, year [UI#]

Study characteristics	Study design and follow-up duration	Inclusion/ Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth years: # Enrolled: # Evaluated: Mean GA (range): wks Mean BW (range): g % Male: Race: Mean Apgar (5 min): Country: Sites: Single/Multi Funding:				

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments

A: strong, B: moderate, C: weak	A	B	C
Selection			
Study design			
Confounder			
Blinding			
Data collection			
Withdraw and dropout			
Analyses			
Intervention integrity			

Evidence Table Template, Key Question 3

Author, year [UI#]

Study characteristics	Inclusion / Exclusion Criteria	Population description	Test Protocol	Reference Standard	Definition of Positives
Birth years: # Enrolled: # Analyzed: Mean GA (range): wks Mean BW (range): g % Male: Race: Mean Apgar (5 min): Country: Sites: Single/Multi Design: Prospective/ Retrospective Funding:	**Inclusion:** **Exclusion:**	**Setting:** **Patient selection process:**[A]	**Device:** **Tested sites:** **Timing vs Reference Test:** **Time of measurements:** **Number of measurements:**	**Device:** **Tested sites:** **Time of measurements:** **Number of measurements:**[B]	**Definition of positive Reference Test:** **Definition of positive Index Test:**

[A] consecutive /random sampling from general population /prescreening based on selection criteria (describe)
[B] Implies times the probe was applied on the baby – not how many readings the machine takes each time

Results (Concordance metrics)

Study	Comparison	Metric	Results	Comments

Results (Sensitivity, specificity, and ROC analysis)

Study	Comparison	Index cutoff	Reference Cutoff	TP	FN	FP	TN	Sens	Spec	AUC-ROC	Comments

Other results:

Quality Items

Quality item		Comments
Consecutive patients or random sampling Prospective study No verification bias Index test assessor blinded to Reference Test[A] Index test assessor blinded to clinical Hx or other information (such as any lab values) Reference test assessor blinded to clinical Hx or other information (such as any lab values) Proper analysis of replicate measurements in different times Random order of test measurements Time delay between index and reference test measurements Adequate description of index test[B] Adequate description of reference test[B]		
Overall Quality Grade (A to C)		

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Evidence Table Template, Key Question 6

Author, year [UI#]

Study characteristics	Study design and follow-up duration	Inclusion/Exclusion Criteria/ Comorbidities/modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Adverse events, side effects
Birth years: # Enrolled: # Evaluated: Mean GA: wks Mean BW: g % Male: Race: Country: Sites: Single/Multi Funding:					

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Agarwal, 2002 [UI#12196683]

Study characteristics	Inclusion / Exclusion Criteria	Population description	Test Protocol	Reference Standard	Definition of Positives
Birth yrs: May to September 2001 # Enrolled: 220 # Analyzed: 213 Mean GA (range): 38 (35-42) Mean BW (range): 2827 g %Male: 54% Race: Asian Mean Apgar (5 min): ND Comorbidity: ABO incompatibility (n=1); G6PD (n-3) Location: India Sites: Single Design: Prospective Funding: ND	**Inclusion:** GA ≥35 wks, absence of significant illness requiring NICU admission for >12 hr, absence of major congenital malformations; residing near the hospital and whose parents agreed to come for follow-up All infants were discharged as per unit policy after 72 hr **Exclusion:** NICU admission; Rh hemolysis	**Setting:** Healthy babies, GA ≥35 wks; residing near the hospital **Patient selection process:**[A] Selected, based on the convenience	**Device:** Spectrophotometrer (Bil Micrometer – Auto 2 Type, Kohsoku Denki, Tokyo Japan) **Tested sites:** Venous whole blood **Timing vs Reference Test:** ND **Time of measurements:** 24 ±6 hr (range 20-30 hr) after birth, pre-discharge **Number of measurements:** Triplicate, and average of two closest values was taken	**Device:** Same as test device **Tested sites:** Venous whole blood **Time of measurements:** After discharge at 72 hr **Number of measurements:**[B] Triplicate, and average of two closest values was taken	**Definition of positive Reference Test:** TSB ≥17 mg/dL at 72 hr Only perform post-discharge serum bilirubin if clinical estimation of serum bilirubin >10 mg/dL (unclear how this estimation was done). Clinically detectable jaundice was present in 146 (69%) infants **Definition of positive Index Test:** TSB >6 mg/dL

[A] consecutive /random sampling from general population /prescreening based on selection criteria (describe)
[B] Implies times the probe was applied on the baby – not how many readings the machine takes each time

Results (Concordance metrics): No data

Study	Comparison	Metric	Results	Comments

Results (Sensitivity, specificity and ROC analysis):

Study	Comparison	Index cutoff	Reference Cutoff	TP	FN	FP	TN	Sens	Spec	AUC-ROC	Comments
Agarwal, 2002	Pre-discharge TSB vs. post-discharge TSB	>6 mg/dL	≥17 mg/dL @ 72 hr	21	1	56	135	95%	70.6%	ND	≥17 mg/dL @ 72 hr is ≥95 %tile on Bhutani's nomogram
Agarwal, 2002	Bhutani risk zone vs. post-discharge TSB	≥Bhutani high intermediate or high-risk zone	≥17 mg/dL @ 72 hr	20	2	50	141	91%	73.8%	ND	≥17 mg/dL @ 72 hr is ≥95 %tile on Bhutani's nomogram

Other results:

143 (67%) infants were in the low risk or low intermediate risk zone classified according to Bhutani's nomogram. In other word, 70 infants were classified as in the high intermediate or high-risk zone. Subsequently hyperbilirubinemia developed in 20/70 (28.6%) of these infants. This also means that 2 (14%) of the 143 infants in the low risk or low intermediate risk zone developed hyperbilirubinemia.

Quality items:

Quality item		Comments
Consecutive patients or random sampling	No	
Prospective study	Yes	
No verification bias	No	69% infants had post-discharged serum bilirubin measurements
Index test assessor blinded to Reference Test[A]	Yes	
Index test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Reference test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Proper analysis of replicate measurements in different times	N/A	
Random order of test measurements	N/A	
Time delay between index and reference test measurements	N/A	
Adequate description of index test[B]	Yes	
Adequate description of reference test[B]	Yes	
Overall Quality Grade (A to C)	C	31% infants were unverified

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Bader, 2006 UI 16450744

<table>
<tr><th>Study characteristics</th><th>Study design and follow-up duration</th><th>Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors</th><th>Phototherapy procedures</th><th>Dose (time under phototherapy) (hours)</th><th>Adverse events, side effects</th></tr>
<tr>
<td>Birth years: nd
Enrolled: 10
Evaluate: 10
Mean GA: 38.6 wks
Mean BW: 3203 g
%Male: nd
Race: nd
Country: Israel
Sites: Single
Funding:</td>
<td>Before phototherapy vs. during phototherapy study on cardio-respiratory activity using polysomnography (PSG)</td>
<td>Healthy term infants with physiologic (no hemolysis or G6PD) jaundice; >37 wk; Apgar >8, birth weight 2500 – 4000 g; excluded sepsis, anemia, dehydration</td>
<td>Nd

PSG before phototherapy at 3.6±0.8 d
PSG during phototherapy at 4.5±0.8 d</td>
<td>Mean TSB before phototherapy: 14.5±1.4 mg/dL</td>
<td>
<table>
<tr><th></th><th>Before phototherapy</th><th>During phototherapy</th><th>P</th></tr>
<tr><td colspan="4">Active sleep</td></tr>
<tr><td>Respiratory Rate</td><td>54.3 ± 10.3</td><td>49.1 ± 10.8</td><td><0.05</td></tr>
<tr><td>Heart Rate</td><td>125.9 ± 11.7</td><td>129.7 ± 15.3</td><td><0.05</td></tr>
<tr><td colspan="4">Quiet sleep</td></tr>
<tr><td>Respiratory Rate</td><td>46.0 ± 9.9</td><td>45.7 ± 12.0</td><td>NS</td></tr>
<tr><td>Heart Rate</td><td>123.1 ± 12.5</td><td>127.7 ± 14.4</td><td>NS</td></tr>
<tr><td colspan="4">Mean ratio of breath depth before/after apnea (active sleep)</td></tr>
<tr><td></td><td>1.1 ± 0.2</td><td>1.3 ± 0.3</td><td><0.02</td></tr>
</table>
6 infants had apnea in and out of phototherapy, trend towards increase in central apnea duration while under phototherapy (P=0.07), and increased heart rate under phototherapy as compared to no phototherapy (P<0.02).
</td>
</tr>
</table>

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Bhutani, 2006 [UI#16881988]

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth yrs: 1993-1995, 1996-1998, 1999-2000; 2001-2003 birth cohorts # Enrolled: 11,114 (1993-1995), 10,701 (1996-1998), 7,178 (1999-2000), ND (2001-2003) # Evaluate: 7,929 (1993-1995), 8,186 (1996-1998), 6,395 (1999-2000), 11,995 (2001-2003) Mean GA (range): ≥35 wks Mean BW (range): ≥2500 g for GA ≥35 wk, or ≥2000 g for GA ≥36 wk %Male: ND Race: ND Mean Apgar (5 min): ND Country: US Sites: Single Funding: Private	Comparisons of historical birth cohorts in the same urban hospital Note: For the purpose of this review, we focus only on the birth cohort from 1996-1998 (universal TSB screening the post-discharge follow-up as Bhutani's hour-specific bilirubin nomogram was implemented), and on the birth cohort from 1999-2000 (an organized institutional systems-based management of newborn jaundice was implemented).	Term or near-term infants Exclusion criteria: low BW preterm infants admitted to well baby nursery and any infant admitted to and treated in the intensive care nursery for neonatal illness	Universal TSB screening (1993-1995): (a) universal TSB, (b) unfettered nursing access to TSB orders, (c) individualized lactation support Universal TSB screening and postdischarge follow-up as per the hour-specific bilirubin nomogram (1996-1998): Institutional approach consisted of (a) universal TSB, (b) unfettered nursing access to TSB orders, (c) lactation support program, (d) nursing and parent education program for newborn jaundice Systems-based guideline (1999-2000): (a) visual recognition of jaundice, (b) measurement of bilirubin values, (c) lactation and nutrition support, and (d) parent education including the need for follow-up. Well baby care was provided by >18 practicing pediatricians, several pediatric nurse practitioners, and home care nursing agencies. All babies were recommended for jaundice follow-up within 24 or 48 hrs. This is a framework rather than a rigid rule that allowed for individual physician practice variations. Data on clinical and demographic risk factors for hyperbilirubinemia were recorded pre-discharge. Interventions with PhotoRx followed AAP (1994) guideline. Home-based PhotoRx was used on an occasional basis (<15%) by a small group of physicians.	1993-1995 (universal TSB screening without nomogram) 1996-1998 (universal TSB screening with nomogram) 1999-2000 (systems-based approach) 2001-2003 (established program, follow-up)

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Use of intensive PhotoRx

Use of exchange transfusion</td>
<td>No statistical testing

Frequencies only</td>
<td>
• Use of intensive PhotoRx and exchange transfusion:
<table>
<tr><th>Phases</th><th>Years</th><th>Well Baby Discharges (N)</th><th>Hospital-based Intensive PhotoRx (%)</th><th>Exchange Transfusion</th></tr>
<tr><td>Universal TSB (pre-nomogram)</td><td>1993-1995</td><td>7,929</td><td>356 (4.5%)</td><td>6 (1:1,322)</td></tr>
<tr><td>Universal TSB with nomogram</td><td>1996-1998</td><td>8,186</td><td>446 (5.4%)</td><td>5 (1:1,637)</td></tr>
<tr><td>Systems-based approach</td><td>1999-2000</td><td>6,395</td><td>159 (2.5%)</td><td>2 (1:3,198)</td></tr>
<tr><td>Established program</td><td>2001-2003</td><td>11,995</td><td>156 (1.3%)</td><td>1 (1:11,995)</td></tr>
</table>
Precise data for home PhotoRx administration were not available. However, the usage and prescriptions for home PhotoRx by hime nursing agencies were not increased during 1995 to 2000.
There was no effort to promote home PhotoRx and the behavior of practice pediatricians appeared unchanged.

• During the nomogram development phase and the initiation of a systems-based program, a steady and significant decline in readmission was noted from 14 (in 1994) to 5.5 infants per 1000 well babies discharged in 2001 to 2003.
</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td></td><td></td><td>x</td></tr>
<tr><td>Confounder</td><td></td><td>x</td><td></td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td></td><td>x</td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td></td><td></td><td>x</td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td>x</td></tr>
</table>
Overall: C

Unclear when and how the clinical and demographic risk factors for hyperbilirubinemia were used in management of jaundice; Unclear whether TcB measurements were used and how often they were used in systems-based approach.
Author stated that “the behavior of practice pediatricians appeared unchanged” but not sure how this “appearance” was observed.
</td>
</tr>
</table>

Boo, 2006 UI 16924356

Study characteristics	Study design and follow-up duration	Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Adverse events, side effects
Birth years: 2005 # Enrolled: 106 # Evaluate: 106 Mean GA: 38.8 wks Mean BW: 3042 g %Male: 57% Race: Asian Country: Singapore Sites: Single Funding:	RCT of clingfilm vs. no clingfilm with X-over; only data from the no clingfilm arm were extracted	Healthy term infants who needs phototherapy; eligible infants with severe hyperbilirubinemia recruited only after TSB decreased to <17.5 mg/dL	No clothing except for diaper; phototherapy light panel (Madela, Switzerland) 25 cm above infant	2 h	2/81 (2.5%) infants with initial core temperature of 36.5-37.5º decreased to <36.5º C after 2 h of phototherapy; 29/81 (36%) infants with initial core temperature of 36.5-37.5º increased to >37.5º C after 2 h of phototherapy

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Djokomuljanto, 2006 U 16877479

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Adverse events, side effects
Birth year: 2005 # Enrolled: 100 # Evaluate: 97 Mean GA: wks Mean BW: 3040g %Male: 56% Race: Country: Malaysia Sites: Single Funding:	RCT, subjects were enrolled based on the convenience of the main investigator (when he was working or on call); phototherapy with white curtain (n=51) vs. phototherapy without white curtain (n=49); followup 24 h after stopping phototherapy	Uncomplicated hyperbilirubinemia requiring only single phototherapy; included subjects with G6PD↓ and ABO incompatibility; excluded patients with TSB close to exchange transfusion criteria; all breastfeeding; subjects who were not rooming-in received formula at night	TSB at start of phototherapy: 15.4 mg/dL	Median duration of phototherapy: with white curtain: 12 h; Without white curtain: 34 h	No hypo or hyperthermia; no significant weight loss; no skin or gastrointestinal problems; no detectable abnormalities on neurological exam before discharge

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Eggert, 2006 [UI#16651290]

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth yrs: March 1, 2001 to December 31, 2002 (pre universal TSB/TcB screening); January 1, 2003 to December 31, 2004 (post universal TSB/TcB screening) # Enrolled: ND # Evaluate: 48,798 (March 1, 2001 to December 31, 2002); 52,483 (January 1, 2003 to December 31, 2004) Mean GA (range): ≥35 wks Mean BW (range): ND %Male: ND Race: ND Mean Apgar (5 min): ND Country: US Sites: Multi Funding: ND	Historic cohorts	All infants delivered at ≥35 weeks's gestation, within the 18-hospital system during 2 periods of time: March 1, 2001 to December 31, 2002, and January 1, 2003 to December 31, 2004	A bilirubin screening program, instituted in December 2002, called for a TSB or TcB bilirubin measurement to be performed on every infant, either at the recognition of clinical jaundice or before discharge, regardless whether jaundice was observed. Two (out of 18) hospitals used a screening jaundice meter for TcB estmation of bilirubin levels (BiliCheck). Modified Bhutani's hour-specific bilirubin nomogram was used because high number of infants had bilirubin values in the intermediate- and high-risk zones of the Bhutani's nomogram. If ≥40 %tile, the care provider was notified and intervention, evaluation, and follow-up was arranged as deemed necessary.	Post universal TSB/TcB screening vs. pre universal TSB/TcB screening

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Readmissions for hyperbilirubinemia: taking the birth cohort of patients at ≥35 weeks's gestation seen in the well nursery and then querying case mix for any admission with a matching Master Patient Index number and a diagnosis of jaundice.</td>
<td>Chi-square test</td>
<td>
• The incidence of severe hyperbilirubinemia among infants ≥35 weeks's gestation
<table>
<tr><th></th><th>No. of Infants</th><th>TSB, mg/dL ≥20</th><th>≥25</th><th>≥30</th></tr>
<tr><td>March 1, 2001 to Dec 31, 2002</td><td>48,798</td><td>1:77</td><td>1:1522</td><td>1:9742</td></tr>
<tr><td>Jan 1, 2003 to Dec 31, 2004</td><td>52,483</td><td>1:142</td><td>1:4037</td><td>1:17494</td></tr>
<tr><td></td><td>P-value</td><td><.0001</td><td><.005</td><td>.24</td></tr>
</table>
• The incidence of hospital readmission for hyperbilirubinemia
<table>
<tr><th></th><th>No. of Infants</th><th>No. Readmitted (%)</th></tr>
<tr><td>March 1, 2001 to Dec 31, 2002</td><td>48,798</td><td>268 (0.55)</td></tr>
<tr><td>Jan 1, 2003 to Dec 31, 2004</td><td>52,483</td><td>226 (0.43)</td></tr>
<tr><td>P-value</td><td></td><td><.005</td></tr>
</table>
• 13 infants developed extreme hyperbilirubinemia (≥25 mg/dL). Age at discharged ranged from 23 to 48 hours. Age at readmission ranged from 3 to 11 days. Peak TSB ranged from 25.1 to 36.7 mg/dL. Two had hemolysis and one had sepsis. All treated by PhotoRx, but none underwent exchange transfusion. None had abnormal signs of brainstem auditory evoked response.
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>x</td><td></td></tr>
<tr><td>Study design</td><td></td><td></td><td>x</td></tr>
<tr><td>Confounder</td><td></td><td></td><td>x</td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td>x</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td></td><td>x</td><td></td></tr>
<tr><td>Analyses</td><td></td><td></td><td>x</td></tr>
<tr><td>Intervention integrity</td><td></td><td>x</td><td></td></tr>
</table>
Overall: C

Did not control for potential confounding
</td>
</tr>
</table>

Ho, 2006 [UI#16849367]

Study characteristics	Inclusion / Exclusion Criteria	Population description	Test Protocol	Reference Standard	Definition of Positives
Birth yrs: April to September 2005 # Enrolled: 1,621 # Analyzed: 997 Mean GA (range): 39 (35-42) wks Mean BW (range): ND %Male: ND Race: 95.2% Chinese Mean Apgar (5 min): ND Country: Hong Kong Sites: Single Design: Retrospective Funding: ND	**Inclusion:** Healthy term or near-term newborns with a GA of >35 wks Paired TSB was measured if the TcB was >40th %tile on Bhutani monogram **Exclusion:** Sick newborns who required admission to special care baby or neonatal ICU Infants received PhotoRx	**Setting:** Healthy term or near-term newborns with a GA of >35 wks, with TcB was >40th %tile **Patient selection process:**[A] Selected, based on pre-screening	**Device:** JM-103 Minolta Airshields **Tested sites:** mid-sternum **Timing vs Reference Test:** 30 min **Time of measurements:** 97% were taken within the first 3 days of life (median age = 32.9 hrs, ranged 12.1-139.6 hr) **Number of measurements:** 1	**Device:** Photometric analyser **Tested sites:** blood **Time of measurements:** Within 30 min if the initial TcB level was >40th %tile **Number of measurements:**[B] 1	**Definition of positive Reference Test:** AAP low risk for PhotoRx AAP medium risk for PhotoRx AAP high risk for PhotoRx **Definition of positive Index Test:** >75 %tile by TcB >95th %tile by TcB

[A] consecutive /random sampling from general population /prescreening based on selection criteria (describe)
[B] Implies times the probe was applied on the baby – not how many readings the machine takes each time

Results (Concordance metrics):

Study	Comparison	Metric	Results	Comments
Ho, 2006	TcB vs. TSB	Bland and Altman LOA	• Mean difference = 21.7 µmol/l (SD 21.2, p<0.001) • 95% limits of agreement: -19.9 to 63.3 µmol/l • The range of difference increased in patient with TSB level >200 µmol/l	

Results (Sensitivity, specificity and ROC analysis):

Study	Comparison	Index cutoff	Reference Cutoff	TP	FN	FP	TN	Sens	Spec	AUC-ROC	Comments
Ho, 2006	TcB vs. AAP Low risk	>40th %tile	AAP Low risk	Improper analysis	Improper analysis	Improper analysis	Improper analysis	Improper analysis	Improper analysis		Because they have the used 40%tile as inclusion criterion, and to decide when to take TSB measurements, these analyses are improper.
Ho, 2006	TcB vs. AAP Medium risk	>40th %tile	AAP Medium risk	Improper analysis	Improper analysis	Improper analysis	Improper analysis	Improper analysis	Improper analysis		
Ho, 2006	TcB vs. AAP High risk	>40th %tile	AAP High risk	Improper analysis	Improper analysis	Improper analysis	Improper analysis	Improper analysis	Improper analysis		
Ho, 2006	TcB vs. AAP Low risk	>75th %tile	AAP Low risk	1	0	441	555	100	55.7		
Ho, 2006	TcB vs. AAP Low risk	>95th %tile	AAP Low risk	1	0	96	900	100	90.4		
Ho, 2006	TcB vs. AAP Medium risk	>75th %tile	AAP Medium risk	8	0	434	555	100	56.1		
Ho, 2006	TcB vs. AAP Medium risk	>95th %tile	AAP Medium risk	6	2	92	897	75	90.7		
Ho, 2006	TcB vs. AAP High risk	>75th %tile	AAP High Risk	52	8	390	547	86.7	58.4		
Ho, 2006	TcB vs. AAP High risk	>95th %tile	AAP High Risk	27	33	70	867	45	92.7		

Quality items:

Quality item		Comments
Consecutive patients or random sampling	No	
Prospective study	No	
No verification bias	Yes	They included only infants with paired measurements; Technically they have no verification bias if one disregards the 40th %tile for the index test (TcB). However, see general comment below.
Index test assessor blinded to Reference Test[A]	Yes	
Index test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Reference test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Proper analysis of replicate measurements in different times	N/A	
Random order of test measurements	N/A	
Time delay between index and reference test measurements		
Adequate description of index test[B]	Yes	
Adequate description of reference test[B]	Yes	
Overall Quality Grade (A to C)	C	Spectrum effects make the sensitivity and specificity difficult to interpret. This study focused on 1) children with TcB >40%tile (n=1621); 2) among them, those with paired measurements (997/1621 with TcB >40%tile). Moreover, the authors did improper analyses – see comment on results section

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Keren, 2005 [UI#15781937]

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth yrs: 1993-1997 # Enrolled: 996 # Evaluate: 899 Mean GA (range): 20% <38 wks, 55% 38-39 wks; 25% ≥ 40 wks Mean BW (range): 3,300 g %Male: 52% Race: 43% White, 39% Black, 4% Hispanic, 8% Asian; 5% Other Mean Apgar (5 min): ND Location: US Sites: Single Funding: Government	Retrospective cohort study	BW ≥2000 g if GA ≥36 weeks; BW ≥2500 g if GA ≥35 weeks Infants who participated in the hospital's early discharge follow-up program (n=2,976), which was offered to all mothers discharged within 48 hours after vaginal deliveries or 72 hours after caesarean sections who could not have their infant seen by a provider within a day or two; Coombs negative Infants with both pre- and post-discharge TSBs measured in the study period (n=899) Exclusion: PhotoRx during the birth hospitalization (n=18), treated in the intensive care nursery for nay period of time prior to discharge (n=118)	Hospital-supervised early discharge follow-up program for healthy term or near-term infants As part of the early discharge follow-up program, an effort was made to obtain TSB levels in the hospital for all infants prior to discharge and on follow up. In 199-94, most infants had pre-discharge TSBs but only about 40% had both pre-and post-discharge TSBs. In 1995-97, more than 75% of all infants in the program had both TSB measurements. No PhotoRx during birth hospitalization	Not applicable

Keren, 2005 [UI#15781937] - Q2 Results

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Significant hyperbilirubinemia: post-discharge TSB >95th centile on Bhutani hour specific bilirubin nomogram (nearly identical to the PhotoRx threshold curve recommended for “medium risk” infants in the AAP’s 2004 clinical practice guideline</td>
<td>
Clinical risk factor score:
<table>
<tr><th></th><th>Score</th></tr>
<tr><td>BW (g)–</td><td></td></tr>
<tr><td>2000-2500</td><td>0</td></tr>
<tr><td>2501-3000</td><td>3</td></tr>
<tr><td>3001-3500</td><td>6</td></tr>
<tr><td>3501-4000</td><td>9</td></tr>
<tr><td>4001-4500</td><td>12</td></tr>
<tr><td>4501-5000</td><td>15</td></tr>
<tr><td>GA <38 wk</td><td>5</td></tr>
<tr><td>Oxytocin</td><td>4</td></tr>
<tr><td>Vacuum delivery</td><td>4</td></tr>
<tr><td>Exclusive BF</td><td>5</td></tr>
<tr><td>Breast and bottle feeding</td><td>4</td></tr>
</table>
Factors associated with the outcome in univariate analyses at the p<0.2 level of significance were considered for inclusion in multivariable logistic regression model. To translate the final logistic regression model into a clinical risk factor score, each infant was assigned points, equal to the sum of the odds ratios (ORs (multiplied by 2 and the rounded down) corresponding to risk factors present for that infant.
</td>
<td>
• Predictive properties of the clinical risk factor score using various cut-off points for a positive test:
<table>
<tr><th>Risk factor score</th><th>Test+ (n)</th><th>Post-discharge TSB >95th centile (n)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>≥0</td><td>884</td><td>97</td><td>1.0 (0.96-1.00)</td><td>0 (0-0)</td></tr>
<tr><td>≥8</td><td>777</td><td>95</td><td>0.98 (0.93-1.00)</td><td>0.13 (0.11-0.16)</td></tr>
<tr><td>≥12</td><td>547</td><td>83</td><td>0.86 (0.77-0.92)</td><td>0.41 (0.38-0.45)</td></tr>
<tr><td>≥16</td><td>244</td><td>52</td><td>0.54 (0.43-0.64)</td><td>0.76 (0.72-0.79)</td></tr>
<tr><td>≥20</td><td>86</td><td>21</td><td>0.22 (0.14-0.31)</td><td>0.92 (0.90-0.94)</td></tr>
<tr><td>≥24</td><td>7</td><td>2</td><td>0.02 (0-0.07)</td><td>0.99 (0.99-1.00)</td></tr>
</table>
• Likelihood ratios (LR) and post-test probabilities (PTP) for specific clinical risk score levels:
<table>
<tr><th>Risk score</th><th>Post-discharge TSB >95th centile (n)</th><th>Post-discharge TSB ≤95th centile (n)</th><th>LR</th><th>PTP</th></tr>
<tr><td>0-7</td><td>2</td><td>105</td><td>0.15</td><td>0.02</td></tr>
<tr><td>8-11</td><td>12</td><td>218</td><td>0.45</td><td>0.05</td></tr>
<tr><td>12-15</td><td>31</td><td>272</td><td>0.92</td><td>0.10</td></tr>
<tr><td>16-19</td><td>31</td><td>127</td><td>1.98</td><td>0.20</td></tr>
<tr><td>20-23</td><td>19</td><td>60</td><td>2.57</td><td>0.24</td></tr>
<tr><td>≥24</td><td>2</td><td>5</td><td>3.25</td><td>0.29</td></tr>
</table>
Note: 15 infants were missing data on clinical risk factors and therefore could not be assigned a clinical risk factor score
• Area under the ROC curve = 0.71 (95% CI 0.66-0.76)
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td>x</td><td></td><td></td></tr>
<tr><td>Blinding</td><td></td><td>x</td><td></td></tr>
<tr><td>Data collection</td><td>x</td><td></td><td></td></tr>
<tr><td>Withdraw and dropout</td><td>x</td><td></td><td></td></tr>
<tr><td>Analyses</td><td>x</td><td></td><td></td></tr>
<tr><td>Intervention integrity</td><td>x</td><td></td><td></td></tr>
</table>
Overall: B*
Did not assess the predictability of the risk score in an independent sample

*This quality grading is for Keren, 2005 - Q2 Results only
</td>
</tr>
</table>

Keren, 2005 [UI#15781937] – Q3 Results

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th></tr>
<tr>
<td>Significant hyperbilirubinemia: post-discharge TSB >95th centile on Bhutani hour specific bilirubin nomogram (nearly identical to the PhotoRx threshold curve recommended for “medium risk” infants in the AAP’s 2004 clinical practice guideline</td>
<td>When more than one pre-discharge TSB, the TSB measurement closet to the time of hospital discharge was selected as the predictor TSB.

To approximate commonly occurring newborn lengths of stay, pre-discharge TSB was reassigned to a post-discharge TSB for 213 (7.5%) infants, and a post-discharge TSB was reassigned to a pre-discharge TSB for 96 (3.4%) infants.</td>
<td>
• Predictive properties of the pre-discharge TSB risk zone using various cut-off points for a positive test:
<table>
<tr><th>Risk zone</th><th>Test+ (n)</th><th>TSB >95th centile (n)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>≥0th</td><td>899</td><td>98</td><td>1.0 (0.96-1.00)</td><td>0 (0-0)</td></tr>
<tr><td>≥40th</td><td>727</td><td>97</td><td>0.99 (0.94-1.00)</td><td>0.21 (0.19-0.24)</td></tr>
<tr><td>≥75th</td><td>329</td><td>87</td><td>0.89 (0.81-0.94)</td><td>0.70 (0.66-0.73)</td></tr>
<tr><td>≥95th</td><td>56</td><td>30</td><td>0.31 (0.22-0.41)</td><td>0.97 (0.95-0.98)</td></tr>
</table>
• Likelihood ratios (LR) and post-test probabilities (PTP) for specific pre-discharge TSB risk zones:
<table>
<tr><th>Pre-discharge TSB %tile</th><th>TSB >95th centile (n)</th><th>TSB ≤95th centile (n)</th><th>LR</th><th>PTP</th></tr>
<tr><td>0-40</td><td>1</td><td>171</td><td>0.05</td><td>0.006</td></tr>
<tr><td>40-75</td><td>10</td><td>388</td><td>0.21</td><td>0.03</td></tr>
<tr><td>75-95</td><td>57</td><td>216</td><td>2.16</td><td>0.21</td></tr>
<tr><td>95-100</td><td>30</td><td>26</td><td>9.43</td><td>0.54</td></tr>
</table>
• Area under the ROC curve = 0.83 (95% CI 0.80-0.86)
</td>
</tr>
</table>

Quality items (for Keren, 2005 – Q3 Results):

Quality item		Comments
Consecutive patients or random sampling	No	Only infants with both pre- and post-discharge TSBs measured were studied
Prospective study	No	
No verification bias	Yes	
Index test assessor blinded to Reference Test[A]	Yes	
Index test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Reference test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Proper analysis of replicate measurements in different times	N/A	
Random order of test measurements	N/A	
Time delay between index and reference test measurements	Yes	When more than one pre-discharge TSB, the TSB measurement closet to the time of hospital discharge was selected as the predictor TSB. To approximate commonly occurring newborn lengths of stay, pre-discharge TSB was reassigned to a post-discharge TSB for 213 (7.5%) infants, and a post-discharge TSB was reassigned to a pre-discharge TSB for 96 (3.4%) infants.
Adequate description of index test[B]	Yes	
Adequate description of reference test[B]	Yes	
Overall Quality Grade (A to C)	B	

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Maitchard, 2006 UI 17178986

Study characteristics	Study design and follow-up duration	Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Outcome Definition
Birth years: 1994-1995 # Enrolled: 58 # Evaluate: 58 Mean GA: nd Mean BW: nd %Male: 48% Race: white Country: France Sites: Single Funding: nd	Comparative (retrospective collection of phototherapy exposure); subjects were examined for melanocytic nevi	Group 1 (n=18): received blue light phototherapy during the first few days Control (n=40): no phototherapy Excluded children with Fitzpatrick IV through VI (rarely to never burns)	nd	"Results not shown"	Melanocytic nevus: a brown to black macule or papule; freckles and café au lait macules were excluded.

Statistical analyses and adjustment for confounders	Results	Bias/limitations Comments
Univariate analysis: t test and median Wilcoxon test Multivariate analysis including phototherapy, age, skin type I or II, color of skin, eye, and hair, freckles, sun exposure during vacation, and severe sunburn	Univariate analysis: • Mean number of nevi ≥2 mm : 3.5/child (SD 3.05) in phototherapy vs. 1.45/child (SD 1.99) in no phototherapy (P=0.02) • Mean number of nevi 2-5 mm : 3.17/child (SD 2.67) in phototherapy vs. 1.23/child (SD 1.49) in no phototherapy (P=0.008) • Association between phototherapy and nevus count for nevi <2mm or >5mm was not significant Multivariate analysis: • An association between phototherapy and nevi sizes (2-5 mm, P<0.001; ≥ 2 mm, P=0.003) after adjusting for all other risk factors in the model	Unclear how the subjects in the phototherapy group were selected Did not control for number of melanocytic nevi in parents

Newman, 2005 [UI#15699303] – Study 1

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth yrs: Jan 1, 1997 to Dec 31, 1998 # Enrolled: 53,997 # Evaluate: 275 Mean GA (range): ≥36 wks Mean BW (range): ≥2000 g %Male: ND Race: ND Mean Apgar (5 min): ND Location: US Sites: Multi Funding: NIH; private	Nested case-control study	Cohort: BW ≥2000 g; GA ≥36 weeks (N=53,997) Cases: infants with a maximum TSB level ≥25 mg/dL in the first 30 days after birth (N=67) Control: randomly sampled from the cohort (N=208)	For the entire cohort (N=53,997): 14,053 (26%) with at least 1 TSB level sent Average length of hospital stay: 45.7 hours Highest recorded TSB level – ≥15 mg/dL: 5,455 (10.1%) ≥20 mg/dL: 1,098 (2.0%) ≥25 mg/dL: 68 (0.13%) Treatment with (inpatient) PhotoRx: 1,455 (2.7%)	Birth year 1995-1996 cohort, in Newman, 2000 (UI# 11074857) previous described See Appendix F

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments
Hyperbilirubinemia: a TSB level ≥25 mg/dL (428 µmol/L) in the first 30 days after birth	Modified risk index for predicting hyperbilirubinemia in infants who do not have early jaundice: Modified risk index = 6 (Exclusive BF at hospital discharge) + 4 (Bruising noted) + 4 (Asian race) + 3 (Cephalohematoma noted) + 3 (Maternal age ≥ 25 y) + 1 (Male sex) –2 (Black race) + 2 (40-GA) Note: The modified risk index is identical to the risk index used in Newman, 2000 except that the item for jaundice in a previous sibling (or family history of jaundice in a newborn) was deleted	• Comparing the original derivation cohort (1995-1996) with the validation cohort (1997-1998): Cohort: Area under the ROC curve (95% CI) 1995-1996: 0.84 (0.79-0.89) 1997-1998: 0.83 (0.77-0.89) P=0.08 for the difference in areas Eliminating the family history variable had little effect on the prediction. The area under the ROC curve for the 1995-1996 cases declined from the previous reported value of 0.84 to 0.83.	A: strong, B: moderate, C: weak — A: ; B: x ; C: Selection — B: x Study design — B: x Confounder — B: x Blinding — B: x Data collection — B: x Withdraw and dropout — B: x Analyses — B: x Intervention integrity Overall: B Some infants received phototherapy No cut-offs of the modified risk index was used

Newman, 2005 [UI#15699303] – Study 2

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth yrs: 1995-1998 # Enrolled: 5,711 # Evaluate: 5,706 Mean GA (range): ≥36 wks Mean BW (range): ≥2000 g %Male: ND Race: ND Mean Apgar (5 min): ND Location: US Sites: Multi Funding: NIH; private	Retrospective cohort	Newborns discharged before 48 hours after birth who had a TSB level measured before 48 hours (n=5711) Exclusion: TSB level ≥20 mg/dL before 48 hours (n=5)	Not described, but this is a combined 1995-1996 (in Newman, 2000 UI# 11074857, see Appendix F) and 1997-1998 birth cohorts (Newman, 2005 – Study 1) so it is assumed same managements of hyperbilirubinemia as previously described	Not applicable

Newman, 2005 [UI#15699303] – Study 2

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations Comments</th></tr>
<tr>
<td>Developed a TSB level of 20 mg/dL (342 µmol/L) or higher at age 48 hours or older</td>
<td>Age-specific %tile was estimated using Bhutani monogram, categorizing gin to 4 %tile groups: <40th, 40th-74th, 75th-94th, and ≥95th %tile
TSB levels was also transformed into age-specific z scores by assuming TSB levels up to the 95th %tile were approximately normally distributed

Partial risk index was use: partial risk index = 4 (Asian race) + 3 (Cephalohematoma noted) + 3 (Maternal age ≥ 25 y) + 1 (Male sex) –2 (Black race) + 2 (40-GA)
Note: The partial risk index did not include breastfeeding or bruising that was included in the modified risk index used in Newman, 2005 [UI#15699303] – Study 1</td>
<td>
• % Developing a TSB ≥20 mg/dL, predicted by TSB %tile groups before 48 hours:
<table>
<tr><th>TSB %tile at <48 hr</th><th>No. of infants</th><th>No. (%) of infants with a TSB of ≥20 mg/dL at age 48 hr or older</th></tr>
<tr><td><40th</td><td>994</td><td>5 (0.50)</td></tr>
<tr><td>40-74.9</td><td>1508</td><td>11 (0.73)</td></tr>
<tr><td>75-94.9</td><td>1780</td><td>58 (3.26)</td></tr>
<tr><td>≥95th</td><td>1424</td><td>196 (13.76)</td></tr>
</table>
• Combination of the partial risk index with early TSB levels enhanced prediction: Within each TSB %tile category, 5- to 15-fold increase in risk of developing a TSB level of 20 mg/dL or higher for those with a partial risk index ≥10 compared with those with a partial risk index <4
For example:
<table>
<tr><th>TSB %tile at <48 hr + Partial risk index</th><th>% of infants with a TSB of ≥20 mg/dL at age ≥48 hr</th></tr>
<tr><td>≥95th + Partial risk index ≥10</td><td>36%</td></tr>
<tr><td>≥95th + Partial risk index <4</td><td>6%</td></tr>
</table>
• The risk of developing a TSB level of 20 mg/dL or higher for a 36-week newborn with an early TSB level at the 75th to 94th %tile was greater than that for a full-term newborn with a TSB level at the 95th %tile or higher
• Area under the ROC curve for prediction of developing a TSB level of 20 mg/dL or higher at age 48 hours or older:
<table>
<tr><th>Prediction method</th><th>Area under the ROC curve (95% CI)</th></tr>
<tr><td>Partial risk index</td><td>0.69 (ND)</td></tr>
<tr><td>TSB %tile category at <48 hr</td><td>0.79 (0.77-0.81)</td></tr>
<tr><td>TSB z score</td><td>0.83 (0.80-0.85)*</td></tr>
<tr><td>TSB z score + Partial risk index</td><td>0.86 (0.84-0.88)**</td></tr>
</table>
*P<0.001, compared with TSB %tile category alone
**P=0.001, compared with TSB z score alone
</td>
<td>
<table>
<tr><th>A: strong, B: moderate, C: weak</th><th>A</th><th>B</th><th>C</th></tr>
<tr><td>Selection</td><td></td><td>x</td><td></td></tr>
<tr><td>Study design</td><td></td><td>x</td><td></td></tr>
<tr><td>Confounder</td><td>x</td><td></td><td></td></tr>
<tr><td>Blinding</td><td></td><td>x</td><td></td></tr>
<tr><td>Data collection</td><td></td><td>x</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td>x</td><td></td><td></td></tr>
<tr><td>Analyses</td><td>x</td><td></td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td></td></tr>
</table>
Overall: B*

* This quality grading is for risk index results only (Q2)

Only infants with TSB measured before 48 hours were selected (potential selection bias)

Some infants received phototherapy, and not sure the TSB measurements were taken before or after phototherapy

Only partial risk index was used
</td>
</tr>
</table>

Quality items (for TSB %tile at <48 hr results only, or Q3) :

Quality item		Comments
Consecutive patients or random sampling	No	
Prospective study	No	
No verification bias	Yes	
Index test assessor blinded to Reference Test[A]	Yes	
Index test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Reference test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Proper analysis of replicate measurements in different times	Unclear	Not described
Random order of test measurements	N/A	
Time delay between index and reference test measurements	Unclear	Not described
Adequate description of index test[B]	Yes	
Adequate description of reference test[B]	Yes	
Overall Quality Grade (A to C)	B	

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Nuntnarumit, 2002 UI 12549790

Study characteristics	Study design and follow-up duration	Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Adverse events, side effects
Birth years: 2001-2002 # Enrolled: 51 # Evaluate: 51 Mean GA: 38.8 wks Mean BW: 3104 g %Male: Race: Asian Country: Thailand Sites: Single Funding: nd	RCT of single vs. double phototherapy	Term newborns, birth weight ≥ 2500 g and GA > 37 wk, need phototherapy per AAP guideline; exclude ventilator support, on phototherapy before enrollment, direct hyperbilirubinemia	Single phototherapy: 3 daylights and 2 blue lights, 38 cm away; double phototherapy: added a lower light of 8 lamps of 20-watt daylight fluorescents, 32 cm away	Single phototherapy: 43.7±17.5 h; Double phototherapy: 34.9±12.6 h	

	1X	2X	P
wt↓ (%/d)	1.2±0.8	1.7±1.3	0.25
Stooling (times/d)	2.2±17.5	2.8±1.7	0.10
Temp >38º C	12.5%	7.4%	0.65

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Petersen, 2005 [UI#15738516]

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria	Managements of Hyperbilirubinemia (or Interventions)	Definitions of the Comparison group(s)
Birth yrs: Aug 2002 to March 2003 (before TcB) and May 2003 to Dec 2003 (after TcB) # Enrolled: 6603 # Analyzed: 6603 Mean GA (range): ND Mean BW (range): ND %Male: 51.3% (before TcB); 53.2% (after TcB) Race: 71.5% Hispanic, 16% Caucasian, 9.8% Afrecan-American; 2.7% Other Mean Apgar (5 min): ND Country: US Sites: Single Funding: ND	Retrospective cohorts (comparison of two historical birth cohorts)	"Normal newborn" (determined by the diagnosis-related group designation) born within the study periods. None of the newborns was treated with home PhotoRx or required exchange transfusion.	TcB testing (BiliCheck; Respironics) was formally initiated in April 2003 The decisions to measure TcB or serum bilirubin and to initiate PhotoRx were determined by the attending physician if clinically significant jaundice was suspected. The decision to start PhotoRx or obtain additional bilirubin measurements was made using the Bhutani nomogram.	Comparing newborns born after TcB introduction (May 2003 to Dec 2003) to those born before TcB used (Aug 2002 to March 2003)

Outcome Definition	Statistical analyses and confounders adjusted	Results	Bias/limitations Comments

<table>
<tr><th>Outcome Definition</th><th>Statistical analyses and confounders adjusted</th><th>Results</th><th>Bias/limitations
Comments</th></tr>
<tr>
<td>Number readmission for hyperbilirubinemia

Number of serum bilirubin testing

Number of newborns received PhotoRx</td>
<td>Wilcoxon rank-sum two sample test</td>
<td>

After initiation of TcB testing, the mean (SD) number of readmission for hyperbilirubinemia decreased from 4.5 (2.8) to 1.8 (1.7) per 1000 Births per month (P=0.044)
The mean number of serum bilirubin per newborn did not change after introduction of TcB testing (1.51 vs. 1.56 serum bili per newborn before vs. after TcB, respectively)
Both the number and proportion of newborns treated by PhotoRx in the nursery increased significantly:

<table>
<tr><th></th><th colspan="2">Newborns treated by PhotoRx [Mean (SD)]</th></tr>
<tr><th>Time frame</th><th>Number per month</th><th>%</th></tr>
<tr><td>Before TcB</td><td>23.6 (5.2)</td><td>5.9 (1.3)</td></tr>
<tr><td>After TcB</td><td>32.1 (3.9)</td><td>7.7 (1.3)</td></tr>
<tr><td>P value</td><td>0.0089</td><td>0.014</td></tr>
</table>
</td>
<td>
<table>
<tr><td>A: strong, B: moderate, C: weak</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Selection</td><td>x</td><td></td><td></td></tr>
<tr><td>Study design</td><td></td><td></td><td>x</td></tr>
<tr><td>Confounder</td><td></td><td></td><td>x</td></tr>
<tr><td>Blinding</td><td></td><td></td><td>x</td></tr>
<tr><td>Data collection</td><td></td><td>x</td><td></td></tr>
<tr><td>Withdraw and dropout</td><td>x</td><td></td><td></td></tr>
<tr><td>Analyses</td><td></td><td>x</td><td></td></tr>
<tr><td>Intervention integrity</td><td></td><td></td><td>x</td></tr>
</table>
Overall: C

Not sure if the same attending physician made decisions in the two study periods. No information on how the physician determined the baby had significant jaundice.
</td>
</tr>
</table>

Sanpavat, 2005 [UI#16536103]

Study characteristics	Inclusion / Exclusion Criteria	Population description	Test Protocol	Reference Standard	Definition of Positives
Birth yrs: Nov. 2003 to May 2004 # Enrolled: 392 # Analyzed: 392 Mean GA (range): 38.6 wks Mean BW (range): ≥2500 g %Male: 52% Race: nd Mean Apgar (5 min): nd Country: Bangkok Sites: Single Design: Unclear Funding: University	**Inclusion:** Infants born by C-section whose birth weight was ≥2500 g and GA ≥37 weeks **Exclusion:** Sick newborns, congenital anomaly, infants of diabetic mothers, infants who had asphyxia, hypothermia, hypoglycemia, polycythemia, concealed hemorrhage, and infants who were discharged before 72 hours of age	**Setting:** Healthy term infants born by C-section **Patient selection process:**[A] Consecutive	**Device:** Bilicheck (SpecRx, Inc, Norcross, GA, USA) **Tested sites:** forehead **Timing vs Reference Test:** nd **Time of measurements:** Every 24 hours until 3-4 days after birth or until jaundice, determined by TSB, was severe enough to require PhotoRx, whichever condition came first **Number of measurements:** 5	**Device:** nd **Tested sites:** blood **Time of measurements:** "jaundice" **Number of measurements:**[B] 1	**Definition of positive Reference Test:** TSB levels indicate the need for PhotoRx: Age (hr) / PhotoRx / Double PhotoRx ≤24* / / / 25-48 / 10-12 / ≥15 49-72 / ≥13 / ≥16 >72 / ≥15 / ≥17 *abnormal: investigation, phototherapy and repeat TSB within 4-6 hr **Definition of positive Index Test:** TcB hour-specific percentile monogram, developed from TcB of 284 normal infants in this study (without ABO incompatibility, G6PD deficiency, requirement of PhotoRx) >10, >25, >50, >75, >85, >90, >95 %tile

[A] consecutive /random sampling from general population /prescreening based on selection criteria (describe)
[B] Implies times the probe was applied on the baby – not how many readings the machine takes each time

Results (Concordance metrics): No data

Study	Comparison	Metric	Results	Comments

Results (Sensitivity, specificity and ROC analysis):

Study	Comparison	Index cutoff	Reference Cutoff	TP	FN	FP	TN	Sens	Spec	AUC-ROC	Comments
Sanpavat 2005	TcB %tile vs. TSB	>95 %tile	Sever hyperbilirubinemia that required PhotoRx					75	89.4		32/392 (8.2%) had significant hyperbilirubinemia required PhotoRx
		>90 %tile						96.9	78.8		
		>85 %tile						100	57.2		
		>75 %tile						100	48.3		
		>50 %tile						100	24.4		
		>25 %tile						100	5.0		
		>10 %tile						100	5.0		

Other results:
Cases of hyperbilirubinemia were ABO incompatibility (n=51), G6PD (n=34), Combined ABO incompatibility and G6PD (n=3)

Quality items:

Quality item		Comments
Consecutive patients or random sampling	Y	
Prospective study	Unclear	
No verification bias	N	Only 154 infants (39%) had TSB measured; PhotoRx was determined by TSB levels only
Index test assessor blinded to Reference Test[A]	Y	
Index test assessor blinded to clinical Hx or other information (such as any lab values)	Y	
Reference test assessor blinded to clinical Hx or other information (such as any lab values)	Y	
Proper analysis of replicate measurements in different times	Unclear	
Random order of test measurements	N/A	
Time delay between index and reference test measurements	Unclear	
Adequate description of index test[B]	Y	
Adequate description of reference test[B]	N	
Overall Quality Grade (A to C)	C	

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Sarici, 2001 UI 11765155

Study characteristics	Study design and follow-up duration	Inclusion / Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)		Adverse events, side effects reported
Birth years: nd # Enrolled: 109 # Evaluate: 100 Mean GA: 39 wks Mean BW: 3380 g %Male: 54% Race: Country: Turkey Sites: Single Funding:	RCT: fiberoptic (n=50) vs. conventional phototherapy (n=50); followup for 24 h post phototherapy	Healthy term newborn ≥ 2500 g with non-hemolytic jaundice; formula feeding during phototherapy	Phototherapy initiated when TSB ≥ 15 mg/dL; Fiberoptic group placed on fiberoptic pad; conventional group placed under standard unit (5 daylight fluorescent lamps) Prone position in both groups with eye patches only in the conventional group	Conventional	49.4 ±14.4	1 in each group had transient erythema; 3 in each group had mild watery stool; no other complications noted
				Fiberoptic	61 ±13.1	

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Sarici, 2004 [UI#15060227]

Study characteristics	Inclusion / Exclusion Criteria	Population description	Test Protocol	Reference Standard	Definition of Positives
Birth yrs: Nov. 2001 to May 2002 # Enrolled: 366 # Analyzed: (146 near-term- see below) Mean GA (range): Term – 39.7(38-42) wks Near-term – 36.6 (35-37) wks Mean BW (range): Term – 3194 g Near-term – 2777 g %Male: Term – 52% Near-term – 53% Race: ND Mean Apgar (5 min): Term – 9.6 Near-term – 9.4 Country: Turkey Sites: Single Design: Prospective Funding: ND	**Inclusion:** All newborns with a GA 35-42 completed weeks were consecutively enrolled **Note: data on predictive values only reported for near-term (35-37 weeks) infants only (N=146) **Exclusion:** Preterm infants, GA <35 weeks; postterm infants, GA >42 weeks SGA or LGA, determined on the basis of Colorado intrauterine growth charts Multiple gestation, any congenital malformation, respiratory distress, G6PD, clinical or culture-proven sepsis, and inability to initiate or maintain oral feeding within 3 hours after birth due to various reasons Evidence of hemolysis, ABO incompatibility with a first-day (6th-hour) serum bilirubin level of ≥6 mg/dL	**Setting:** All newborns GA 35-42 **Patient selection process:**[A] Consecutive	**Device:** Colorimetic method (diazotized sulfanilic acid reaction, Germany) **Tested sites:** Serum **Timing vs Reference Test:** 24 hours **Time of measurements:** 6th hour of life, before discharge **Number of measurements:** 1	**Device:** Same as test protocol **Tested sites:** Serum **Time of measurements:** Daily for 4 days; and the last measurement was performed on the 7th day (150th hour) of life **Number of measurements:**[B] 1	**Definition of positive Reference Test:** Any of the first week's serum bilirubin measurements in the ≥95th %tile of the monogram **Definition of positive Index Test:** Percentile cutoffs on the monogram for the 6th hour or 30th hour of serum bilirubin measurement: 5th, 30th, 60th; 95th %tiles

[A] consecutive /random sampling from general population /prescreening based on selection criteria (describe)
[B] Implies times the probe was applied on the baby – not how many readings the machine takes each time

Results (Concordance metrics): No data

Study	Comparison	Metric	Results	Comments

Results (Sensitivity, specificity and ROC analysis):

Study	Comparison	Index cutoff	Reference Cutoff	TP	FN	FP	TN	Sens	Spec	AUC-ROC	Comments
Sarici, 2004	For near-term infants (35-37 wks) only: 6th hour serum bilirubin %tile vs. first week (day 1 to 7) daily serum biliruin %tile	95th %tile	≥95th %tile in any of the first week's serum bilirubin	6	31	2	107	16.2	98.2	ND	Unclear why only near-term infants were analyzed here No data for term infants
		60th %tile		27	10	32	77	72.9	70.6		
		30th %tile		33	4	70	39	89.1	35.7		
		5th %tile		37	0	102	7	100	6.4		
Sarici, 2004	For near-term infants (35-37 wks) only: 30th hour serum bilirubin %tile vs. first week (day 1 to 7) daily serum biliruin %tile	95th %tile	≥95th %tile in any of the first week's serum bilirubin	13	24	2	107	35.1	98.2	ND	Unclear why only near-term infants were analyzed here No data for term infants
		60th %tile		28	9	31	78	75.7	71.6		
		30th %tile		34	3	69	40	91.9	36.7		
		5th %tile		37	0	102	7	100	6.4		

Other results:

Daily mean serum bilirubin levels of the term and pre-term babies did not differ significantly in the first 4 days. The mean serum bilirubin levels on the 5th and 7th days of life were significantly higher in the near-term babies than in the term babies (p=0.04 and P<0.01, respectively). However, serum bilirubin values of the newborns in the near-term group demonstrated a gradual increase during the first days of life and tended to persist high through the end of the first week.

In this study, near-term infants (35-37 wks) were 2.4 times more likely to develop significant hyperbilirubinemia (≥95th %tile of the nomogram) than term infant (38-42 wks): 37/149 (24.8%) vs. 23/219 (10.5%)

Quality items:

Quality item		Comments
Consecutive patients or random sampling	Yes	BUT: Data on term infants are not presented for predictive abilities.
Prospective study	Yes	
No verification bias	Yes	
Index test assessor blinded to Reference Test[A]	Yes	
Index test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Reference test assessor blinded to clinical Hx or other information (such as any lab values)	Yes	
Proper analysis of replicate measurements in different times	N/A	
Random order of test measurements	N/A	
Time delay between index and reference test measurements	N/A	
Adequate description of index test[B]	Yes	
Adequate description of reference test[B]	Yes	
Overall Quality Grade (A to C)	B	They do not present data on term infants on predictive ability. 12.5% lost-to follow-up; their characteristics were not described

[A] Or any other test in case multiple tests were evaluated
[B] Please make a judgment, based on the items recorded in the 1st table

Sarin, 2006 UI 16891677

<table>
<tr><th>Study characteristics</th><th>Study design and follow-up duration</th><th>Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors</th><th>Phototherapy procedures</th><th>Dose (time under phototherapy) (hours)</th><th>Adverse events, side effects</th></tr>
<tr>
<td>Birth years: nd
Enrolled: 100
Evaluate: 100
Mean GA:
Preterm and Term
Mean BW: g
%Male:
Race:
Country: India
Sites: Single
Funding: nd</td>
<td>RCT of compact fluorescent lamp vs. standard phototherapy; data on infants not extracted because data on preterm and term could not be segregated; data on effects on staff were extracted; 50/64 nurses in the neonatal unit answered a questionnaire: Does the light cause a) a glare and hurt the eyes? B) giddiness C) a headache? Answers were: no, minimal, moderate, or extreme</td>
<td></td>
<td>Compact fluorescent (Phoenix India Ltd) (4 compact special blue and 2 compact white tubes) vs. standard (4 special blue tube and 2 white tubes); maintain irradiance >15 μW/cm^2/nm at all times</td>
<td>Mean irradiance: 18.39±2.38 (compact) vs. 17.77±1.81 (standard) μW/cm^2/nm; phototherapy from start to end: 40.66±23.94 (compact) vs. 40.78±21.83 (standard) h</td>
<td>
<table>
<tr><td colspan="4">Effect of compact fluorescent on staff</td></tr>
<tr><td></td><td>no</td><td>minimal</td><td>Moderate or extreme</td></tr>
<tr><td>Eyes hurt</td><td>nd</td><td>nd</td><td>38%</td></tr>
<tr><td>Giddiness</td><td>nd</td><td>nd</td><td>14%</td></tr>
<tr><td>Headache</td><td>nd</td><td>nd</td><td>6%</td></tr>
</table>
<table>
<tr><td colspan="4">Effect of standard fluorescent on staff</td></tr>
<tr><td></td><td>no</td><td>minimal</td><td>Moderate or extreme</td></tr>
<tr><td>Eyes hurt</td><td>nd</td><td>nd</td><td>48%</td></tr>
<tr><td>Giddiness</td><td>nd</td><td>nd</td><td>20%</td></tr>
<tr><td>Headache</td><td>nd</td><td>nd</td><td>8%</td></tr>
</table>
Differences between groups: NS
</td>
</tr>
</table>

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Seidman, 2003 UI 12673261

Study characteristics	Study design and followup duration	Inclusion/ Exclusion Criteria/ Co-morbidities/ modifying factors	Phototherapy procedures	Dose (time under Phototherapy) (hours)	Adverse events, side effects reported
Birth years: 1998-1999 # Enrolled: 114 # Evaluate: 114 Mean GA: 39.4±1.7 Mean BW: nd %Male: nd Race: Country: Israel Sites: Multi Funding: government /university	Open randomized study: Conventional phototherapy (n=57); LED blue (n=25); LED blue-green (n=22) No postdischarge followup noted	Jaundiced but otherwise healthy term infants; breastfeeding	Open crib, unclothed except for a diaper, eyes covered; Bilirubin (mg/dL) at start of phototherapy: Conventional: 15.1 (14.0-16.2) LED blue: 14.3 (12.6-16.0) LED blue-green: 14.2 (12.3-16.1)	Conventional: 35.4 (29.8-41.0) LED blue: 31.6 (23.1-40.0) LED blue-green: 39.2 (30.0-48.4)	No side effects (e.g., erythema) were noted. Nurses did not complain of nausea or dizziness under the blue LED light. "Parents/nurses noted blue-green lights gave a more disturbing hue to the newborn's skin than the blue or halogen-quartz lamps."

Statistical analyses and confounders adjusted	Bias/limitations Comments

Turan, 2004 UI 15346824

Study characteristics	Study design and follow-up duration	Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Adverse events, side effects
Birth years: 2000-2001 # Enrolled: 61 # Evaluate: 61 Mean GA: 38.6 wks Mean BW:3356 g %Male: nd Race: nd Country: Turkey Sites: Single Funding: University and industry	RCT of phototherapy 15 cm away (15-18 μW/cm^2/nm) (n=29) vs. 30-45 cm away (10-12 μW/cm^2/nm) (n=32); primary aim of the study was to compare NO and vascular endothelial growth factor levels (data not extracted here)	≥ 37 wk GA	Phototherapy initiated per AAP guidelines: phototherapy 15 cm away vs. phototherapy 30-45 cm away; eyes covered, diaper	nd	See nested table below

	15 cm	30-45 cm
Baseline temperature	36.43±0.21	36.49±0.34
Temperature at 6th h phototherapy	36.70±0.25*	36.82±0.26*
Baseline heart rate	140.96±13.28	142.06±12.21
Heart rate at 6th h phototherapy	146.75±8.14*	144.62±9.60
Baseline mean blood pressure	61.03±11.29	60.12±7.61
Mean blood pressure at 6th h phototherapy	57.65±8.46	55.50±8.07*
*P comparing baseline with 6th h : <0.05; All other comparisons: NS		

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Zainab, 2004 UI 15727387

Study characteristics	Study design and follow-up duration	Inclusion/ Exclusion Criteria/ Comorbidities/ modifying factors	Phototherapy procedures	Dose (time under phototherapy) (hours)	Adverse events, side effects
Birth years: 2002 # Enrolled: 36 # Evaluate: 36 Mean GA: Term Mean BW: 3040 g %Male: Race: 95% Malays, 5% Chinese Country: Malaysia Sites: Single Funding:	Comparative study of home (n=18) vs. hospital (n=18) phototherapy	>37 wk GA; birth weight 2500-4000 g, Apgar[5] ≥7, >2 d but <7 d at start of phototherapy, TSB >10.5 but <18.4 mg/dL; no G6PD or hemolysis	Home: Bluelite mobile unit with reflectors on both sides of the neonate, distance 30 cm, irradiance ≥ 15.5 μW/cm^2/nm; Hospital: self-made unit with top (50 cm, 14-16 μW/cm^2/nm) and bottom (30 cm, 18-19 μW/cm^2/nm) lights; Phototherapy per AAP guideline (1985) with modification, phototherapy stopped when TSB <11.7 mg/dL	Home: 1.17±0.73 d; Hospital: 1.72±0.73 d Mean TSB at start of phototherapy: 13.9 mg/dL	<table><tr><th></th><th>home</th><th>hospital</th></tr><tr><td>No complications</td><td>78%</td><td>78%</td></tr><tr><td>rash</td><td>5.5%</td><td>11%</td></tr><tr><td>hyperthermia</td><td>0</td><td>0</td></tr><tr><td>Diarrhea >5x</td><td>16.7%</td><td>11%</td></tr></table> Differences between groups: NS

Statistical analyses and adjustment for confounders	Bias/limitations Comments

Appendix D. List of Excluded Studies

Arya VB, Agarwal R, Paul VK, Deorari AK. Efficacy of oral phenobarbitone in term "at risk" neonates in decreasing neonatal hyperbilirubinemia: a randomized double-blinded, placebo controlled trial. Indian Pediatrics. 2004;41:327-32. **treatment was not phototherapy**

Bader D, Yanir Y, Kugelman A, Wilhelm-Kafil M, Riskin A. Induction of early meconium evacuation: is it effective in reducing the level of neonatal hyperbilirubinemia? American Journal of Perinatology. 2005;22:329-33. **treatment was not phototherapy**

Barko HA, Jackson GL, Engle WD. Evaluation of a point-of-care direct spectrophotometric method for measurement of total serum bilirubin in term and near-term neonates. Journal of Perinatology. 2006;26:100-105. **cannot figure out TSB percentile**

Bernaldo AJ, Segre CA. Bilirubin dosage in cord blood: could it predict neonatal hyperbilirubinemia? Sao Paulo Medical Journal = Revista Paulista de Medicina. 2004;122:99-103. **umbilical cord blood**

Boo NY, Lee HT. Randomized controlled trial of oral versus intravenous fluid supplementation on serum bilirubin level during phototherapy of term infants with severe hyperbilirubinaemia.[erratum appears in J Paediatr Child Health 2002 Dec;38(6):625]. Journal of Paediatrics & Child Health. 2002;38:151-55. **no adverse events reported/assessed**

Boo NY, Ishak S. Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer
8. Journal of Paediatrics & Child Health 43 (4):297 -302 . 2007. **cannot figure out TSB percentile**

Borgard JP, Szymanowicz A, Pellae I, Szmidt-Adjide V, Rota M. Determination of total bilirubin in whole blood from neonates: results from a French multicenter study. Clinical Chemistry & Laboratory Medicine. 2006;44:1103-10. **r; limit of agreement data only**

Briscoe L, Clark S, Yoxall CW. Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies? Archives of Disease in Childhood Fetal & Neonatal Edition. 2002;86:F190-F192. **cannot figure out TSB percentile**

Chen CM, Liu SH, Lai CC, Hwang CC, Hsu HH. Changing position does not improve the efficacy of conventional phototherapy. Acta Paediatrica Taiwanica. 2002;43:255-58. **no adverse events reported/assessed**

Chou SC, Palmer RH, Ezhuthachan S, Newman C, Pradell-Boyd B, Maisels MJ et al. Management of hyperbilirubinemia in newborns: measuring performance by using a benchmarking model. Pediatrics. 2003;112:t-73. **no comparisons**

Dinesh D. Review of positive direct antiglobulin tests found on cord blood sampling. Journal of Paediatrics & Child Health. 2005;41:504-7. **umbilical cord blood**

Duman N, Ozkan H, Serbetcioglu B, Ogun B, Kumral A, Avci M. Long-term follow-up of otherwise healthy term infants with marked hyperbilirubinaemia: should the limits of exchange transfusion be changed in Turkey? Acta Paediatrica. 2004;93:361-67. **no outcome**

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Appendix E. Peer Reviewers

The peer reviewer comments on a preliminary draft of this report were considered by the EPC in preparation of this final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers. The authors gratefully acknowledge the peer reviewers.

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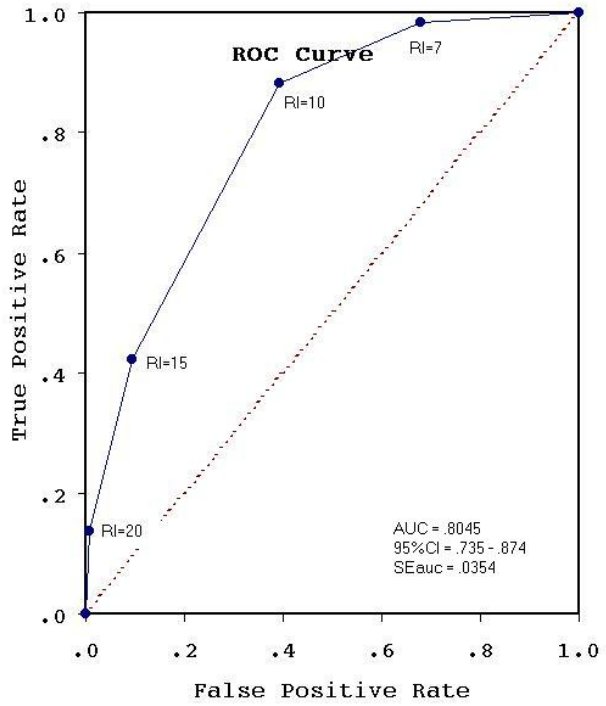
Appendix F. Newman et al 2000 Study

Accuracy of Predischarge Risk Index as a Test for Predicting Later Development of Hyperbilirubinemia

Newman, Xiong, Gonzales, et al. (2000) reviewed the medical records of 73 neonates with maximum TSB of ≥ 25 mg/dl, compared with 423 randomly selected controls with TSB <25 mg/dl, in order to determine biological and health service predictors of extreme hyperbilirubinemia. The strongest predictors were found to be family history of jaundice in a newborn (OR=6.0), exclusive breastfeeding (OR=5.7), bruising (OR=4.0), Asian race (OR=3.5), cephalhematoma (OR=3.3), maternal age ≥ 25 years (OR=3.1), and lower gestational age (OR=0.6/wk). The authors developed a risk index with this data, assigning a numerical value to each characteristic. In the 32 percent of neonates with an index score of ≤ 7, the risk of developing a TSB level of ≥ 25 mg/dl was about 1 in 16,000. In the one percent of neonates with an index score of > 20, the risk of developing a TSB of ≥ 25 mg/dl was about two percent. If a score of ≤ 10 was used at a cutoff for low risk, 61 percent of newborns would be in the low risk group and about 1 in 4200 would develop a TSB ≥ 25 mg/dl. Even the remaining 39 percent classified as high risk would have only a 1 in 370 risk (0.27 percent) of developing a TSB ≥ 25 mg/dl. Figure 3.7 shows the ROC curve from the Newman, Xiong, Gonzales, et al. (2000) study.

Figure 3.7 Test Performance of Predischarge Risk Index



Data Source: Newman, 2000 [UI#20529193]

Newman, 2000 [#11074857] – Part I

Demographics	Inclusion Criteria	Exclusion Criteria	Study Design
Location: US Setting: Hospital Study period: 1995 to 1996 Mean GA (range): ≥ 36 wk Mean BW (range): > 2000 g Mean Apgar score at 1 min: ND Breastfed proportion: ND Male: Cases: 67% Controls: 54% Race: Cases: 44% White, 4% Black, 15% Hispanic, 32% Asian; 5% Others Controls: 49% White, 9% Black, 22% Hispanic, 17% Asian; 3% Others Enrolled subjects: 75 Cases; 427 Controls Evaluated subjects: 73 Cases; 423 Controls Number of centers: 11	All: BW > 2000 g; GA > 36 weeks Cases: TSB within the first 30 days of life ≥ 25 mg/dl Controls: randomly selected sample with TSB < 25 mg/dl	Cases: GA < 36 weeks (2) Controls: hospitalization record not found (1); BW or GA didn't meet criteria (3)	Case-control study

Newman, 2000 [#11074857] – Part II

Disease/Condition Type (N)	Strategies for Predicting Hyperbilirubinemia	Definition of True Positive	Reference Standard
Near-term or term infants (496) – Cases: infants with hyperbilirubinemia (73) Controls: infants without hyperbilirubinemia (423)	Risk index = 6 (Exclusive breastfeeding) + 6 (Family history of jaundice in a newborn)+ 4 (Bruising noted) + 4 (Asian race) + 3 (Cephalhematoma noted) + 3 (Maternal age ≥ 25 y) + 1 (Male sex) –2 (Black race) + 2 (40-GA)	Risk index > 10 in predicting maximum TSB ≥ 25 mg/dl in infants without early jaundice	Laboratory-base assay of TSB: data from the KPMCP integrated laboratory information system

Newman, 2000 [#11074857] – Part III

Results	Biases or Limitations	Comments
Predischarge Risk Assessment:	Case-control study (retrospective) is subject to selection bias	Study was government and privately funded Internal validity: B

Risk Zone or Risk Index	Total # of Subject	Outcome present	Outcome absent	Likelihood Ratio	PPV
Risk Index ≤ 7	130	1	129	0.053	1/15653
Risk Index 8-10	121	6	115	0.36	1/2327
Risk Index 11-15	147	27	120	1.5	1/540
Risk Index 16-20	52	17	35	3.3	1/251
Risk Index > 20	11	8	3	18.2	1/47

For near-term or term infants without early jaundice (N=461), the sensitive, specificity, PPV, and NPV (Risk Index > 10 in predicting TSB ≥ 25 mg/dl) was 88%, 61%, 25%, and 97%, respectively.

Of 23 cases exceeded the AAP PhotoRx threshold before their TSB ≥ 25 mg/dl, only 26% received PhotoRx within 8 hrs of exceeding the threshold. The use of PhotoRx within 8 hrs of the AAP guidelines in the control group and in additional group of 30 randomly selected newborns whose maximum TSB were 20-24.9 mg/dl was only 33%. No significant difference was found between cases and controls.