Revised Final Draft

EVIDENCE REVIEW: Neonatal Hyperbilirubinemia

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MATERNAL AND CHILD HEALTH BUREAU

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*Appendices C, D, and E available upon request

i. List of Tables and Figures

ii. Abbreviations used

AAP	American Academy of Pediatrics
ABE	Acute bilirubin encephalopathy
BAEP	Brainstem auditory evoked potential (also known as brainstem auditory evoked response, BAER, and auditory brainstem response, ABR)
BNBAS	Brazelton Neonatal Behavioral Assessment Scale
BSID	Bayley Scales of Infant Development
DDST	Denver Developmental Screening Test
EcT	Exchange transfusion
G6PD	Glucose-6-phosphate dehydrogenase
ICD	International Classification of Diseases
mg/dL	Milligrams per deciliter
NPV	Negative predictive value
PPV	Positive predictive value
TSB	Total serum bilirubin
TcB	Transcutaneous bilirubin

I. Introduction

Neonatal hyperbilirubinemia is a term for elevated total serum bilirubin in newborns and infants less than one month of age. Neonatal hyperbilirubinemia has multiple etiologies and is a detectable risk factor for acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy, the latter also known as kernicterus. ABE is clinically characterized by decreased feeding, lethargy, hypo/hypertonia, high-pitched cry, retrocollis, impaired upgaze, fever and seizures (Shapiro, 2005). The term kernicterus, introduced in the early 1900s, arose as a pathological term for the yellow staining of the basal ganglia from bilirubin deposition (Dennery, Seidman, & Stevenson, 2001). Clinically, chronic bilirubin encephalopathy is characterized by four manifestations 1) movement disorder (aethetosis, dystonia, spasticity, hypotonia), 2) auditory dysfunction, 3) oculomotor impairment, and 4) dental enamel hypoplasia (Shapiro, 2005), and has a mortality rate of at least 10% (Ip et al., 2004). The specific pathogenesis of bilirubin encephalopathy, the progression from acute to chronic, and determining the presence and severity of the disease have been studied for decades, but is not yet fully understood. However, a number of risk factors are known and one, neonatal hyperbilirubinemia, is the focus of this evidence review.

The physiologic causes of neonatal hyperbilirubinemia are typically categorized into one of three groups: bilirubin overproduction, decreased bilirubin conjugation, and impaired bilirubin excretion. Unconjugated bilirubin is a product of normal hemoglobin degradation during red blood cell turnover. Unconjugated bilirubin is lipid soluble, water insoluble and neurotoxic (Shapiro, 2003). In the liver, unconjugated bilirubin is converted to its water-soluble, less toxic conjugated form, which is excreted through the bile. Unconjugated bilirubin in the blood is most often bound to albumin. Unbound, unconjugated bilirubin can cross the blood-brain barrier and has been implicated in bilirubin encephalopathy.

Because neonatal hyperbilirubinemia is a known, treatable risk factor for bilirubin encephalopathy, and is detectable by several methods, universal predischarge newborn screening for hyperbilirubinemia has been proposed as a method to screen for risk of developing chronic bilirubin encephalopathy. The immediate goal of screening for elevated bilirubin levels is to assess risk for hyperbilirubinemia requiring treatment. In 2004, the American Academy of Pediatrics (AAP) published updated guidelines on screening and management of neonatal hyperbilirubinemia which emphasized 1) assessing newborns for risk of subsequent hyperbilirubinemia by examination, transcutaneous bilirubin (TcB) or total serum bilirubin (TSB) screening in the nursery; 2) evaluation of the risk of subsequent hyperbilirubinemia with a nomogram standardized to age in hours; and, 3) revised treatment guidelines, based upon consensus and limited evidence (Appendix A) (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004). The practice of stratifying screened newborns for risk of developing subsequent hyperbilirubinemia is used to determine the frequency of follow-up evaluations and potential need for treatment. Lowering serum bilirubin levels presumably lowers the risk of progression to a spectrum of bilirubin-induced morbidities, including acute and chronic bilirubin encephalopathy.

II. Methods for developing case definition

At the onset of this review, we developed a case definition focused on neonatal hyperbilirubinemia and two clinical outcomes (acute bilirubin encephalopathy and chronic bilirubin encephalopathy), thought to most likely benefit from a newborn screening program. To do so, we contacted specialists identified as authors of relevant literature or by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) and Evidence Review Group (ERG) recommendation (Vinod Bhutani, MD, PhD; Lois Johnson-Hamerman, MD [nominator]; M. Jeffrey Maisels, MD; Thomas B. Newman, MD, MPH; Ann Stark, MD; and David Stevenson, MD). ERG members held a conference call with these experts to discuss the nomination and pertinent key questions. A case definition was drafted and subsequently discussed and agreed upon by the members of the ERG and the SACHDNC Nomination and Prioritization committee.

III. Case definitions

Neonatal Hyperbilirubinemia

Clinically significant hyperbilirubinemia in the neonatal period has been defined as TSB levels >95th percentile for age in hours, which may require follow-up and treatment (Bhutani, Johnson, & Sivieri, 1999).

Acute Bilirubin Encephalopathy (ABE)

ABE is a term to describe the variable spectrum, from subtle to advanced manifestations of bilirubin toxicity present in the first weeks of life (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004; Van Praagh, 1961). Symptoms associated with ABE include a range of neurological manifestations, somnolence, hypotonia, loss of the Moro reflex, followed by a stage characterized by hypertonia of the extensor muscle groups (backward arching of the neck and backward arching of the trunk). Additionally, fever and/or a high-pitched cry may be present. Different investigators have used different methods to characterize and define clinical manifestations of ABE in the infant (Harris et al., 2001; Van Praagh, 1961). Investigators have also referred to ABE in older literature as acute kernicterus. For this review, we limit the use of ABE to describe well-documented neurologic manifestations including loss of the Moro and extensor hypertonia.

Chronic Bilirubin Encephalopathy (Kernicterus)

Chronic bilirubin encephalopathy is a term reserved to describe persistent and permanent brain damage caused by bilirubin toxicity (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004). Chronic bilirubin encephalopathy is characterized by four clinical manifestations 1) movement disorder (aethetosis, dystonia, spasticity, hypotonia), 2) auditory dysfunction, 3) oculomotor impairment and, 4) dental enamel hypoplasia (Shapiro, 2005). (Hyperbilirubinemia has been associated with other longer term neurologic dysfunction, and we also address these associations in this review.) Investigators also refer to chronic bilirubin encephalopathy as kernicterus, chronic kernicterus, and permanent bilirubin-related or bilirubin-induced brain damage.

IV. Rationale for review

The SACHDNC has directed the ERG to produce this report for the nominated condition of neonatal hyperbilirubinemia. Neonatal hyperbilirubinemia has been nominated for the following reasons:

i. Neonatal hyperbilirubinemia can lead to chronic bilirubin encephalopathy, causing permanent damage to the central nervous system (CNS). Once damage is permanent, there are few, if any, therapeutic options to improve outcomes.
ii. Early identification of risk factors for chronic bilirubin encephalopathy, including elevated serum bilirubin, may allow interventions to lower the risk.
iii. The ability to measure TcB or TSB is widely available.
iv. Treatment is widely available for neonatal hyperbilirubinemia (phototherapy, exchange transfusion [EcT]).

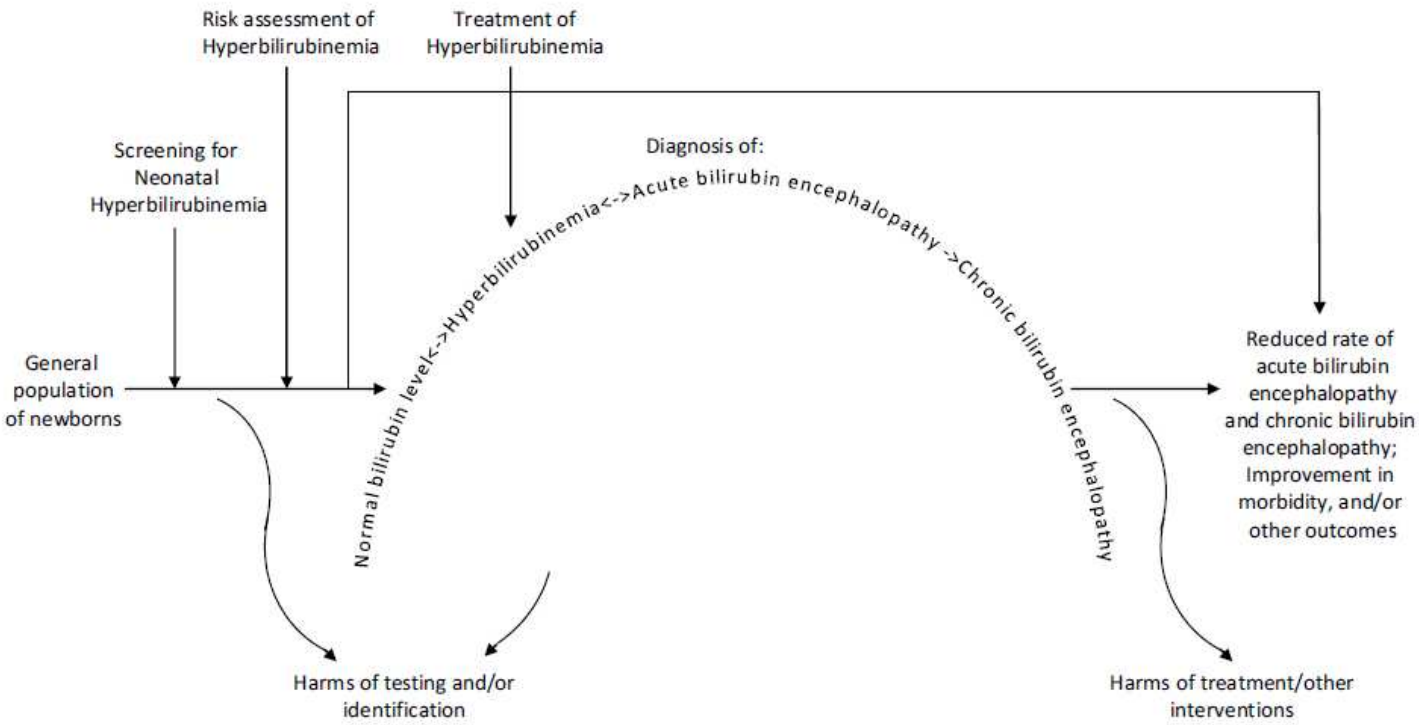
V. Objectives

The objective of this review is to provide information to the SACHDNC about the potential benefits, harms, and costs of adding neonatal hyperbilirubinemia to the list of primary conditions for newborn screening, based on evidence from published studies and other data available from experts in the field.

VI. Conceptual framework

The conceptual framework below (Figure 1) illustrates our approach to evaluating the evidence regarding the potential benefits and harms of newborn screening for neonatal hyperbilirubinemia. Our main goals are to assess (1) the potential effectiveness of screening and (2) the potential impact of treatment for those identified at risk through newborn screening compared to those identified later through clinical diagnosis.

Figure 1 – Conceptual framework



VII. Key questions

With the help of the initial specialist group and members of the SACHDNC, we developed a series of questions specific to neonatal hyperbilirubinemia screening for review.

Condition

- Is neonatal hyperbilirubinemia well-defined (natural history, incidence, prevalence, and spectrum of severity)? When does it appear clinically? What are the known risk factors, if any?
- What characterizes acute and chronic bilirubin encephalopathy (natural history, incidence, prevalence, and spectrum of severity)?
- What evidence is available regarding the relationships among neonatal hyperbilirubinemia and acute and chronic bilirubin encephalopathy?
- Is neonatal hyperbilirubinemia associated with more subtle adverse outcomes other than acute and chronic bilirubin encephalopathy?

Screening Test

- What methods exist to screen newborns for neonatal hyperbilirubinemia? What are their analytic validity, sensitivity and specificity?
- What tools are available to interpret the risk of developing hyperbilirubinemia associated with a newborn's bilirubin value? What is the predictive validity of these tools?

- How do timing of screening after birth, gestational age, threshold levels, and other considerations affect the number of infants identified with or being at significant risk for developing neonatal hyperbilirubinemia?
- What are the recommended follow-up and monitoring procedures for newborns found to be at risk of developing hyperbilirubinemia?
- Do outpatient facilities have the capacity to handle follow-up visits for at-risk infants?
- Have there been population-based universal predischarge hyperbilirubinemia screening trials?
- What are the potential harms or risks associated with screening?

Treatment

- What methods exist to treat neonatal hyperbilirubinemia and what is their effectiveness? What is the relationship between outcomes and the timing of treatment intervention?
- What is the availability of treatment?
- What are the potential harms or risks associated with treatment?
- Does treating neonatal hyperbilirubinemia reduce the incidence of acute and chronic bilirubin encephalopathy?
- What proportion of cases of chronic bilirubin encephalopathy would be prevented with earlier detection and treatment of hyperbilirubinemia? What proportion of cases of other neonatal hyperbilirubinemia manifestations would be preventable?

Economics

- What are the costs associated with the screening test?
- What are the costs associated with the failure to find at risk newborns in the pre-symptomatic period?
- What are the costs associated with treatment of neonatal hyperbilirubinemia?
- What are the costs associated with treatment of acute and chronic bilirubin encephalopathy?
- What is the cost-effectiveness of newborn screening for neonatal hyperbilirubinemia?

Other

- What would be the effect of taking predischarge bilirubin screening in its current form to state mandated newborn screening?
- What critical evidence appears lacking that may inform screening recommendations for neonatal hyperbilirubinemia?

VIII. Literature review methods

We conducted a systematic evidence review by searching both MEDLINE and EMBASE for all relevant studies published over the 20-year period from 1990 to October 2011. We completed searches combining the National Library of Medicine Medical Subject Heading (MeSH) and keywords: “hyperbilirubinemia,” “bilirubin encephalopathy,” and “kernicterus” for relevant citations of all articles written about natural history, screening, treatment, or economics of

neonatal hyperbilirubinemia over this time period. In order to capture articles that have not yet been assigned MeSH terms, we also searched the same keywords within the OVID In-Process and Other Non-Indexed Citations database. Each search was limited to human studies, all infants, and English language publications. To ensure completeness of the literature search, we reviewed reference lists and the nomination form submitted to the SACHDNC. This search strategy yielded 3075 abstracts for potential articles.

Three investigators (AAK, DRM, and JPC) reviewed all abstracts to select articles for inclusion in the review. Studies focused on neonatal hyperbilirubinemia were selected through a multi-stage process. Articles were eliminated if they were: not human studies; did not focus on hyperbilirubinemia or acute or chronic bilirubin encephalopathy; reviews or editorials that did not include new data in forms that allowed assessment of their quality; case reports; focused on a non-relevant population or age group; did not have outcomes; did not answer a key question; or case reports. Where disagreements occurred, they were resolved through discussion with emphasis on inclusion of any potentially useful data. After abstract review, 201 manuscripts were reviewed in full. All full-length articles were subjected to the inclusion and exclusion criteria above and studies that met the predefined and explicit criteria were selected for the review. In cases of duplicate publications, the most recent or complete versions were selected. After this process, 112 articles met all inclusion criteria and were included in this evidence review.

The three investigators each independently abstracted one-third of the articles, and a fourth investigator (LP) assisted in reviewing economic manuscripts only. All investigators reviewed a subset (20%) to ensure consistency. Each article was evaluated, using standardized tools, for the quality of the study design (Atkinson et al., 2003) and the value of the evidence, as it relates to the category of evidence (Pandor et al., 2004; Pollitt et al., 1997). A given article received only one rating per reader for study design, but may have received multiple quality evaluations for the type of evidence. For example, a study that discusses prevalence and natural history would be evaluated for the quality of the evidence in each of those domains. There were no significant differences in the data extracted by the reviewers.

Table 1 – Study design among abstracted articles

Study Design	Number of Articles
Experimental intervention	5
Cohort study	17
Case-control study	13
Case series	57
Sample size ≤ 10	6
Sample size 11 to 50	7
Sample size 51 to 100	4
Sample size 101 to 1000	24
Sample size ≥ 1001	16
Cross-Sectional study	13
Time-Series study	4
Before and After study	1
Economic Evaluation*	2
Total studies	**112**

*Five papers contained economic information but only two classified as economic evaluations

To assure completeness and clarity of the report, a draft of the report was sent to an independent external review panel. The report was revised based on their suggestions.

IX. Methods for interviews with experts

The ERG and the SACHDNC recognize that there may be important but unpublished data regarding hyperbilirubinemia. We identified experts, including researchers and neonatal hyperbilirubinemia newborn screening advocates, to help us identify this information (Table 2). These individuals were identified as authors of key papers included in the literature review, through discussions with content experts, and through recommendations from the ERG and SACHDNC.

Experts were sent a letter via e-mail (Appendix D for researchers and Appendix E for advocates) explaining the purpose of the review, a conflict of interest form (Appendix C) and an open-ended survey. Experts had two weeks to respond, and extensions were granted when requested. The project coordinator sent at least one reminder e-mail to experts who did not reply by the deadline. In cases where clarifications were needed regarding the responses, individuals were either sent a follow-up e-mail or contacted via telephone by the authors. When experts and advocates provided evidence regarding the key questions not otherwise available from the selected articles, we include their responses.

Table 2 – Key experts and advocates and level of contact (in alphabetical order)

Name	Title	Replied	Completed written survey	Telephone interview
Rachel Avchen, MS, PhD	Senior Research Scientist, Developmental Disabilities Branch, National Center for Birth Defects and Developmental Disabilities, Atlanta, Georgia	✓		
Vinod Bhutani, MD, PhD	Professor of Pediatrics (Neonatology), Lucile Salter Packard Children's Hospital, Stanford University School of Medicine, Department of Pediatrics, Division of Neonatal and Developmental Medicine, Palo Alto, California	✓	✓	✓
Coleen Boyle, PhD, MSH	Director, Division of Birth Defects and Developmental Disabilities, National Center for Birth Defects and Developmental Disabilities, Atlanta, Georgia	Deferred to other experts		
Karen Dixon, PhD	Co-Founder, Parents of Infants and Children with Kernicterus (PICK); Assistant Professor of Neurobiology, University of Alabama at Birmingham, Birmingham, Alabama	X		
Gabriel Escobar, MD	Research Scientist III, Division of Research, Kaiser Permanente Northern California; Staff Pediatrician, Kaiser Permanente Medical Center, Walnut Creek, California, Oakland, California	Deferred to other experts		
James G. Flood, PhD	Director, Chemistry lab, Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts	✓	✓	
Scott Grosse, PhD	Associate Director for Health Services Research and Evaluation, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia	✓		✓
Thomas Hegyi, MD	Program Director, Division of Neonatology; Professor and Vice-Chair, Department of Pediatrics; Director, SIDS Center of New Jersey; Director, Kernicterus Prevention and Research Center; Director, High-risk Infant Follow-up Program, New Brunswick, New Jersey	Deferred to other experts		
Lois Johnson-Hamerman, MD	Pennsylvania Center for Kernicterus, Philadelphia, Pennsylvania	✓	✓	✓
Michael Kaplan, MB, ChB	Department of Neonatology, Shaare Zedek Medical Center and Faculty of Medicine of the Hebrew University, Jerusalem, Israel	✓	✓	
Michael Kuzniewicz, MD, MPH	Assistant professor, Division of Neonatology, Department of Pediatrics, University of California, San Francisco, California	X		
M. Jeffrey Maisels, MD	Professor of Pediatrics; Chair, Department of Pediatrics; and Chair, Practice Parameter for Management of Neonatal Hyperbilirubinemia, Beaumont Hospitals, Michigan	✓	✓	✓

Marie Mann, MD, MPH	Integrated Services Branch, Division of Children with Special Health Needs/ Maternal and Child Health Bureau/ Health Resources and Services Administration /Health and Human Services, Rockville, Maryland	✓	✓	
Thomas B. Newman, MD,MPH	Professor, Division of Clinical Epidemiology, University of California, San Francisco	✓	✓	✓
Lu-Ann Papile, MD	Professor of Pediatrics, Neonatology; Director of Developmental Care and Follow-up, Baylor College of Medicine, Houston, Texas	✓	✓	
Michael Sgro, MD, FRCPC	Deputy Chief of Paediatrics & Director of Research Assistant Professor, University of Toronto, Department of Paediatrics, St. Michael's Hospital, Toronto, Ontario	✓		✓
Steven M. Shapiro MD, MSHA	Professor of Neurology, Pediatrics, Physical Medicine and Rehabilitation, Otolaryngology-Head & Neck Surgery, and Physiology and Biophysics; Vice Chairman, Division of Child Neurology; Department of Neurology, Medical College of Virginia Campus, Virginia Commonwealth University Medical Center, Richmond, Virginia	✓		
Sue Sheridan, MIM, MBA	Cofounder, Advisor to the Partnership for Patient Safety, Parents of Infants and Children with Kernicterus	✓		
Ann Stark, MD	Professor of Pediatrics, Neonatology; Director, Neonatal-Perinatal Medicine Fellowship Program; Associate Program Director, General Clinical Research Center; Chief, Neonatology Service, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas	✓	✓	✓
David Stevenson, MD	Director, Charles B. and Ann L. Johnson Center for Pregnancy and Newborn Services, Lucile Packard Children's Hospital at Stanford; Harold K. Faber Professor of Pediatrics, Stanford University School of Medicine, Palo Alto, California	✓		✓
Marshalyn Yeargin-Allsopp, MD	Chief, Developmental Disabilities Branch, National Center on Birth Defects and Developmental Disabilities, Center for Disease Control and Prevention; Adjunct Assistant Professor of Pediatrics, Emory University School of Medicine, Atlanta, Georgia	✓	✓	✓

X. Results: evidence findings to address the key questions

This section presents the evidence from the included articles. Each subsection includes a summary of findings from the literature review, assessment of the quality of the evidence from each included article and information from the experts when they provided evidence regarding the key questions not otherwise available from the selected articles.

A. Condition:

Key questions pertaining to condition:

- Is neonatal hyperbilirubinemia well-defined (natural history, incidence, prevalence, and spectrum of severity)? When does it appear clinically? What are the known risk factors, if any?
- What characterizes acute and chronic bilirubin encephalopathy (natural history, incidence, prevalence, and spectrum of severity)?
- What evidence is available regarding the relationships among neonatal hyperbilirubinemia and acute and chronic bilirubin encephalopathy?
- Is neonatal hyperbilirubinemia associated with more subtle adverse outcomes other than acute and chronic bilirubin encephalopathy?

Literature review:

Incidence

We found 17 studies that address the incidence of hyperbilirubinemia and chronic bilirubin encephalopathy. Reported incidence rates vary due to factors such as case definition (i.e. level of TSB), ascertainment (i.e. ICD codes) and risk factors in the population being studied. The ranges of reported incidence of hyperbilirubinemia and chronic bilirubin encephalopathy are summarized in Tables 4 and 5. Estimates of the incidence of neonatal hyperbilirubinemia depend on the definition of hyperbilirubinemia used; ranging from 5% at bilirubin levels >12mg/dL, to 0.01% at >30mg/dL. Specifically, bilirubin levels >30mg/dL range from 3-12 cases per 100,000 (Bjerre, Petersen, & Ebbesen, 2008; Mah et al., 2010; Manning et al., 2007; Newman et al., 1999; Newman, Liljestrand, & Escobar, 2003), in the abstracted literature. Estimates of the incidence of chronic bilirubin encephalopathy range from 0.49-2.7 per 100,000 (Brooks et al., 2011; Burke et al., 2009; Jangaard et al., 2008; Maimburg et al., 2009; Manning et al., 2007; Newman et al., 2006). Excluding one study which defined cases by ICD9 code only, the estimated incidence ranges from 0.49-1.3 per 100,000.

Spectrum of Severity

Several studies addressed the subtle, acute and chronic effects of neonatal hyperbilirubinemia. Tables 6 and 7 summarize the findings from the abstracted literature for acute and chronic manifestations, respectively. These studies varied substantially in population characteristics (methods of ascertainment, mean TSB level, inclusion of infants with hemolytic disease), type of neurodevelopmental assessment (Brazelton Neonatal Behavioral Assessment Scale [BNBAS], clinical evaluation, visual evoked potential [VEP], brainstem auditory evoked potential [BAEP]),

timing of initial assessment, follow-up period, and treatment. Thus, differences in study design limit the ability to compare study data (Tables 6 and 7).

Subtle Manifestations

Several small studies assessed neonates for clinical manifestations potentially associated with elevated bilirubin levels, at levels less than that used to meet the complete case definition for acute bilirubin encephalopathy. Among neonates with TSB >13mg/dL, the Brazelton Neonatal Behavior Assessment Scale (BNBAS) showed statistically significant differences between the 28 study and 28 control neonates in orientation, range of state, regulation of state and autonomic regulation (Mansi et al., 2003). Another study using the BNBAS with 50 neonates with hyperbilirubinemia (TSB 13.2-20 mg/dL), as compared to 50 controls showed significant differences at first evaluation, but no differences 24 hours later and at three weeks of age (Paludetto et al., 2002). No further follow-up was reported.

Another small study compared the neurological exams of 20 term neonates with TSB >12.9 mg/dL to 20 age-matched controls (Soorani-Lunsing, Woltil, & Hadders-Algra, 2001). No infant had a definitively abnormal exam, although minor neurologic dysfunction was statistically significantly higher in the neonates with hyperbilirubinemia (14/20) than in the control group (5/20) ($p < 0.05$). This trend was also seen at three and 12 months follow-up but not significant. In summary, published reports provide little evidence of important or persistent subtle neurologic findings.

Acute Manifestations

Several studies assessed a large number of newborns and monitored them for hyperbilirubinemia and subsequent manifestations of acute bilirubin encephalopathy during the newborn period. Data on infants with hyperbilirubinemia were collected prospectively through the Canadian Paediatric Surveillance Program from 2002 to 2004 (Sgro et al., 2011). Of the 258 infants, 32 (12.4%) identified had neurological abnormalities consistent with ABE, and infants in the highest peak bilirubin level group (>32 mg/dL) had a higher number of acute neurological abnormalities consistent with ABE (9/27 or 30%). The mid range (26-32 mg/dL) and lowest level (≤ 26 mg/dL) bilirubin groups had less neurological abnormalities (OR=0.174; P=0.0013 and OR=0.402; P=0.06, respectively). These findings suggest a 1 in 20,000 incidence of ABE (lethargy, poor sucking or hypotonia) and 1.8 per 100,000 incidence of advanced ABE (opisthotonos and/or seizures). This study did not provide long-term neurodevelopmental follow-up, thus it is unclear if ABE in these subjects resolved or progressed to permanent neurological sequelae.

A Danish population study identified 113 neonates, among a population of 249,308 births, with hyperbilirubinemia (TSB >23.4 mg/dL) (Bjerre et al., 2008). Among the 113 neonates, peak TSB ranged from 26.3-42.9 mg/dL (median = 28.3mg/dL). The most common cause was ABO incompatibility (52/113) and the second was of unknown etiology (43/113). 44/113 (39%) had symptoms associated with bilirubin toxicity. Forty-three had subtle changes (lethargy, poor sucking or hypotonia) and one had advanced phase ABE (retrocollis, opisthotonos, shrill cry, no feeding, seizures, apnoea, fever or deep stupor). This infant had a peak TSB of 42.9 mg/dL, ABO

incompatibility, and received an exchange transfusion. Follow-up was available for 32 of the 113 infants. At 33 months, the infant with history of advanced phase ABE symptoms had motor deficits, hypotonia and hearing loss. All other infants were developing normally (with the exception of one infant whose impairments were attributed to galactosemia). This study suggests a rate of ABE of less than 1 per 200,000 live births.

A second Danish study identified 32 neonates with a TSB level above the Danish Pediatric Society's exchange transfusion limit among 128,344 (Ebbesen et al., 2005). Peak TSB levels ranged from 22.5-40.2 mg/dL (median = 28.7 mg/dL). Eleven of the 32 neonates (38%) exhibited subtle symptoms (lethargy, poor sucking, hypotonia, stupor or weak Moro reflex) and one advanced symptoms (hypertonia, retrocollis, opisthotonos, pronation of the upper extremities, irritability, seizures, apnoea, cyanotic attacks). This infant had a peak TSB of 38.0 mg/dL and at 23 months of age, had mental retardation and dystonic cerebral palsy. Specific follow-up information was not available for the other 31 subjects.

A study of neonates with TSB levels ≥30 mg/dL identified 11 among a birth cohort of 111,009 in the United States (Newman et al., 2003). Peak TSB values ranged from 30.7-45.5 mg/dL. None of the 11 exhibited symptoms of ABE. On follow-up, one infant had died (attributed to sudden infant death syndrome, no evidence of kernicterus at autopsy) and the remaining 10 were neurologically normal (ranging from six months to four and a half year data available). A retrospective chart review of neonatal intensive care unit admissions from 1990-2000 in a Canadian hospital revealed 12 infants with a history of hyperbilirubinemia >23.4 mg/dL (range peak TSB 23.7-48.2 mg/dL) (AlOtaibi, Blaser, & MacGregor, 2005). Seven infants had glucose-6-phosphate dehydrogenase (G6PD) deficiency. On follow-up (ranging from seven months to six years), two subjects were lost to follow-up, three developed normally and seven had abnormal development (delayed gross and fine motor, delayed adaptive and social skills). The neonatal TSB values for five of the children with abnormal development were: 23.7, 37.1, 38.0, 44.8, 48.2mg/dL, four of which had G6PD deficiency. This study does not clarify what other neonatal conditions may account for the long-term findings.

A recently published retrospective study from Iraq followed 162 term and near-term neonates (age range 1-23 days, 90% <10 days old) admitted to the hospital with hyperbilirubinemia (mean TSB 22.6 mg/dL) (Hameed et al., 2011). The authors reported 87 of the 160 neonates (54%) had symptoms of ABE. The investigators found no evidence of a specific bilirubin level confirmed to lead to bilirubin encephalopathy; however, higher bilirubin levels were consistent with higher occurrence of bilirubin encephalopathy (found by physical exam at 3 months) and death (Table 8).

A 2009 case series (Hansen et al., 2009) reported on six infants with hyperbilirubinemia and intermediate ABE (moderate stupor, irritability and hypertonia) or advanced ABE (retrocollis／opisthotonos, shrill cry, anorexia, apnea, fever, deep stupor to coma, sometimes seizures and death) in the first week of life. All received phototherapy and four received exchange transfusion. All were reported to be neurologically normal on follow up (ranging from 17

months to 9 years). Two of the subjects had speech delay. Studies on the reversibility of advanced ABE are limited to case series.

Chronic Manifestations and Death

A subset of the literature focused on infants with high bilirubin levels in the newborn period and associated chronic manifestations or death. A study by the British Paediatric Surveillance Unit identified 14 infants with chronic bilirubin encephalopathy among 108 identified cases of physician-reported severe hyperbilirubinemia (≥29.8 mg/dL during the first month of life) (Manning et al., 2007). Among the 108 infants, the mean TSB level was 33.9mg/dL (range 29.8-46.8mg/dL); however the mean among infants with chronic bilirubin encephalopathy was 36.6mg/dL compared to 33.5 among infants with no bilirubin encephalopathy. Infants with chronic bilirubin encephalopathy were also likely to have a coexisting infection (p=0.007). Of the 14 infants with bilirubin encephalopathy, at follow up at 12 months of age, three subjects had died (all with history of infection), three were described as normal, two were lost to follow up, four had abnormal development felt to be related to chronic bilirubin encephalopathy (hearing loss, athetosis and severe hearing loss, athetosis and epilepsy, and cerebral palsy and severe hearing loss), and two had abnormal development felt to be unrelated.

A report from the Pilot USA Kernicterus Registry presented information on 125 individuals with chronic bilirubin encephalopathy (kernicterus) who were voluntarily reported to the registry between 1992 and 2004 (Johnson et al., 2009). All six of the deaths among the 125 in the first year of life were attributed to bilirubin toxicity (researchers stated 'hazardous hyperbilirubinemia'), and five of the six were within the first week of life. There was no evidence of a specific bilirubin level confirmed to lead to chronic bilirubin encephalopathy or death. Twenty-six of the 125 individual had documented G6PD deficiency; the remaining individuals with tested negative or were not tested.

A study of 710,533 births in the Danish National Hospital Register (DNHR) identified 15 individuals with an ICD-10 code for chronic bilirubin encephalopathy (kernicterus) (Maimburg et al., 2009). Upon further review of the medical records, six of 15 were determined to have a valid diagnosis of chronic bilirubin encephalopathy by the investigators as indicated by 1) history of TSB ≥26.3 mg/dL; 2) clinically reported symptoms of acute bilirubin encephalopathy in neonatal period and 3) the child had neurological and/or motor impairments or died as a potential consequence of elevated bilirubin. Three additional validated cases were identified outside of the DNHR. Peak TSB values among the nine neonates ranged from 31.1-43.6 mg/dL. All had symptoms of advanced ABE in the neonatal period. Of the nine total cases, three infants died (at 2, 5 and 19 months) as a potential consequence of elevated bilirubin. Of the six living children, reported outcomes were as follows: two had cerebral palsy and mental retardation, one had cerebral palsy and hearing impairment, one had mental retardation and hearing impairment, one had hearing impairment and one had minor motor impairment.

Two studies of neonatal hyperbilirubinemia in two birth cohorts, one in Canada (n = 56,019) and one in the United States (n = 106,627), identified no cases of chronic bilirubin encephalopathy (Jangaard et al., 2008; Newman et al., 2006).

A recent retrospective study reexamined the incidence of chronic bilirubin encephalopathy in live-borns in California from 1988-1997 (Brooks et al., 2011). The investigator identified children with a strict diagnosis of chronic bilirubin encephalopathy (by ICD-9 code) or a loose diagnosis (ICD-9 code associated with chronic bilirubin encephalopathy) through the Department of Developmental Services database's Client Development Evaluation Reports. The study identified 25 cases that followed the strict diagnosis and 95 who met the loose diagnosis. Both children with a strict and loose diagnosis were compared to all children with cerebral palsy (n = 9962). The presentation in the strict diagnosis group was consistent with descriptions of chronic bilirubin encephalopathy and the loose diagnosis group was consistent with the typical cerebral palsy group. For example, 64% of children with a strict diagnosis had hearing loss, compared to 16% of children with a loose diagnosis or 18% with typical cerebral palsy. Therefore, only the 25 cases of chronic bilirubin encephalopathy (kernicterus) were used to calculate the incidence. Using the number of reported live-borns in California during the study period, the incidence was found to be 0.44 per 100,000. The incidence was corrected to account for a reported 10% mortality rate and estimated at 0.49 per 100,000.

Developmental Follow-up after Neonatal Hyperbilirubinemia

Several large studies looked at developmental follow-up after exposure to elevated levels of bilirubin in the neonatal period. A study of a birth cohort of 56,019 in Canada compared outcomes of neonates with no history of hyperbilirubinemia (n = 52,240), with TSB 13.5-19 mg/dL (n = 3,431) and with TSB >19 mg/dL (n = 348) (Jangaard et al., 2008), with medical record follow up from two to nine years of age. There were no statistically significant differences in composite outcome (including diagnoses of deafness, cerebral palsy, developmental delay, gaze palsy, attention deficit disorder, autism spectrum disorders) as compared to controls in either the TSB 13.5-19mg/dL group (adjusted RR: 1.1; 95% CI: 1.0 –1.2) or the TSB >19 mg/dL group (adjusted RR: 1.1; 95% CI: 0.8 –1.4). The risk of developmental delay was significantly increased in the TSB 13.5-19mg/dL group (adjusted RR: 1.6; 95% CI: 1.3–2.0) and the risk of attention-deficit disorder was significantly increased in the TSB >19 mg/dL group (adjusted RR: 1.9; 95% CI: 1.1–3.3).

Two United States studies looked at children with neonatal hyperbilirubinemia. Among 41,324 infants, peak TSB level in the newborn period was not associated with IQ at seven years of age. Peak TSB was associated with abnormal or suspicious neurological examination results with increasing TSB level ($p<0.001$). The incidence of sensorineural hearing loss at age eight years was approximately 2%, regardless of bilirubin level (Newman & Klebanoff, 1993). Another study of a birth cohort of 106,627 identified 140 neonates with a TSB level >25mg/dL (Newman et al., 2006) and found no statistically significant differences in intelligence or visual–motor integration testing. Fourteen (17%) of the children with hyperbilirubinemia had "questionable" or abnormal findings on neurologic examination vs. 48 controls (29%), ($p = 0.04$).

A Danish study paired neonatal medical records to military records at 18-20 years of age to determine the association of neonatal hyperbilirubinemia with neuropsychiatric diagnoses or cognitive abilities in adulthood (Ebbesen et al., 2010). Of 13,181 subjects, 463 were diagnosed with neonatal non-hemolytic hyperbilirubinemia (peak TSB ranging from 6.1-28.1 mg/dL).

Neonatal exposure to non-hemolytic hyperbilirubinemia was not associated with any statistically higher risk of neuropsychiatric diagnosis or cognitive differences in adulthood. A similar Israeli study also paired neonatal records to military records at age 17 years (Seidman et al., 1991) found no association between mean IQ scores or school achievement with bilirubin level, after adjusting for confounders. In summary, evidence for long-term outcomes other than chronic bilirubin encephalopathy (kernicterus) is limited and inconsistent.

A summary of all abstracted literature pertaining to developmental follow-up, including smaller studies and studies without control groups, for subtle, acute and chronic manifestations is included in Tables 6 and 7.

Risk factors

A 1992 study of infants with 454 infants with TSB >12mg/dL (Singhal et al., 1992) categorized these infants into three groups based on cause of hyperbilirubinemia, peak TSB level, and response to treatment. The "mild" group consisted of cases with non-hemolytic origins and had the lowest peak TSB level, which required phototherapy at a later age and minimum duration. The "moderate" group consisted of cases caused by oxytocin, bruising or cephalohematoma, and prematurity; this group had peak TSB levels similar to the former group but required phototherapy significantly earlier. Within this group, the cases due to prematurity had significantly higher TSB levels and required phototherapy significantly longer. The "severe group," caused by ABO and Rh isoimmunization and G6PD deficiency, had significantly higher peak TSB levels at a significantly earlier age and required phototherapy at a significantly earlier age for a longer duration.

Newman et al. (1999) studied independent predictors for an infant ≥36 weeks gestation developing a TSB level >20mg/dL. They found positive associations for gestational age 36-37 weeks when compared to 39-40 weeks gestation (OR: 3.78), gestational age of 38 weeks when compared to 39-40 weeks gestation (OR: 2.02), Asian race when compared to all non-Asian and non-Black infants (OR: 2.16), and male sex (OR: 1.48). Burgos et al. (2008) analyzed factors associated with readmission of infants (≥34 weeks gestation) for jaundice within 14 days of birth. Factors associated with an increased chance of readmission included gestational age 34-38 weeks when compared to 40 weeks' gestation (34 week OR: 2.75; 35 week OR: 3.18; 36 week OR: 3.04; 37 week OR: 2.33; 38 week OR: 1.64), Medicaid or private insurance when compared to maternal insurance of HMO/PPO (OR: 1.45), Asian race when compared to white non-Hispanic (OR: 1.53), male gender (OR: 1.37), and birth weight <2500 grams when compared to a birth weight of 2500-4000 grams (OR: 1.24).

One population-based study noted that risk factors for chronic bilirubin encephalopathy include Asian race and prematurity (Burke et al., 2009). Other case series of children with chronic bilirubin encephalopathy noted factors such as early discharge and G6PD deficiency (AlOtaibi et al., 2005).

One recent study quantitatively evaluated risk factors for the development of adverse outcome (defined as death or chronic bilirubin encephalopathy) in newborns with hyperbilirubinemia by

looking at the presence of neurotoxicity findings in association with TSB levels (Gamaleldin et al., 2011). This study analyzed the interaction of TSB and risk factors (Rh hemolytic disease, sepsis, low admission weight, ABO incompatibility) as determinants of ABE and chronic bilirubin encephalopathy development in 249 newborns admitted with a TSB level ≥25 mg/dL (Gamaleldin et al., 2011). The threshold TSB level that identified 90% of infants with acute bilirubin encephalopathy was 25.4 mg/dL when neurotoxicity risk factors were present. Alternatively, neurotoxicity was not observed until a TSB level of >31.5 mg/dL in 111 infants without risk factors. The reason for variation in susceptibility of infants to a given TSB level remains unknown.

Late Preterm (Near-term) Population

Several studies stratified the study population by gestational age and included specific subgroup of late preterm newborns. While the late preterm population represents 9-10% of all births in the United States, it has a potentially greater risk of elevated bilirubin levels. In a study of hospital readmission trends over a 10-year period, Burgos et al. found a newborn with gestational age of 34-37 weeks had an increased likelihood (OR: 2.33–3.18) of readmission for hyperbilirubinemia (Burgos et al., 2008). Of the five infants followed in the Pilot USA Kernicterus Registry who died in the first week of life, four were born between ≥35 and <37 weeks gestational age (Johnson et al., 2009). Late prematurity was considered a risk factor for mortality due to chronic bilirubin encephalopathy in this study, as well as in a related study of the same population (Bhutani & Johnson, 2006).

Expert Information for Condition:

Dr. Kaplan reports no diagnosed case of chronic bilirubin encephalopathy in his department in the last 30 years.

Dr. Johnson-Hamerman submitted a review paper including answers to frequently asked questions (Bhutani & Johnson, 2009). This review reports the inability of linking the occurrence of chronic bilirubin encephalopathy to a specific level of TSB or the onset of bilirubin neurotoxicity. However, the review does state that a bilirubin rate of rise (ROR) of 0.2mg/dL per hour or more, if untreated, is likely to result in neonatal hyperbilirubinemia at levels >25 mg/dL and associated with bilirubin neurotoxicity.

B. Screening:

Key questions pertaining to screening:

- What methods exist to screen newborns for neonatal hyperbilirubinemia? What are their analytic validity, sensitivity and specificity?
- What tools are available to interpret the risk of developing hyperbilirubinemia associated with a newborn's bilirubin value? What is the predictive validity of these tools?
- How do timing of screening after birth, gestational age, threshold levels, and other considerations affect the number of infants identified with or being at significant risk for developing neonatal hyperbilirubinemia?
- What are the recommended follow-up and monitoring procedures for newborns found to be at risk of developing hyperbilirubinemia?
- Do outpatient facilities have the capacity to handle follow-up visits for at-risk infants?
- Have there been population-based universal predischarge hyperbilirubinemia screening trials?
- What are the potential harms or risks associated with screening?

Literature review:

Our systematic review process found 42 articles pertaining to screening. Three forms of screening for neonatal hyperbilirubinemia are described in this section, visual assessment, TcB, and TSB. Visual assessment of hyperbilirubinemia involves clinically examining a newborn and classifying the degree of yellowness of the skin or grading the cephalocaudal progression of hyperbilirubinemia (Kramer scale) (De Luca et al., 2008; Kaplan et al., 2008; Keren et al., 2009; Moyer, Ahn, & Sneed, 2000; Riskin, Abend-Weinger, & Bader, 2003). Noninvasive TcB measurement is an optical method for determining the yellowness of skin by measuring reflected light (Bhat & Rao, 2008; Boo & Ishak, 2007; Briscoe, Clark, & Yoxall, 2002; Dai, Krahn, & Parry, 1996; Karon et al., 2008; Laeeq, Yasin, & Chaudhry, 1993; Mishra et al., 2009; Sanpavat & Nuchprayoon, 2007; Schmidt et al., 2009). TSB measurement is the laboratory test for estimating the amount of bilirubin in the blood (Agarwal et al., 2002; Alpay et al., 2000; Prasarnphanich & Somlaw, 2007). This method requires blood sampling.

TcB and TSB

A comparison of several screening methods for bilirubin, including transcutaneous and laboratory methods, found TcB values correlated with TSB values ($r = 0.92$-0.97) (Grohmann et al., 2006; Leite et al., 2007). In the latter study, TcB best correlated to TSB at lower concentrations of bilirubin and had the highest sensitivity (88.2%) and specificity (97.8%) at 14mg/dL (Leite et al., 2007). A study comparing TcB to TSB in healthy hyperbilirubinemic newborns indicated a correlation coefficient of 0.80 at the forehead and 0.86 at the sternum (Boo & Ishak, 2007). Specifically in healthy late preterm (34-36 weeks gestation) infants, there was a significant correlation between TcB and TSB values ($F2 = 0.89$) (Fouzas et al., 2010). Given variations in each institution's populations, laboratory standards, observer differences, and TcB technology, the authors of these studies emphasize the importance of using TcB

screening cutoffs that provide the best correlation to TSB given the specific institution's population and methods for measuring TcB and TSB (Laeeq et al., 1993; Leite et al., 2007).

A study concluded that a TcB value <5 at 24 hours and <8 at 48 hours in healthy term newborns resulted in no measurable risk of developing hyperbilirubinemia (defined as ≥17mg/dL at >72 hours); none of the 135 infants with a value <5 at 24 hours and none of the 200 infants with a value of <8 at 48 hours developed hyperbilirubinemia within the first week of life (Bhat & Rao, 2008).

Table 10 summarizes TcB screening characteristics for detection of an elevated TSB value in both term and preterm infants. Table 11 summarizes TcB screening characteristics for detection of subsequent hyperbilirubinemia, that is, the development of hyperbilirubinemia after the initial TcB reading.

Table 12 summarizes TSB screening characteristics for detection of subsequent hyperbilirubinemia. These studies are in agreement on the utility of using such screening to rule out subsequent hyperbilirubinemia in infants with TSB values below a selected cutoff that provides a high negative predictive value (Agarwal et al., 2002; Alpay et al., 2000; Prasarnphanich & Somlaw, 2007). Authors report decreasing numbers of blood draws in the newborn nursery for TSB as a result of TcB screening, with percent reduction ranging from 20%-34% (Briscoe et al., 2002; Dai et al., 1996; Mishra et al., 2009).

Visual Assessment

The reliability of clinicians' visual assessment of neonatal hyperbilirubinemia has been compared to TcB and TSB measurements to determine the accuracy of visual assessment. Underestimation of TSB level was the most common diagnostic error when visual assessment alone was used, occurring in the range of 16.7-40.4% cases. Adding TcB screening to visual assessment reduced underestimating TSB to 0-9.2% of cases. Combining visual assessment with TcB reduced the range of overestimating TSB from 4.9-35.7% to 2.1-11.1%. Combining visual assessment with TcB also increased the sensitivity of predicting TSB levels of 12.1-15 mg/dL from 5.7% to 30.8% and specificity from 99.1% to 100% (De Luca et al., 2008). A study comparing blood draws for TSB based on visual assessment and TcB in 346 healthy term and late-term newborns revealed screening with TcB resulted in fewer blood draws (14% vs. 24%) with a similar yield for newborns in the >75th percentile than using visual assessment alone (37% compared to 25%, respectively) (Kaplan et al., 2008).

The Kramer scale is a clinical tool for the visual assessment of hyperbilirubinemia. The grade on the Kramer scale indicates the progression of the yellowing on the infant's body, and is used to quantify the yellow color of an infant's skin by dividing the body into five zones. The yellowing of the skin initially presents at the head and extends to the feet as the bilirubin level rises, thus grade 1 is at the head and grade 5 at the feet. A study of the Kramer hyperbilirubinemia grading scale showed the absence of hyperbilirubinemia (Kramer grade of "0") corresponded to bilirubin values in the low-risk zone on the hour-specific bilirubin nomogram 84% of the time. Additionally, of the 91 (out of 522 total) infants with a grade of

"0," one developed significant hyperbilirubinemia, giving a negative predictive value of 99% (Keren et al., 2009). In another study on VA, hyperbilirubinemia not present below the middle of the chest was 97% sensitive predicting bilirubin values of <12mg/dL (Moyer et al., 2000).

Risk assessment

Clinicians have developed hour-specific bilirubin nomograms for interpreting risk of hyperbilirubinemia based on TSB (Bhutani et al., 1999; Sarici et al., 2004) or TcB values (Engle et al., 2009; Fouzas, Mantagou et al., 2010; Varvarigou et al., 2009). Bhutani et al. plotted an hour-specific nomogram based on the predischarge and follow-up TSB values of 2840 healthy term and near-term newborns. From these values, low to high risk zones were defined by the 40th, 75th and 90th percentiles of TSB values in the study population (Table 13, Appendix A) (Bhutani et al., 1999). More recent studies have shown that TcB measurements can be applied to the same nomogram to assess risk (Table 14) (Bhutani et al., 2000; Dalal et al., 2009).

Dalal et al. compared timing of TcB measurements by comparing the predictive value of samples taken at 1) 24 ±6 hours, 2) 12 hours later but not after 48, and 3) the difference in samples at the two time points (Dalal et al., 2009). The sensitivity for detecting infants in the >75th percentile (consistent with the high-intermediate risk zone on the Bhutani hour-specific TSB nomogram) of these three sampling methods was comparable (80.4%, 82.6%, and 82.5%, respectively). However, the positive likelihood ratio for the 30-48 hour time point was higher than that of the 24±6 hour time point (4.0 vs. 1.9). The positive likelihood ratio of the change in the two time points was 4.8.

A recent prospective study of a risk assessment strategy combined predischarge bilirubin values plotted on the hour-specific nomogram (Bhutani et al., 1999), paired with gestational age (Goncalves et al., 2011). Data from 396 newborns (≥35 weeks and ≥2500g or ≥36 weeks and ≥2000g), found the predischarge bilirubin risk zone was the strongest predictor of developing subsequent significant hyperbilirubinemia. Combining the risk zone with gestational age data significantly improved the predictability of using risk zone alone (area under the curve 0.90 compared to 0.86).

Current Practice and Implementation of Bilirubin Newborn Screening

A retrospective analysis of 11 California hospitals revealed inter-hospital variation in bilirubin screening practice (Newman et al., 1999). The number of infants receiving at least one TSB at the birth hospital within the first 30 days of life varied from 17% to 52%. The proportion of infants having a TSB performed was strongly correlated with the proportion having a maximum TSB level <10mg/dL; with more frequent TSB testing associated with detection of more infants with a low TSB.

Petersen et al. reviewed the incidence of hyperbilirubinemia after implementing predischarge TcB screening in hyperbilirubinemic newborns in a single newborn nursery (Peterson et al., 2005). The number of TSB tests ordered did not change significantly after TcB screening was implemented. However, the proportion of newborns treated with phototherapy did increase after implementing TcB screening, from 5.9% to 7.7%. In the study period, the mean number of

readmissions for hyperbilirubinemia within seven days of discharge decreased from 4.5 to 1.8 per 1000 births per month.

The results of universal neonatal predischarge bilirubin screening in response to the 2004 AAP revised clinical practice guidelines have been documented in the literature. Mah et al. presented a five-year study before, during and after implementation of universal screening in 116 hospitals (Mah et al., 2010). The study followed the occurrence of TSB of 25-29.9mg/dL and ≥30mg/dL and use of phototherapy during this time. The study showed the incidence of infants with TSB levels 25-29.9mg/dL declined from 43 to 27 per 100,000. The incidence of infants with TSB of ≥30mg/dL decreased from nine to three per 100,000. During the study period, there was a small but significant increase in the use of phototherapy.

In a similar study, Kuzniewicz, Escobar, and Newman studied 11 hospitals in California from 1995-2007 (Kuzniewicz, Escobar, & Newman, 2009). They found universal bilirubin screening (TSB or TcB) was associated with a significantly lower incidence of hyperbilirubinemia at or above the AAP threshold for EcT and increased phototherapy use. The study concluded that a newborn at a hospital with universal bilirubin screening had an adjusted odds ratio (OR) for developing a TSB level of ≥25mg/dL of 0.22 for those using TSB screening and 0.25 for those using TcB screening, compared with facilities and years when universal screening was not being performed.

Eggert et al. followed 18 hospitals before and after predischarge screening was implemented (Eggert et al., 2006). The incidence of TSB levels >20mg/dL dropped from 1 per 77 to 1 per 142 and for levels >25mg/dL from 1 per 1522 to 1 per 4037. Hospital readmissions for hyperbilirubinemia dropped from 0.55% to 0.43%.

Facchini et al. report on the outcomes of an outpatient follow-up program in Brazil for newborns discharged with a bilirubin level falling above the 40th percentile on the Bhutani nomogram (Facchini et al., 2007). Of the cohort, 21.8% were asked to follow-up in the hyperbilirubinemia clinic at 24-72 hour intervals, based on the predischarge screening values. Of these, 80 of 2,452 (3.7%) newborns were readmitted at the follow-up visit for treatment with phototherapy. Of the newborns asked to follow-up due to a bilirubin value that placed them between the 40th and 75th percentile, 0.6% reached ≥ 20 mg/dL, requiring phototherapy treatment. Of the 8,807 newborns not asked to follow-up in the hyperbilirubinemia clinic, one returned with a bilirubin value requiring treatment.

Expert Information for Screening:

The experts agreed that a United States population-based large-scale (whole city or state) predischarge bilirubin newborn screening effort does not currently exist. Additionally, the experts stated that there is not a database or other tracking method to know the amount of nurseries/hospitals in the United States that have adopted the AAP guidelines and implemented predischarge bilirubin newborn screening.

Drs. Bhutani and Stark shared information from their manuscript under review, a multi-center United States study of 1157 infants who were screened and followed up to age 33 days over a one and a half year period. This study prospectively looked at and selected six different models to predict hyperbilirubinemia including taking into account, bilirubin levels, hour-specific bilirubin levels, gestational age and multiple clinical risk factors separately and together. The investigators found that assessments of risk factors and hour-specific bilirubin levels used together were able to better predict hyperbilirubinemia (as defined by bilirubin level high enough for the need for phototherapy).

C. Treatment:

Key questions pertaining to treatment:

- What methods exist to treat neonatal hyperbilirubinemia and what is their effectiveness? What is the relationship between outcomes and the timing of treatment intervention?
- What is the availability of treatment?
- What are the potential harms or risks associated with treatment?
- Does treating neonatal hyperbilirubinemia reduce the incidence of acute and chronic bilirubin encephalopathy?
- What proportion of cases of chronic bilirubin encephalopathy would be prevented with earlier detection and treatment of hyperbilirubinemia? What proportion of cases of other neonatal hyperbilirubinemia manifestations would be preventable?

Literature review:

Our systematic review process found 33 articles pertaining to treatment. The two currently accepted forms of treatment for the management of neonatal hyperbilirubinemia are phototherapy and exchange transfusion (EcT). Multiple studies reference the 1994 or 2004 treatment guidelines proposed by the AAP. For reference, the AAP treatment guidelines are summarized in Appendix A.

Phototherapy

Light therapy is used to treat cases of neonatal hyperbilirubinemia through the photons' ability to transform bilirubin into compounds that are more water soluble, allowing the infant to excrete excess via urine and stools. Published in 1990, but from a trial that took place from 1974-1976, the National Institute of Child Health and Human Development Randomized, Controlled Trial of phototherapy for neonatal hyperbilirubinemia investigated whether or not phototherapy effectively lowered serum bilirubin levels and what adverse outcomes were present at one and six years of age (Scheidt et al., 1990). The study was conducted at six neonatal care centers and randomly assigned 1,339 newborn infants to phototherapy or control groups (treatment with EcT) using the following subgroups: (1) birth weight <2000g; (2) birth weight 2000-2499g and bilirubin level >10mg/dL; or (3) birth weight ≥2500g and bilirubin level >13mg/dL. Follow-up with neurological and developmental examinations were completed at one and six years of age and it was found that phototherapy and control groups had similar rates of cerebral palsy (5.8% vs. 5.9%), other motor abnormalities including clumsiness and hypotonia (11.1% vs. 11.4%), sensorineural hearing loss (1.8% vs. 1.9%) and intelligence (verbal, 96.8 vs. 94.8; performance, 95.8 vs. 95.1, for phototherapy and control groups, respectively). Phototherapy treatment was found to effectively decrease the concentration of serum bilirubin levels, but the evidence did not state the rate or levels of decrease.

A recent study analyzed the effect of phototherapy on TSB levels (De Carvalho et al., 2011), using medical records of 116 newborn infants with hyperbilirubinemia (TSB ≥20 mg/dL) and a mean initial TSB concentration of 22.4±2.4 mg/dL. The mean birth weight and gestational age were 3161±466 grams and 37.8±1.6 weeks. All study subjects received phototherapy, and no infant necessitated exchange transfusion. The decline in TSB levels (mg/dL/hour) at 2, 6, 12

and 24 hours of treatment was, respectively, 1.5 ± 0.7 (CI 95% 1.37– 1.62), 0.83 ± 0.5 (CI 95% 0.73–0.92), 0.73 ± 0.26 (CI 95% 0.68–0.77) and 0.46 ± 0.12 (CI 95% 0.42–0.49). This translates into percentage declines of 9.4%, 16%, 23%, 40%, 44% and 50%, respectively. The mean duration of phototherapy was of 35.4 ± 19.5 hours (range, 10–132 hours). After 24 hours, only 36% of the patients (n = 42) were still receiving phototherapy treatment. BAEP was performed in all of the patients and abnormal in three initially. However, when repeated three months later, 100% of the BAEP examinations were normal, and all patients had normal neurological examinations.

Other effectiveness of phototherapy evidence includes a study in Turkey that followed 30 otherwise healthy term newborns with marked hyperbilirubinemia (20-24mg/dL) who were treated with intensive phototherapy during the newborn period in the hospital until they reached serum bilirubin levels below 20 mg/dL, and 30 age-matched controls without elevated bilirubin levels (Duman et al., 2004). None of the study subjects developed hearing loss, developmental delay or abnormal neurological findings as found at follow-up between two and six years of age. In addition to hospital phototherapy, a pilot study of 18 babies given home phototherapy were compared with matched controls given hospital phototherapy in Malaysia, and investigated the efficacy of home phototherapy in term babies with uncomplicated hyperbilirubinemia (Zainab & Adlina, 2004). Phototherapy-related complications included skin rash (1 home; 2 hospital) and diarrhea (3 home; 2 hospital). The mean daily decrease in bilirubin levels was more in the home (3.12 + 2.16 mg/dL) group as compared with the hospital group (1.29 + 1.50 mg/dL) and this difference was significant (t=2.95, df=17, P <0.01). No other evidence reported home phototherapy use and outcomes.

Two studies investigated the impact of universal screening on phototherapy use. In one study, a total of 38,182 infants (10.6%) were born at facilities that had implemented universal bilirubin screening and were compared with infants born at facilities that were not screening (Kuzniewicz et al., 2009). The screened infants had a 62% lower incidence of TSB levels exceeding the AAP EcT guideline (0.17% vs. 0.45%), received twice the inpatient phototherapy (9.1% vs. 4.2%), and had slightly longer birth hospitalization lengths of stay (50.9 vs. 48.7 hours). Newman et al. looked at a similarly screened study population of over 20,000 newborns (Newman et al., 2009). They found that for those who had phototherapy, 75.4% began within 8 hours of the qualifying TSB level (within 3mg/dL of the AAP recommended phototherapy threshold) and that hospital phototherapy in 22,547 newborns was 85% effective in preventing TSB levels from rising to levels at which the AAP recommends EcT. The estimated number needed to treat from this study was 222 for boys and 339 for girls to prevent one infant from developing a bilirubin level at which the AAP recommends EcT.

Two studies looked at decreasing exposure of phototherapy while maintaining effectiveness of lowering bilirubin levels. One observational study in Israel found that phototherapy interventions decreased after the publication and enactment of the AAP guidelines (1994) in their two hospitals, from 7.9% (514/6499) before to 2.9% (251/8650) ($p < 0.0001$) after among full-term infants, and from 20.9% (102/489) before to 9.4% (47/502) ($p < 0.0001$) after in near-term infant interventions (Seidman et al., 2001). Following strict guidelines for the initiation of

phototherapy also decreased readmission rate due to hyperbilirubinemia (15.7 hospital days may have been saved per 1000 live full-term births). In a separate study of 58 newborns also in Israel, Lazar and colleagues (1993) found that when they discontinued phototherapy earlier and arbitrarily at an average bilirubin concentration of 13 ± 0.7 mg/dL in full term and 10.7± 1.2 mg/dL in preterm infants, rise of bilirubin concentration post discontinuation of treatment ('rebound bilirubin') in both groups were similarly small (0.86 mg/dL vs. 0.83 mg/dL, respectively) (Lazar, Litwin, & Merlob, 1993). Additionally, no infant required reinstitution of phototherapy.

Harms of Phototherapy

Reported phototherapy side effects include fluid loss, temperature instability, skin rash, diarrhea, and corneal damage (numbers affected not stated) (Seidman et al., 2001). In a study where phototherapy was used with 4,126 infants in Australia, the most common side effects were pyrexia and diarrhea (numbers affected not stated) and no deaths were attributable to its use (Guaran et al., 1992). One study looked at the effect of phototherapy on cognitive performance and compared IQ test scores at 17 years of age for subjects born four months before and ten months after the introduction of phototherapy (Seidman et al., 1994). Phototherapy was found to have no independent effect on IQ scores, and phototherapy had no effect on intellectual ability in late adolescence (Seidman et al., 1994). A rare side effect, bronze baby syndrome, was found in the literature in only one unabstracted case report (Bertini et al., 2005, section XIII Table of case reports). Siegfried, Stone, and Madison (1992) reported two premature infants who underwent phototherapy treatment and experienced ultraviolet light burns. No abstracted evidence assessed the levels of intensity of phototherapy and associated harms at varying levels of intensity.

Four other papers specifically focused on the potential harms of neonatal hyperbilirubinemia treatment with phototherapy. One study looked at whether hyperbilirubinemia and phototherapy together with transient separation during the neonatal period in 107 infants is associated with impaired mother-child attachment after the first year of life (Schedle & Fricker, 1990). At one year of age, infants were given a pediatric examination and Denver test, and mother-infant pairs were observed in Ainsworth's strange situation. Results had a similar distribution in the three different groups, whereby infants with no hyperbilirubinemia, hyperbilirubinemia without phototherapy and hyperbilirubinemia with phototherapy all had similar attachment patterns.

Among 30 infants and untreated age-matched controls before and after phototherapy from 24 to 48 hours (Abrol & Sankarasubramanian, 1998), the phototherapy group had more crying episodes and poorer scores ($p<0.01$) in three orientation items at the first and follow-up assessments. Alertness levels in the study group were unaffected. The researchers noted that hyperbilirubinemia, covering of the eyes, exposure to light and maternal separation could all be contributing to the behavior changes. In particular, the infant's eyes must be covered during phototherapy and blindfolding has been found to result in abdominal distention.

A retrospective cohort study from the United Kingdom looked at the impact of neonatal phototherapy on risk and development of subsequent skin cancer from 1976-1990 and comprised 77,518 subjects (Brewster et al., 2010). The researchers found no statistically significant evidence of an excess risk of skin cancer following neonatal phototherapy; however, due to limited statistical power and follow-up duration, the researchers could not rule out the potential carcinogenic effect of phototherapy completely. A separate cross-sectional study used 58 sets of monozygotic and dizygotic twins and 1 set of triplets to determine the effect of phototherapy on the development of melanocytic nevi (Csoma et al., 2011). One twin received phototherapy, and the other did not. A whole-body skin examination and ophthalmologic evaluation were performed to determine the density of melanocytic skin lesions and the prevalence of benign pigmented uveal lesions. Phototherapy was associated with a higher prevalence of both cutaneous and uveal melanocytic lesions (P=0.005).

The literature also included evidence on possible increased parental perceptions of infant vulnerability and potentially increased outpatient visit rates in this population (Usatin et al., 2010). The researchers compared three groups: the first never had a documented TSB level ≥12 mg/dL (n=128,417), the second group had a TSB level between ≥17 and <23 mg/dL as outpatients between 48 hours and 7 days of age but did not receive inpatient phototherapy (n=6777), and the last group was identical to the second group, but did receive inpatient phototherapy (n=1765). The investigators studied outpatient visit rates from 15 to 364 days of age, and found that compared with infants who never had a bilirubin level >12 mg/dL, infants with bilirubin levels of 17.0-22.9 mg/dL averaged only 0.36 extra first-year visits when they did not receive phototherapy and 0.73 extra visits when they did. These findings showed that neonatal hyperbilirubinemia and inpatient phototherapy were associated with only a small increase in first-year outpatient visit rates, and is consistent with a mild or infrequent contribution to vulnerable child syndrome.

Exchange Transfusion (EcT)

EcT was developed by Louis Diamond and colleagues more than 50 years ago and is a medical procedure in which the hyperbilirubinemic infant's blood is withdrawn and replaced by unaffected donor blood to lower the infant's total serum bilirubin level (Abu-Ekteish et al., 2000). Until 1965, when phototherapy was introduced as an option for treatment, EcT was considered the only treatment available for hyperbilirubinemia (Guaran et al., 1992). However, the bilirubin level at which EcT is performed still remains controversial (Jackson, 1997). Current guidelines for treatment with EcT from the AAP depend upon different TSB levels at varied birth weights and gestational ages; still, much of the treatment evidence did not state specific bilirubin levels or ages at which investigators performed EcT (Table 16).

Harms of EcT

The mortality rate of EcT has been calculated as 0.53 per 100 patients and 0.3 per 100 procedures (Jackson, 1997). The morbidity rate has been noted as 12-15.3%, and one study indicated that 74% of EcTs were associated with an adverse event (Patra et al., 2004). Additionally, morbidity and mortality are greater in infants undergoing EcT with a prior illness

compared to healthy infants (Jackson, 1997; Sanpavat, 2005). Morbidity and mortality in relation to EcT is shown in Table 17.

Because many of the complications of EcT are unavoidable, the way to reduce complications is to prevent the need for EcT (Jackson, 1997). Two studies found a decline in the frequency of EcT at Yale New Haven Hospital over a two decade period of time ($p=0.01$), as well as an 87% decrease in two Jerusalem hospitals ($p< 0.001$), in particular, after the adoption of the 1994 AAP practice parameter guidelines for the treatment of hyperbilirubinemia and use of phototherapy (Seidman et al., 2001; Steiner et al., 2007).

Early intervention and neurological and developmental outcomes

Neurological and developmental insult due to hyperbilirubinemia presents as a wide clinical spectrum (Table 18). Ethical obstacles prevent prospective randomized controlled trials to address the question of effectiveness of treatment in reversing effects of bilirubin toxicity (Hansen et al., 2009). Case series and cohort studies provide a more limited opportunity to examine treatment outcomes and the potential of treatment to reverse clinical manifestations.

Studies showed mixed results regarding the reversal of neurological and developmental manifestations after treatment (Table 18). Some studies suggest no or minimal resolution of neurological and developmental manifestations after treatment (Chen et al., 2006; Lee, Chen, & Tang, 2002; Newman et al., 2006). Other studies, including ones with longer follow-up periods, show recovery from early clinical manifestations of hyperbilirubinemia (Agrawal et al., 1998; Deorari et al., 1994; Funato et al., 1996; Hansen et al., 2009; Wolf et al., 1999; Wong, Chen, & Wong, 2006).

Expert Information for Treatment:

The experts corroborated the literature findings.

D. Economic evaluation

Key questions pertaining to economics:

- What are the costs associated with the screening test?
- What are the costs associated with the failure to find at risk newborns in the pre-symptomatic period?
- What are the costs associated with treatment of neonatal hyperbilirubinemia?
- What are the costs associated with treatment of acute and chronic bilirubin encephalopathy?
- What is the cost-effectiveness of newborn screening for neonatal hyperbilirubinemia?

Literature review:

Five papers were identified as including cost and/or economic outcomes related to screening for hyperbilirubinemia. Two of the papers were classified as economic evaluations and three had other study designs (Table 1). Of these papers, four were cost analyses that reported some limited cost data but did not evaluate the cost-effectiveness or cost-benefit of newborn screening for hyperbilirubinemia (Burgos et al., 2008; Newman et al., 1990; Petersen et al., 2005; Prasarnphanich & Somlaw, 2007). These studies report some costs related to key questions but the studies, in general, are not of high quality. Table 20 lists reported cost outcomes and major drawbacks for each paper.

One study (Petersen et al., 2005) estimated TcB testing charges and compared them with averted hospitalization charges. This analysis found that the large decrease in readmission hospital charges for the screened group offset much of the charges for increased screening and treatment. However, this did not result in net cost savings due to the large increase in the number of newborns treated by phototherapy and instead resulted in an insignificant increase in charges.

We identified one cost-effectiveness analysis of strategies to prevent chronic bilirubin encephalopathy in newborns (Suresh & Clark, 2004). The study evaluated the cost-effectiveness of three strategies designed to prevent chronic bilirubin encephalopathy compared to current management. Table 21 lists the key design elements of this study. The analysis used a decision analytic model to project costs and outcomes for the 4 different management alternatives:

1. Current management
2. Universal follow-up one to two days after early discharge
3. Routine predischarge serum bilirubin testing with selective follow-up and laboratory testing (TSB)
4. Routine predischarge transcutaneous bilirubin with selective follow-up and laboratory testing (TcB)

The study used a “modified societal” perspective in which indirect costs of lost productivity were included for long-term outcomes but short-term indirect costs related to caregiver time

were excluded. The time horizon of the analysis was lifetime. The target population was defined as an annual cohort of healthy term infants in the United States (approx 2.8 million). Short-term costs included those associated with bilirubin testing, phototherapy, outpatient visits, home nurse visits, and hospitalizations. Long-term costs of medical care, special education, and lost productivity associated with chronic bilirubin encephalopathy were also included. The main outcome measure was cost per case of chronic bilirubin encephalopathy prevented. The base case analysis assumed incidence of chronic bilirubin encephalopathy was 1 in 100,000 healthy newborns and the relative risk ratio for screening strategies was 0.7 (this translated to an additional 20 cases of chronic bilirubin encephalopathy prevented for each screening strategy). Compared to current management, universal follow-up was the most expensive strategy and predischarge serum bilirubin (TSB) was the least expensive. None of the strategies resulted in cost savings. The cost per case prevented for predischarge serum bilirubin was projected to be $5,743,905.

Results were very sensitive to changes in the baseline incidence of chronic bilirubin encephalopathy, the relative risk ratio for preventive strategies. Additional sensitivity analyses were not conducted. This study has some key limitations: the main outcome is cost per case and no estimate of quality-adjusted life years is provided, the sensitivity analyses are insufficient to fully characterize which parameters are driving results, and some of the sources for resource utilization costs are unlikely to be generalizable. As the study did not report additional sensitivity analyses, it is not possible to evaluate the impact of alternative assumptions for costs of testing and follow-up on the cost per case results. It is likely that the results would also be sensitive to assumptions related to testing and follow-up costs. The analysis also does not include the potential benefit of averting other long-term outcomes related to hyperbilirubinemia (e.g., ABE). Without including quality-adjusted life years as an outcome, it is not possible to evaluate the cost-effectiveness of chronic bilirubin encephalopathy prevention strategies to screening for other conditions.

Expert Information for Economics:

Two experts reported cost data from screening experience at their institution. Dr. Bhutani shared that local institutional data collected (self-report) showed no extra handling cost with TSB at time of metabolic screening (he reported minimal cost to use reagents, with no extra cost for personnel). Dr. Johnson-Hamerman submitted a paper resulting from the Evidence vs. Experience in Neonatal Practices conference that estimated the TSB costs at less than a dollar (Bhutani, Vilms, & Hamerman-Johnson, 2010). The estimated cost for a TcB measurements comes from the initial investment in the device ($2,000 to $4,000, no source provided) and cost of disposable probes (for calibration and hygiene) estimated at $5 with estimated range for variable costs of predischarge bilirubin screening testing from less than $1 to $5.

XI. Key findings and summary

Table 22 – Strength of Evidence for Key Neonatal Hyperbilirubinemia Questions

Number of studies; subjects	Design	Risk of bias/study quality	Consistency	Directness	Precision	Strength of evidence
High total serum bilirubin concentration leads to acute clinical manifestations						Moderate
27; 49,276	Case Series (16), Case control (6), Cohort (4), Cross sectional (1)	Poor	Inconsistent	Direct	Imprecise	-
Evidence Summary: Direct evidence that, when compared to controls, newborns with increased total serum bilirubin levels experienced an increase in acute clinical manifestations.						
Additional sensitivity of TcB over visual assessment for hyperbilirubinemia						Fair
2; 863	Prospective Cohort	Good	Inconsistent	Direct	Imprecise	-
Evidence Summary: TcB detects most cases of neonatal hyperbilirubinemia that may necessitate further assessment. Adding TcB to visual assessment increased the sensitivity of predicting TSB levels of 12.1-15 mg/dL from 5.7% to 30.8%. Evidence suggests that TcB leads to less subsequent TSB blood draws and a greater number of newborns identified at and above the higher risk 75th percentile.						
Specificity and sensitivity of risk assessment/ predischarge screening prediction						Moderate
8; 21,541	Prospective Cohort	Good	Inconsistent	Direct	Imprecise	-
Evidence Summary: The specificity of the predischarge screening and risk assessment nomogram for at and above the 75th risk percentile is high 84.7% for TSB, ≥79% for TcB). The sensitivity at and above the 75th risk percentile is also high (90.5% for TSB, >82% for TcB). At and above the 40th percentile, the specificity is 64.7% (TSB) or 38.4% (TcB) and the sensitivity is 100% (TSB) or 94.1% (TcB). The evidence does not address whether this prediction assessment decreased the incidence of chronic bilirubin encephalopathy.						
Screening for hyperbilirubinemia prevents chronic bilirubin encephalopathy						Poor
0; 0	N/A	N/A	N/A	N/A	N/A	-
Evidence Summary: No data provide direct evidence that screening for neonatal hyperbilirubinemia prevents chronic bilirubin encephalopathy.						
Effectiveness of early intervention						Moderate
12; 18,445	Prospective Cohort	Good	Inconsistent	Indirect	Imprecise	-
Evidence Summary: Indirect evidence that early intervention is associated with improved outcomes for those with neonatal hyperbilirubinemia. Direct evidence suggests that earlier treatment with phototherapy decreases the likelihood of necessitating intervention with EcT, and potentially reducing adverse events. Evidence indicates treatment lowers elevated bilirubin concentration levels, and lower bilirubin level is associated with less acute clinical manifestations.Limited evidence suggests treatment prevents chronic bilirubin encephalopathy.						

Condition Key Findings

- Is neonatal hyperbilirubinemia well-defined (natural history, incidence, prevalence, and spectrum of severity)? When does it appear clinically? What are the known risk factors, if any?

  The incidence of neonatal hyperbilirubinemia varies by the level of hyperbilirubinemia used; from 5% at bilirubin levels >12mg/dL to 0.01% at >30mg/dL. Bilirubin levels >30mg/dL range from 3-12 cases per 100,000. Serum bilirubin peaks around 4 days of age, with earlier and higher peaks for neonates with risk factors that include prematurity, isoimmunization, hemolytic disease, low birth weight, and Asian race.

- What characterizes acute and chronic bilirubin encephalopathy (natural history, incidence, prevalence, and spectrum of severity)?

  Acute symptoms can include lethargy, poor sucking, hypotonia, stupor and a week Moro reflex, although advanced symptoms of encephalopathy (ABE) with hypertonia of the extensor muscle groups and seizures in addition to the acute symptoms are substantially less common. Incidence of ABE (not including the subtle-symptom cases) is less than 1 per 200,000 live births. Evidence suggests ABE symptoms present between peak bilirubin levels of 22.5-48.2mg/dL, with well-defined cases of advanced symptoms of ABE occurring at >30.0mg/dL. Of note, not all neonates with high bilirubin levels will present with acute symptoms and/or ABE; evidence suggests subtle manifestations are more common but there is limited evidence of persistence of these symptoms.

  Manifestations of chronic bilirubin encephalopathy (kernicterus) can include cerebral palsy, hearing impairment, mental retardation and motor impairment. Mortality rates among the two studies focused on chronic bilirubin encephalopathy ranged from 4.8% (in the first year of life) to 33.3% (2-15 months of age). Two studies of neonatal hyperbilirubinemia in birth cohorts in Canada and the United States did not identify any cases of chronic bilirubin encephalopathy.

  Estimates of the incidence of chronic bilirubin encephalopathy range from 0.49 to 2.7 per 100,000, with most evidence indicating rates less than 1 per 100,000.

- What evidence is available regarding the relationships among neonatal hyperbilirubinemia and acute and chronic bilirubin encephalopathy?

  The abstracted literature describes a spectrum of subtle, acute and chronic manifestations of neonatal hyperbilirubinemia; however, differences in study population and design limit the ability to compare across studies. No specific bilirubin level is associated with manifestations of acute or chronic bilirubin encephalopathy, although higher levels of bilirubin in the newborn period have been associated with higher occurrence of these manifestations. Evidence demonstrates nearly all cases of chronic bilirubin encephalopathy resulting in otherwise healthy infants have bilirubin levels >25mg/dL; rare cases occurring below bilirubin levels of 25mg/dL have existing comorbidities and/or significant risk factors.

- Is neonatal hyperbilirubinemia associated with more subtle adverse outcomes other than acute and chronic bilirubin encephalopathy?
  Studies of neurodevelopmental outcomes (other than chronic bilirubin encephalopathy [kernicterus]) associated with neonatal hyperbilirubinemia provide little evidence of any persistent abnormalities.

Screening Key Findings

- What methods exist to screen newborns for neonatal hyperbilirubinemia? What are their analytic validity, sensitivity and specificity?
  The three currently practiced forms of screening for neonatal hyperbilirubinemia are visual assessment, TcB measurement, and TSB measurement. TcB appears to be a reliable screening tool for detecting significant hyperbilirubinemia requiring confirmatory follow-up with TSB.

  The reliability of clinicians' visual assessment of neonatal hyperbilirubinemia indicates underestimation of TSB level the most common diagnostic error. Combining visual assessment with TcB increases the sensitivity of predicting TSB levels of 12.1-15 mg/dL from 5.7% to 30.8% and specificity from 99.1% to 100% (De Luca et al., 2008). The visual assessment grading system did not prove accurate in approximating TSB >12mg/dL or high risk of developing subsequent hyperbilirubinemia. In the case of TcB screening characteristics for detection of subsequent hyperbilirubinemia, multiple cutoff levels and time points have been tested. A TcB index value of <5 at 24 hours and <8 at 48 hours can predict subsequent hyperbilirubinemia (≥17mg/dL at >72 hours of age) with a sensitivity and NPV of 100%. Sensitivity, specificity, PPV and NPV vary with the timing and screening cutoff used. Such screening can rule out subsequent hyperbilirubinemia in infants with TSB values below these cutoffs. Furthermore, an hour-specific bilirubin nomogram based on TSB values allows prediction of subsequent hyperbilirubinemia. The risk nomogram can also be applied to TcB values, with sensitivity ranging from 100-82.6% and specificity from 88.1-79% for predicting neonates in the >75th percentile of the nomogram.

- How do timing of screening after birth, gestational age, threshold levels, and other considerations affect the number of infants identified with or being at significant risk for developing neonatal hyperbilirubinemia?
  Current practice and implementation of bilirubin newborn screening includes inter-hospital variability in bilirubin screening practice. Multi-hospital universal bilirubin screening (TSB or TcB) was associated with a significantly lower incidence of hyperbilirubinemia and lower rates of hospital readmissions due to bilirubin levels. Further work should address the most beneficial timing of screening, optimal threshold value for action, and what follow-up and monitoring should occur for the intermediate risk level group. Of note, all screening studies evaluated were completed in large hospital settings and may not generalize to smaller institutions.

- What are the potential harms or risks associated with screening?
  With initial screening with TcB, the number of blood draws in the newborn nursery for TSB can be significantly reduced, preventing unnecessary blood draws and associated harms such as pain and blood loss. The evidence did not indicate other risks or harms associated with screening.

Treatment Key Findings

- What methods exist to treat neonatal hyperbilirubinemia and what is their effectiveness? What is the relationship between outcomes and the timing of treatment intervention?
  The two currently accepted forms of treatment for the management of neonatal hyperbilirubinemia are phototherapy and EcT. Before the introduction of phototherapy, EcT was considered the only effective treatment available for hyperbilirubinemia, although its use has declined dramatically in recent years. Adverse events remain common after EcT, with mortality approximately 0.53 per 100 patients and 0.3 per 100 procedures, and morbidity ranging from 12-15.3%

  Controlled trials indicate that phototherapy effectively decreased levels of total serum bilirubin in the neonatal period without evidence of adverse neurological or developmental outcomes at six years of age. Several studies corroborated these findings, and found phototherapy 85% effective at lowering bilirubin levels to reduce the risk of bilirubin toxicity. Direct evidence suggests that earlier treatment with phototherapy effectively lowers serum bilirubin levels and diminishes the need for treatment with EcT. Effectiveness of phototherapy varies significantly depending on infant age, gender, gestational age and comorbidities.

- What is the availability of treatment?
  Based upon the large number of studies from various locations within the United States and abroad, the vast amount of literature provides indirect evidence of the wide availability of treatment. In addition, home phototherapy was also identified as a feasible option for treatment in one study, but with too small of a population to draw conclusions.

- What are the potential harms or risks associated with treatment?
  Physical complications associated with phototherapy include fluid loss, temperature instability and corneal damage; the two most common reported as skin rash and diarrhea (numbers affected not frequently stated in the evidence). Studies of other potential harms found no disruption in mother-child attachment after the first year of life; inpatient phototherapy was associated with a mild or infrequent contribution to vulnerable child syndrome; and covering of the eyes, exposure to light, and maternal separation could all contribute to behavior changes and stress in infants during treatment. Additionally, one study found no statistically significant evidence of an excess risk of skin cancer later in life following neonatal phototherapy.

- What proportion of cases of chronic bilirubin encephalopathy would be prevented with earlier detection and treatment of hyperbilirubinemia? What proportion of cases of other neonatal hyperbilirubinemia manifestations would be preventable?
  Based on a rough estimate of 4 million births in the United States per year and the incidence of chronic bilirubin encephalopathy in the literature as 0.49-2.7 per 100,000; an upper bound of 20-108 cases per year of chronic bilirubin encephalopathy could be prevented with earlier detection and treatment.

  Similarly, using a bilirubin level of >30mg/dL, with a reported incidence of 3-12 per 100,000; 120-480 cases per year of infants reaching bilirubin levels >30mg/dL could be prevented with earlier detection and treatment. Evidence estimated the number needed to treat at 222 for boys and 339 for girls to prevent one infant from developing a bilirubin level at which the AAP recommends EcT.

  Studies focusing on the effect of predischarge screening programs have found associations with increased phototherapy use, a lower number of readmissions for hyperbilirubinemia, and a lower incidence of hyperbilirubinemia above the AAP's EcT threshold.

Economics key findings

- What are the costs associated with the screening test?
  The abstracted papers included only estimated costs of TcB testing, which relied on various assumptions. The range of estimates was less than a dollar to $7.80. An additional estimate is not included in this summary because the data are from 1980 and unlikely to be applicable today.

- What are the costs associated with the failure to find at risk newborns in the pre-symptomatic period?
  The cost of jaundice readmission was estimated at $2,764 (in 1991$) with a mean length of stay of 2.5 days (Burgos et al., 2008) and $898 (mean LOS = 2 days) in 2002$ (Suresh & Clark, 2004). Charges for a jaundice readmission were estimated at $2,401 (2002-3$) (Petersen et al., 2005) with no adjustment for cost-to-charge ratio (charges typically overstate costs).

  Costs of phototherapy at home were estimated at $654 (4 days of phototherapy, 1 home nurse visit, 2 bilirubin tests) (Suresh & Clark, 2004).

- What are the costs associated with treatment of hyperbilirubinemia?
  Incremental charges associated with in-hospital phototherapy treatment for babies identified with hyperbilirubinemia requiring phototherapy before discharge were estimated at $592. The charges associated with a hyperbilirubinemia-related readmission were estimated at $2,401 (Petersen et al., 2005).

- What are the costs associated with treatment of acute and chronic bilirubin encephalopathy?
  From Suresh and Clark (2004), the lifetime cost for a child with kernicterus was assumed to be $900,000 based on CDC estimates of total lifetime costs for a child with cerebral palsy. These total lifetime costs also included the costs of lost productivity in addition to treatment costs.

- What is the cost-effectiveness of newborn screening for neonatal hyperbilirubinemia?
  TcB screening was not found to be cost-saving in the Peterson et al. (2005) study; however, this study only included short-term costs of hospitalization and did not consider longer-term costs of more severe outcomes.

  The cost to prevent one case of kernicterus was estimated at $5,743,905 for the strategy of routine predischarge serum bilirubin (TSB) with selective follow-up and laboratory testing; assuming an incidence for kernicterus of 1 in 100,000. Sensitivity analysis resulted in ratios from $4 million to $128 million for predischarge serum bilirubin (Suresh & Clark, 2004).

  The cost to prevent one case of kernicterus was estimated at $9,191,352 for the strategy of routine predischarge transcutaneous bilirubin (TcB) with a range of $6 million to $195 million per case prevented.

  Overall level of the quality of economic evidence was weak to moderate. Cost estimates were mostly based on single institutions and/or derived from assumptions, not actual cost data. Cost-effectiveness analysis was of low-to-moderate quality. Many cost estimates were derived from author assumptions, some of which lack face validity such as the omission of staff time for a TcB screen. These studies also did not assess outcomes other than kernicterus.

Gaps in Evidence

We identified several areas that we were unable to thoroughly answer from the available evidence. The following is a summary of the gaps in evidence that arose through our work and remain unanswered:

- Defining the connection between bilirubin levels and chronic bilirubin encephalopathy (kernicterus)
  Evidence does not exist to link a specific bilirubin level to causing permanent neurotoxicity. It is not definitive in the evidence when and at what bilirubin levels chronic bilirubin encephalopathy presents clinically.
- If it is possible to screen directly for chronic bilirubin encephalopathy.
  No evidence directly addressed screening for chronic bilirubin encephalopathy, and instead evidence covered the ability to screen for high levels of bilirubin and risk of chronic bilirubin encephalopathy. No studies directly addressed if screening predischarge bilirubin levels for hyperbilirubinemia in conjunction with risk factor assessments prevents or directly reduces the incidence of chronic bilirubin encephalopathy.

- Predischarge bilirubin newborn screening logistics and large-scale screening impact.
  Evidence did not comprehensively address the optimal protocol for newborn screening and follow-up for hyperbilirubinemia, if there is or has been population-based pilot screening, if outpatient facilities have the capacity to handle follow-up visits for screen positive infants, the potential harms or risks associated with screening and what would be the effect of taking bilirubin screening in its current form to state mandated newborn screening. No evidence exists regarding how many nurseries and/or hospitals in the United States currently perform predischarge bilirubin newborn screening and by what method.
- If treating neonatal hyperbilirubinemia prevents chronic bilirubin encephalopathy.
  No evidence directly addressed whether treating high bilirubin levels prevents chronic bilirubin encephalopathy, limited evidence addressed long-term risk and no evidence addressed potential long-term harms of treatment. No abstracted evidence assessed the levels of intensity of phototherapy and associated harms at varying levels of intensity.
- Cost-effectiveness of predischarge bilirubin newborn screening.
  Evidence did not cover to a great degree costs associated with the screening test, confirmatory testing, and follow-up for newborns found to have an intermediate risk level. Additionally, costs associated with failure to find at risk newborns in the pre-symptomatic period and costs associated with treatment were not available in the evidence.

Secondary Targets

Secondary targets are conditions incidentally detected by laboratory findings during the screening procedure or as a consequence of clarifying the differential diagnosis of a core condition. While this review is focused on the evidence for screening for the core condition of hyperbilirubinemia and the risk of developing subsequent chronic bilirubin encephalopathy, there is a possibility that detecting elevated levels of bilirubin in the newborn screening process may find other conditions. Secondary targets for predischarge screening for hyperbilirubinemia may include: Alagille's syndrome, Alpha-1 antitrypsin deficiency, Alpha-thalassemia, Biliary atresia, Crigler-Najjar Syndrome, Cystic Fibrosis, Dubin-Johnson Syndrome, G6PD deficiency, Galactosemia, Gilbert's syndrome, Progressive familial intrahepatic cholestasis, Pyruvate kinase deficiency, Rh Disease, Rotor Syndrome, Sickle-cell disease, and potentially other hemolytic, hepatic, infectious or metabolic conditions that lead to accumulation of bilirubin in the newborn period.

Standardization of screening practices

Screening for neonatal hyperbilirubinemia is unlike the traditional newborn screening program of using filter-paper-based tests and a laboratory. This difference leads to new issues not previously addressed for dried blood spot screening. In particular, hyperbilirubinemia screening using TcB is a test that occurs at the bedside (in the nursery or otherwise) similar to newborn screening for hearing impairment. Unlike newborn hearing screening, neonates with abnormal screening results need confirmatory testing prior to discharge; results and follow-up are very time-sensitive, which also may be different from some filter-paper-based tests. The evidence identified here has begun to elucidate the most beneficial timing of screening, best screening method, the optimal threshold value for action, and methods of quality control. Future trials may provide information on the benefits, risks, and cost of this technology.

XII. Tables from Results: evidence findings to address the key questions section

Table 3 – Quality assessment of abstracted literature pertaining to condition

Type of evidence	Number of articles
Total	**49**
Incidence (cases per 100,000), average within the U.S.	**17**
Data obtained from whole-population screening or comprehensive national surveys of clinically detected cases.	6
As above, but more limited in geographical coverage or methodology.	9
Extrapolated from class I data for non-U.S. populations.	2
Estimated from number of cases clinically diagnosed in U.S.	0
Other natural history of disease	**38**
Spectrum of Severity	31
Risk Factors	6
Prevalence	1

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Table 4 – Reported incidence of hyperbilirubinemia (in order of increasing TSB level)

Case definition	Estimated Incidence per 100,000 (reported numbers)	Population	Study
TSB <20 mg/dL			
Neonatal discharges with ICD-9 codes for hyperbilirubinemia	15,600/100,000	2,376,294 infants with hyperbilirubinemia (United States)	Burke et al., 2009
TSB value that exceeded the hour-specific threshold for phototherapy	8,071/100,000 (64/793)	793 healthy late preterm neonates born at 34-36 weeks	Fouzas et al., 2010
TSB ≥9 mg/dL	12,417/100,000 (10,944/88,137)	88,137 live-borns (Australia)	Guaran et al., 1992
TSB ≥13.5 and <19mg/dL	6,125/100,000 (3,431/56,019)	56,019 newborns in the Perinatal Database with linkage to a registration file (Canada)	Jangaard et al., 2008
TSB ≥17 mg/dL	17,570/100,000 (81/461)	461 neonates born at 37 to 42 weeks, 2500g to 4000g (India)	Bhat et al., 2008
TSB ≥19 mg/dL	621/100,000 (348/56,019)	56,019 newborns in the Perinatal Database with linkage to a registration file (Canada)	Jangaard et al., 2008
TSB ≥20 mg/dL			
TSB ≥20 mg/dL	1,950/100,000 (1,002/51,387)	51,387 infants born at ≥36 weeks gestation and ≥2000g (United States)	Newman et al., 1999
Serum unconjugated bilirubin beyond EcT limit	25/100,000 (32/128,344)	128,344 live-borns born at ≥35 weeks (Denmark)	Ebbesen et al., 2005
TSB >23.4 mg/dL	480/100,000	50 infants with hyperbilirubinemia at one hospital (study population number of livebirths not given) (Zimbabwe)	Wolf et al., 1999
TSB >24.9 mg/dL or underwent EcT	40/100,000 (1/2480)	258 confirmed neonatal hyperbilirubinemia cases from Canadian Paediatric Surveillance Program (study assumes birth cohort of 320,000 over two year study period) (Canada)	Sgro et al., 2006
TSB ≥25 mg/dL	146/100,000 (75/51,387)	51,387 infants born at ≥36 weeks gestation and ≥2000g (United States)	Newman et al., 1999
TSB 25 to 29.9 mg/dL	43/100,000 (before screening) 27/100, 000 (during screening)	129,345 neonates born before predischarge screening 899 ,472 neonates born during predischarge screening (United States)	Mah et al., 2010
TSB ≥26.3 mg/dL	45/100,000 (113/249,308)	249,308 live-borns born at ≥35 weeks (Denmark)	Bjerre et al., 2008
TSB >29.8mg/dL in the first month of life	7.1/100,000	1,500,052 births (United Kingdom, Ireland)	Manning et al., 2007
TSB ≥29.8 mg/dL	12/100,000	249,308 live-borns born at ≥35 weeks (Denmark)	Bjerre et al., 2008
TSB >30 mg/dL			
TSB ≥30.0 mg/dL	9/100 000 (before screening) 3/100,000 (during screening)	129,345 neonates born before predischarge screening 899 ,472 neonates born during predischarge screening (United States)	Mah et al., 2010

TSB ≥30 mg/dL	9.7/100,000 (5/51,387)	51,387 infants born at ≥36 weeks gestation and ≥2000g (United States)	Newman et al., 1999
TSB ≥30 mg/dL in the first 30 days after birth	10/100,000	111,009 births (United States)	Newman et al., 2003

Table 5 – Reported incidences of chronic bilirubin encephalopathy

Study	Population	Case definition	Incidence
Brooks et al., 2011	64,346 individuals born between 1988 – 1997 and received services from the CA Department of Developmental Services during years 1988 – 2002, among all live births in CA during these years (United States)	ICD-9 codes for kernicterus or diagnoses associated with kernicterus, combined descriptions of functional abilities and disabilities	0.44/100,000 (.49/100,000 when ~10% mortality rate considered)
Burke et al., 2009	1,395 with chronic bilirubin encephalopathy in the Healthcare Cost and Utilization Project Databases, which captures 7-8 million discharges per year (specific population number not given) (United States)	Neonatal discharges with ICD-9 codes for chronic bilirubin encephalopathy (kernicterus)	2.7/100,000
Jangaard et al., 2008	56,019 newborns in the Perinatal Database with linkage to a registration file (Canada)	Reviewed medical records for diagnosis of chronic bilirubin encephalopathy (kernicterus)	No reported cases of chronic bilirubin encephalopathy
Maimburg et al., 2009	710,533 live-borns born at ≥35 weeks Danish National Hospital Register (Denmark)	Chronic bilirubin encephalopathy (kernicterus) diagnosis by ICD-10 code	1.3/100,000 (9/710,533)
Manning et al., 2007	1,500,052 births (United Kingdom, Ireland)	Bilirubin encephalopathy	0.9/100,000
Newman et al., 2006	106,627 live-borns ≥36 weeks (<1996) or at ≥34 weeks (born 1997-1997 - 1998). (California, United States)	Reviewed medical records for diagnosis of chronic bilirubin encephalopathy (kernicterus)	No reported cases of chronic bilirubin encephalopathy

Table 6 – Subtle and acute manifestations of neonatal hyperbilirubinemia

Study	Population and Assessment	Subtle and acute manifestations in neonatal period
Neurodevelopmental evaluation		
AlOtaibi et al., 2005	12 infants with neonatal hyperbilirubinemia Review of medical records, ranging from **7 months – 6 years**	3/9 VEP results abnormal 7/10 BAEP results abnormal 5/5 EEG results abnormal 1/5 CT scan abnormal
Bjerre et al., 2008	113 infants with TSB ≥26.3 mg/dL Review of medical records ranging from **2 – 39 months**	44/113 (39%) evidence of ABE 43/44 early ABE (lethargy, hypotonia and poor suck) 1/44 advanced ABE at 33 months (retrocollis-opisthotonos, shrill cry, no feeding, seizures, apnea, fever, deep stupor, coma, motor deficits, hypotonia, hearing loss)
Ebbesen et al., 2005	32 infants with TSB beyond EcT limit (median max TSB 28.8 mg/dL) Review of medical records	12/32 (38%) signs of CNS involvement 11/12 signs of ABE (lethargy, poor sucking, hypotonia, stupor, weak Moro reflex)
Gkoltsiou et al., 2008	11 infants with unconjugated hyperbilirubinemia of >23.4 mg/dL and/or neonatal or later neurological signs suggestive chronic bilirubin encephalopathy and with at least one cranial ultrasound and one MRI brain scan Brain imaging Neurodevelopmental assessments with Griffith's Mental Developmental Scales and Hammersmith infant neurological exam, BAEP	8/11 with hyperbilirubinemia (24.7–42.1 mg/dL) 3/11 with hyperbilirubinemia (13.7–16.8 mg/dL) 8/10 neonatal neurological exam abnormal (axial hypotonia, variable abnormal limb tone, poor auditory/visual orientation) 3/10 neonatal hearing screening abnormal 9/10 available brain imaging had abnormal findings
Harris et al., 2001	6 infants readmitted in the first week with TSB >25 mg/dL Clinical evaluation and MRI ranging from **3.5 - 6 years**	5/6 infants presented with abnormal neurologic signs including: 4 with lethargy, 1 with irritability, 2 with poor feeding, 2 with a high pitched cry, 4 with abnormal muscle tone, and 2 with arching, opisthotonos or seizures

Mansi et al., 2003	28 neonates with total bilirubin >13mg/dL not treated with phototherapy 28 matched control neonates BNBAS at **4 days of age**	Significant differences in hyperbilirubinemia vs. control neonates in areas (median score): Animate visual – 5 vs. 6 (p = .001) Animate auditory – 6 vs. 6 (p = .002) Animate visual and auditory – 5 vs. 7 (p = .001) Inanimate visual – 4 vs. 6 (p = .001) Inanimate auditory – 6 vs. 6 (p = .01) Alertness – 4 vs. 6.5 (p = .001) Lability of state – 4 vs. 5 (p = .011) Self-quieting – 6 vs. 8.5 (p = .001) Tremors – 7.5 vs. 9 (p = .012)
Newman et al., 2003	11 infants with TSB ≥30mg/dL within first 30 days of life Review of medical records, psychometric testing, neurologic examinations (range **15 days - 4.5 years**), parental report (range **3 - 5 years**)	10/11 no acute symptoms of bilirubin encephalopathy 1/11 had a brief cyanotic episode
Paludetto et al., 2002	50 term neonates with TSB 13.2 -20mg/dL 50 age matched control neonates with TSB 5.3 - 12mg/dL BNBAS at **72-110 hours of age, 24 hours later and at 3 weeks**	Significant differences in TSB 13.2 -20mg/dL vs. TSB 5.3 -12mg/dL groups in areas (median score): Animate visual - 4 vs. 6 (p = .0001) Animate auditory - 5 vs. 7 (p = .0001) Animate visual and auditory - 4 vs. 6 (p = .0001) Inanimate visual - 5 vs. 7 (p = .0001) Inanimate auditory - 5 vs. 6 (p = .0001) Inanimate visual and auditory - 5 vs. 6 (p = .0001) Alertness - 4 vs. 6 (p = .0001) Maturity - 5 vs. 5 (p = .001) Pull-to-sit - 5 vs. 5 (p = .001) Self-quieting - 6 vs. 7 (p = .001) Tremors - 8 vs. 9 (p = .001) 22 infants matched pairs (infants in study group had decreasing bilirubin) reassessed with BNBAS after 24 hours - no significant variation in the BNBAS was noted between the groups 16 matched pairs reassessed at 3 weeks of age - BNBAS scores did not show significant differences

Soorani-Lunsing et al., 2001	20 neonates with TSB >12.8 mg/dL 20 matched control neonates Neurological assessments at **3-8 days, 3 months and 12 months**	None of the neonates showed a definitely abnormal neurologic condition, however the rate of minor neurologic dysfunction (mild abnormalities in postural behavior, the presence of high frequency tremors, mild deviancies in muscle tone regulation and mild asymmetries in reactions and tendon reflexes) was significantly higher in the study group (14/20) than in the control group (5/20); $p<0.05$
Vohr et al., 1990	23 term infants with TSB 10-20mg/dL 27 term infants with TSB <8mg/dL BAEP and BNBAS **1-3 days of life**	Consistent correlations found between a TSB 10-20mg/dL and lower scores in orientation, state range, state regulation, and autonomic stability clusters of the BNBAS Strongest correlations present between increased levels TSB and decreased scores on the individual BNBAS items for inanimate auditory, inanimate visual and auditory, animate auditory, and animate visual and auditory responses
Visual Evoked Potential		
Chen et al., 1995	26 infants with bilirubin between 10-14.9 mg/dL 25 infants with bilirubin between 15.0-19.9 mg/dL 21 infants with bilirubin ≥20 mg/dL 22 control infants VEP Neurological exam and Denver test at **1 year of age**	Levels of max TSB were significantly related to the N1 and P2 latencies ($r = 0.41$, and $r = 0.7$), but less related to the N2 latency ($r = 0.28$) In infants in the severe and moderate groups, the P2 latency is strongly related to the max TSB levels ($rs = 0.58$ and $rs = 0.49$, respectively) within the 1st week of life
Chen et al., 2006	16 neonates with hyperbilirubinemia (TSB 13.2-19.9 mg/dL) 8 neonates with hyperbilirubinemia (TSB ≥20 mg/dL) Repeated VEP **until 2 years of age** Neurodevelopmental follow-up until **3 years**	No significant differences in VEP between the two TSB groups None had an abnormal BAEP or sensorineural hearing impairment

Brainstem Auditory Evoked Potential		
Baradaranfar et al., 2011	35 newborn babies with TSB > 20 mg/dL 35 non-elevated TSB control babies	4 (11.4%) newborns with TSB > 20 mg/dL had mild to moderate hearing loss 5 (14.3%) newborns with TSB > 20 mg/dL had severe to profound hearing loss Blood bilirubin levels in 4 infants with severe to profound hearing loss had TSB > 30 mg/dL 3 with mild to moderate hearing loss had TSB > 30 mg/dL
Chen et al., 2006	29 term infants with hemolytic hyperbilirubinemia 99 with non-hemolytic hyperbilirubinemia BAEP at **range of 1 – 12 months** Neurodevelopmental evaluation up to **3 years of age**	3/29 (10.4%) in the hemolytic group had BAEP abnormalities 9/99 (9.1%) in the non-hemolytic group had BAEP abnormalities 3/29 (10.4%) in hemolytic group had mild motor delay and hypotonia at 3 months 2/99 (2%) in the nonhemolytic group had mild motor delay and hypotonia at 3 months
Jiang et al., 2007	90 term neonates with TSB >10 mg/dL requiring phototherapy or EcT 43 control term neonates BAEP	BAEP threshold in neonates with hyperbilirubinemia were significantly higher than in control subjects (analysis of variance, P<0.0001) Latencies of BAEP waves I, III, and V were all significantly longer than in control subjects (P <0.05-0.0001) In neonates with TSB >20 mg/dL, all wave latencies were significantly longer than those in the controls (P<0.01, 0.001, and 0.0001 for waves I, III, and V) All latencies of waves I, III, and V correlated weakly with the level of TSB (r=0.26-0.28, all P<0.05).
Saluja et al., 2010	13 neonates with hyperbilirubinemia (as defined by AAP guidelines for EcT) with 12 days after birth Comprehensive auditory evaluation (OAE, ABR) **prior to discharge**	13/13 normal OAE results 6/13 diagnosed with auditory neuropathy spectrum disorders not associated with peak bilirubin level

Table 7 – Chronic manifestations of neonatal hyperbilirubinemia

Study	Population and Assessment	Chronic manifestations at follow-up
Neurodevelopmental evaluation		
AlOtaibi et al., 2005	12 infants with neonatal hyperbilirubinemia Review of medical records, ranging from **7 months – 6 years**	2/4 MRI scan abnormal and consistent with chronic bilirubin encephalopathy 3 developed normally 7 with abnormal development (gross motor, fine motor adaptive and social skills) 2 lost to follow-up
Bjerre et al., 2008	113 infants with TSB ≥26.3 mg/dL Review of medical records ranging from **2 – 39 months**	32/113 had follow-up available All except for one with advanced ABE findings had normal neurological outcome at follow-up.
Ebbesen et al., 2005	32 infants with TSB beyond EcT limit (median max TSB 28.8 mg/dL) Review of medical records	1/32 signs of chronic bilirubin encephalopathy at 23 months (hypertonia, retrocollis, opisthotonos, pronation of the upper extremities, jittering, irritability, seizures, apnea, cyanotic attacks, fever, high-pitched cry, mental retardation, dystonic cerebral palsy)
Ebbesen et al., 2010	463 medical records of males with non-hemolytic neonatal hyperbilirubinemia matched with military records 12,718 medical records of males with no history of neonatal hyperbilirubinemia Review of medical records and Boerge Prien IQ test at **18-20 years of age**	Neonatal exposure to non-hemolytic hyperbilirubinemia was not associated with an increased risk of neuropsychiatric diagnosis Cognitive scores slightly lower among hyperbilirubinemia group but did not correlate with peak TSB level within the group
Gkoltsiou et al., 2008	11 infants with unconjugated hyperbilirubinemia of >23.4 mg/dL and/or neonatal or later neurological signs suggestive chronic bilirubin encephalopathy and with at least one cranial ultrasound and one MRI brain scan Brain imaging Neurodevelopmental assessments with Griffith's Mental Developmental Scales and Hammersmith infant neurological exam, BAEP	7/11 developed cerebral palsy (CP), 4/11 were severely dyskinetic and unable to sit or walk at 2–3 years, 3/11 had dyskinetic or athetoid movements, delayed sitting but independent walking by 2–3 years 6/8 infants with an abnormal neonatal examination developed CP ¾ with neonatal seizures and abnormal EEG had a poor motor and auditory outcome ¾ with hyperechogenicity in the basal ganglia and white matter on cranial ultrasound developed CP

Harris et al., 2001	6 infants readmitted in the first week with TSB >25 mg/dL Clinical evaluation and MRI ranging from **3.5 – 6 years**	¾ with MRIs had abnormal findings consistent with chronic bilirubin encephalopathy 5/6 had resolutions of abnormal neurologic signs by 12 months, and remained normal at follow-up, however 1 patient did have residual bilateral hearing loss 1/6 had residual neurologic abnormalities with mental retardation and cerebral palsy at 6 years of age 4/5 with normal follow-up MRI (1 abnormal was child with neurological abnormalities)
Jangaard et al., 2008	3431 newborns with hyperbilirubinemia (13.5-19mg/dL) 348 newborns with hyperbilirubinemia (>19mg/dL) 52,240 newborns with no hyperbilirubinemia Review of medical records ranging from **2 to 9 years**	No significant difference in composite outcome (deafness, cerebral palsy, developmental delay, gaze palsy, attention deficit disorder, autism spectrum disorders) in either moderate group (adjusted RR: 1.1; 95% CI: 1.0 –1.2) or severe group (adjusted RR: 1.1; 95% CI: 0.8 –1.4), compared with controls Risk of developmental delay was significantly increased in the TSB 13.5-19mg/dL group as compared to controls (adjusted RR: 1.6; 95% CI: 1.3–2.0) There was a significant increase in the risk of attention-deficit disorder among infants exposed to TSB levels of ≥19 mg/dL (adjusted RR: 1.9; 95% CI: 1.1–3.3)
Maimburg et al., 2009	9 children born at ≥35 weeks gestation with chronic bilirubin encephalopathy Max bilirubin score ranged from 31.1 – 43.6 mg/dL Review of medical records	3/9 died before the age of 2 years 5/9 had mental retardation 4/9 had cerebral palsy 4/9 had hearing impairment
Mukhopadhyay et al., 2010	25 neonates born at ≥35 weeks gestation with >20mg/dL TSB and signs of ABE who underwent double volume exchange transfusion Mean TSB at admission 36.9 mg/dL Denver Developmental Screening Test (DDST-1) and neurological exam at **3, 6, 9 and 12 months** Brainstem evoked response audiometry (BERA) at **3 months**	13/24 (54%) tested at 3 months had abnormal neurological status 5/18 (28%) tested at 6 months had abnormal neurological status 4/14 (29%) tested at 9 months had abnormal neurological status 4/15 (27%) tested at 12 months had abnormal neurological status Of the 15 available for follow-up at 1 year, 3 had a normal outcome on all assessments (neurological exam, DDST and BERA)

Newman et al., 1993	41,324 infants with birth weight ≥2500g who survived at least one year and had one bilirubin level recorded Max TSB levels: <10.0 mg/dL = 14,919 infants 10.0– 14.9 mg/dL = 1,426 15.0 -19.9 mg/dL = 404 ≥20.0 mg/dL = 137 IQ at **7 years** Neurological exam at **1 and 7 years** Hearing evaluation at **3 and 8 years**	Max TSB was not associated with IQ Risk of abnormal or suspicious examination results at 7 years increased from 14.9% in the group with max TSB <10 mg/dL to 22.4% in the >20mg/dL group, p<.001 Neurological exam items associated with increasing neonatal TSB - nonspecific gait abnormalities (p < .001), awkwardness (p < .001), equivocal Babinski reflexes (p < .001 on right; p = .006 on left), abnormal cremasteric reflex (p = .001), abnormal abdominal reflex (p = .008), failure at fine stereognosis (p = .008), vasomotor abnormality (p = .005), questionable hypotonia (p values ranged from .005 for the right upper extremity to .07 for the trunk), and gaze abnormalities (p .001 to .05) Occurrence of sensorineural hearing loss at age 8 years was ~2% regardless of bilirubin level
Newman et al., 2003	11 infants with TSB ≥30mg/dL within first 30 days of life Review of medical records, psychometric testing, neurologic examinations (range **15 days – 4.5 years**), parental report (range **3 – 5 years**)	1/11 died of sudden infant death syndrome, no signs of chronic bilirubin encephalopathy at autopsy 9/10 with normal neurological exam, 1/10 with “questionable” exam 7/8 parental report had no concerns, follow-up ranged from 3 to 5 years, 1/8 parental report noted speech therapy 3/3 with intelligence testing, tested in normal range at age 5
Newman et al., 2006	140 infants with TSB ≥25mg/dL, treated with phototherapy, EcT or observation/follow-up 419 randomly selected control infants Neurodevelopmental evaluations at mean of **5.1 years**	No significant differences between the study group and the control group in the results of intelligence testing or visual–motor integration 14 (17%) of the children with hyperbilirubinemia had “questionable” or abnormal findings on neurologic examination vs. 48 controls (29%) (p = 0.04)

Seidman et al., 1991	1948 neonatal medical records matched to military draft records 308 with hyperbilirubinemia (TSB 5 to 8 mg/dL) 144 with hyperbilirubinemia (TSB >8 mg/dL on the first day of life, 15 mg/dL on the second day of life, 20 mg/dL thereafter) Remaining 1496 considered controls Intelligence test and physical exam at **17 years**	Mean IQ score was significantly lower (P < .03) only for males in severe neonatal hyperbilirubinemia group, no difference after adjusting for confounders Risk for IQ score <85 was found to be significantly higher (P = .014) among full-term male subjects with TSB >20 mg/dL) (OR = 2.96) School achievement (<12 years of schooling; ≥12 years of schooling and professional nontechnologic education) was not influenced by bilirubin levels in both males and females No association was found between neonatal hyperbilirubinemia levels and the subjects' health profile (physical exam)
Soorani-Lunsing et al., 2001	20 neonates with TSB >12.8 mg/dL 20 matched control neonates Neurological assessments at **3-8 days, 3 months and 12 months**	At 3 month follow-up, results consistent with findings in neonatal period At 12 months, the rate of minor neurologic dysfunction was still significantly higher in the study group (10/20) than in the control group (2/20), p<0.05, neurologic outcome at 12 months was strongly related to max TSB
Wolf et al., 1999	50 infants with TSB >23.4mg/dL Bayley Scales of Infant Development (BSID) and clinical exam at **12 months of age**	2 infants died (cause not noted), 7 lost to follow-up 11/43 (26%) had abnormal or suspect BSID scores, 32/43 normal at 12 months Infants with the highest TSB levels scored lower on the BSID, p<0.03 5/43 (12%) infants had cerebral palsy, 2/43 (5%) had severe motor delay, 4/43 (9%) moderate motor delay
Visual Evoked Potential		

Chen et al., 1995	26 infants with bilirubin between 10-14.9 mg/dL 25 infants with bilirubin between 15.0-19.9 mg/dL 21 infants with bilirubin ≥20 mg/dL 22 control infants VEP Neurological exam and Denver test at **1 year of age**	None of the infants in the low and moderate follow-up groups showed any abnormality in the DDST and neurological examination 4/18 infants who followed up in the severe group, were abnormal in gross motor and fine motor skills of DDST, 1 also showed general hypotonia
Chen et al., 2006	16 neonates with hyperbilirubinemia (TSB 13.2-19.9 mg/dL) 8 neonates with hyperbilirubinemia (TSB ≥20 mg/dL) Repeated VEP **until 2 years of age** Neurodevelopmental follow-up until **3 years**	VEP testing of all subjects was normal after 12 months 1 term infant from the severe group with hyperbilirubinemia owing to ABO incompatibility had mild hypotonia and motor delay at 10 months, neurodevelopment status was normal at 3 years
Brainstem Auditory Evoked Potential		
Chen et al., 2006	29 term infants with hemolytic hyperbilirubinemia 99 with non-hemolytic hyperbilirubinemia BAEP at **range of 1 – 12 months** Neurodevelopmental evaluation up to **3 years of age**	2/3 in hemolytic group with abnormalities had normal results at 2 years of age, 1/3 had a slightly increased hearing threshold 7/9 in the non-hemolytic group with abnormalities had normal results at 2 years of age, 2/9 had a slightly increased hearing threshold 29/29 in hemolytic group had normal neurodevelopment at 3 years of age 99/99 in non-hemolytic group had normal neurodevelopment at 3 years of age No relationship between BAEP results and neurodevelopmental outcomes

Nickisch et al., 2009	15 children with neonatal TSB >20mg/dL and/or diagnosed bilirubin encephalopathy by MRI 15 randomly selected matched controls with neonatal TSB 12.5-19.5mg/dL Audiological examination **ranging from 11 months to 9 years**	13/15 (87%) children in the hyperbilirubinemia group had clinically significant findings, 4 children had bilateral deafness, 1 with unilateral deafness 2/15 (13%) of children in the control group had clinically significant findings

Table 8 – TSB levels and associated infant clinical presentations at <3 months*

TSB (mg/dL)	Infants total	Asymptomatic on admission	Survived with no sequelae (<3 months)	Bilirubin encephalopathy (abnormal muscle tone and movement disorder at 3 months)	Death	Percentage of bilirubin encephalopathy and death
<20	62	35	60	1	1	3.2%
20.0-24.9	48	34	34	7	7	29.9%
25.0-29.9	33	9	12	12	6	54.6%
30.0-35	12	4	3	7	2	75%
>35	7	1	0	5	2	100%

*data from Hameed et al., 2011, discrepancy in number of 25.0-29.9 subjects as stated in report

Table 9 – Quality assessment of abstracted literature pertaining to screening

Type of evidence	Number of articles
Total	**42**
Overall sensitivity and specificity of screening	**24**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than from whole population screening.	23
Estimated from the known biochemistry of the condition.	0
False positive rate	**10**
Data obtained from screening programs in U.S. population or similar.	1
Data from systematic studies other than from whole population screening.	9
Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	**0**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	0
Estimated from the known biochemistry of the condition.	0
Second-tier testing	**2**
Data obtained from screening programs in US population or similar.	1
Data from systematic studies other than whole population screening.	1
Estimated from the known biochemistry of the condition.	0
Other screening test characteristics	**20**
Methods	9
Implementation	5
Risk Assessments	5
Harms	1

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Table 10 – TcB screening for elevated TSB values

Study	Population	Cutoff, Timing, Placement	TSB comparison value	Sensitivity (%)	Specificity (%)
Boo & Ishak, 2007*	345 healthy term neonates with hyperbilirubinemia	14.6 mg/dL, median 70 hours, forehead	>17.5 mg/dL	100	39.2
		11.7 mg/dL, median 70 hours, sternum	>17.5 mg/dL	100	33.6
Briscoe et al., 2002*	303 infants >34 weeks gestation having blood drawn in first week of life	18 TcB value, mean 36 hours, forehead	>14.6 mg/dL	100	45.0
Dai et al., 1996*	45 healthy term infants	17 TcB value, >24 hours, forehead	>15.2 mg/dL	100	68.0
Sanpavat & Nuchprayoon,2007*	196 premature infants <38 weeks gestation with visually observed hyperbilirubinemia	TcB value 6, mean 4.5 days, forehead	≥6 mg/dL	97.8	40.0
		TcB value 12, mean 4.5 days, forehead	≥12 mg/dL	53.1	88.9
Schmidt et al., 2009*	31 preterm neonates 32-34 weeks gestational age	>4mg/dL, mean 58.8 hours, sternum	>6mg/dL	98.0	29.0
		>8mg/dL, mean 58.8 hours, sternum	>10mg/dL	93.0	74.0

*Raw data values used in calculations for sensitivity and specificity not stated

Table 11 – TcB screening for subsequent significant hyperbilirubinemia

Study	Population	Cutoff, Timing	Subsequent hyperbilirubinemia	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Bhat & Rao, 2008	461 healthy term newborns born between 37 and 42 weeks gestational age	>5 TcBI, 24 hours	≥17mg/dL at >72 hours of age	100 (81/81)	35.5 (135/380)	24.8 (81/326)	100 (135/135)
		>8 TcBI, 48 hours		100 (81/81)	52.6 (200/380)	31.0 (81/261)	100 (200/200)
		>7 TcBI, 24 hours		83.9 (68/81)	83.6 (318/380)	52.3 (68/130)	96.0 (318/331)
		>11 TcBI, 48 hours		44.4 (36/81)	95.5 (363/380)	67.9 (36/53)	88.9 (363/408)
Carbonell et al., 2001*	2004 healthy term newborns of 37-42 weeks gestational age	>13 TcBI, 48 hours, sternum	≥17mg/dL at >72 hours of age	98.0	32.0	08.0	99.6

*Raw data values used in calculations for sensitivity, specificity, PPV and NPV not stated

Table 12 – TSB screening for subsequent significant hyperbilirubinemia

Study	Population	Cutoff, Timing	Subsequent Hyperbilirubinemia	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Agarwal et al., 2002*	220 infants ≥35 weeks gestation	>6mg/dL, 24 hours	≥17mg/dL >24 hours of age	95.0	70.6	27.2	99.3
Alpay et al., 2000	498 healthy term newborns ≥38 weeks gestation	≥6mg/dL, 24 hours	≥17mg/dL >24 hours of age	90.0 (54/60)	65.3 (286/438)	26.2 (54/206)	97.9 (286/292)
Carbonell et al., 2001*	2004 healthy term newborns of 37-42 weeks gestational age	≥6mg/dL, 24 hours	≥17mg/dL >72 hours of age	100	60.0	13.0	100
		≥9mg/dL, 48 hours		98.0	45.0	10.0	99.6
Prasarnphanich & Somlaw, 2007	1983 healthy term neonates	12mg/dL, 48-72 hours	≥13mg/dL 49-72 hours of age, ≥15mg/dL >72 hours of age	36.6 (15/41)	87.9 (604/687)	15.3 (15/98)	95.9 (604/630)
Seidman et al., 1999*	1177 healthy term newborns	>5mg/dL, 8-24 hours	>10 mg/dL on day 2, >14 mg/dL on day 3, >17 mg/dL on days 4 and 5 of life	63.1	94.2	-	-

*Raw data values used in calculations for sensitivity, specificity, PPV and NPV not stated

Table 13 – Predictive characteristics of TSB risk zones on Bhutani nomogram for subsequent hyperbilirubinemia*

Percentile	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Above 95th	54.0 (68/126)	96.2 (2610/2714)	39.5 (68/172)	97.8 (2610/2668)
Above 75th	90.5 (114/126)	84.7 (2300/2714)	21.6 (114/528)	99.5 (2300/2312)
Above 40th	100 (126/126)	64.7 (1756/2714)	11.6 (126/1084)	100 (1756/1756)

**From Bhutani et al, 1999*

Table 14 – Predictive characteristics of predischarge TcB values on Bhutani nomogram for subsequent hyperbilirubinemia

Study	Population	Timing, Cutoff (%tile)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Bhutani et al., 2000	490 term and near-term newborns at discharge from well nursery	12-98 hours, >75th	100 (23/23)	88.1 (349/396)	32.86 (23/70)	100 (349/349)
Dalal et al., 2009*	358 neonates born at ≥35 weeks of gestation	30-48 hours, >75th	82.6	79	41.2	95.1

*Raw data values used in calculations for sensitivity, specificity, PPV and NPV not stated

Table 15 – Quality assessment of abstracted literature pertaining to treatment

Type of evidence	Number of articles
Total	**33**
Effectiveness of treatment	**11**
I. Well-designed RCTs.	1
II-1. Well-designed controlled trials with pseudo randomization or no randomization.	1
II-2. Well-designed cohort studies:	5
A. prospective with concurrent controls	*4*
B. prospective with historical control	*0*
C. retrospective with concurrent controls.	*1*
II-3. Well-designed case-control (retrospective) studies.	0
III. Large differences from comparisons between times and/or places with and without intervention	2
IV. Opinions of respected authorities based on clinical experience, descriptive studies and reports of expert committees.	2
Other treatment characteristics	**23**
Morbidity and/or mortality	12
Harms	7
Methods	3
Implementation	1

Adapted from Pandor et al. 2004, Pollitt et al. 1997

Table 16 – Bilirubin concentration levels and timing of EcT

	Abu-Ekteish et al., 2000 (Irbid, Jordan)	**Guaran et al., 1992 (Victoria, Australia)**	**Jackson, 1997 (Seattle, WA USA)**	**Patra et al., 2004 (Cleveland, OH USA)**	**Sanpavat, 2005 (Bangkok, Thailand)**	**Singhal et al., 1992 (New Delhi, India)**	**Steiner et al., 2007 (New Haven, CT USA)**
Total treated with EcT	336	248	106	55	165	66	141
Mean age at EcT (range)	98.2 hours old (18-192)	Not stated	Mean gestational age: 36.6 ± 3.6 (24-41) weeks old	Mean gestational age: 35 ± 4 weeks old	111.2 (19-384) hours old; preterm 117.1 (25-216) hours old	Not stated	3.6 ± 3.1 days old
Median bilirubin at time of EcT, (range)	21.9 (10.6-38.7) mg/dL	>9 mg/dL; not stated	Not stated	18 (4-37) mg/dL	24 (15-35) mg/dL; preterm 19 (7-28) mg/dL	>12 mg/dL; not stated	Not stated

Table 17 – Morbidity and mortality related to EcT

Study	Total treated with EcT	Deaths attributable to exchange transfusion procedure	Chronic bilirubin encephalopathy	Other complications attributable to EcT (number affected)
Abu-Ekteish et al., 2000	336	1 (septicemia)	2 treated with EcT (bilirubin levels were 34.3 and 38.7 mg/dL)	Cardio-respiratory arrest (3), bradycardia (15), hypothermia (6), septicemia (10), anemia (18), bleeding diathesis (1), hypernatremia (1)
Guaran et al., 1992	248	3 (2 necrotizing entercolitis; 1 massive pulmonary hemorrhage)	None mentioned	Apnea (1), transient hypocalcaemia and hypoglycemia, asymptomatic bacteraemia, perforated bowel, nonfatal necrotizing entercolotis, inspissated bile syndrome, disseminated intravascular coagulopathy (1)
Jackson, 1997	106	2 (1 cardiac arrest and hemorrhage; 1 respiratory failure and heart block)	None mentioned	Renovascular hypertension (1), bacteremia (1), ompalitis (2), apnea, bradycardia requiring resuscitation (6), jitteriness associated with hypocalcemia (4), necrotizing entercolitis (2), other
Patra et al., 2004	55	1 (potentially attributable respiratory distress; multi-organ system failure prior to EcT)	None mentioned	Seizures (1), hypotension (5), low platelets (29), low calcium (19), low HCO_3 (16), catheter malfunction (6), hypoglycemia (2), bradycardia (1), respiratory distress (4), hypokalemia (2), vessel thrombus (2), acute renal failure (1), omphalitis (1)
Sanpavat, 2005	165	0	No chronic bilirubin encephalopathy ; but 5 infants pre-EcT might be considered to be enter phase 1 of acute form of clinical bilirubin encephalopathy (poor suckling, stupor or hypotonia); all disappeared after EcT	Omphalitis/ infected wound (9), septicemia (4), necrotizing entercolitis (2), pneumonia (2), diarrhea (2), anemia (7), apnea (1), cardiac arrest (1)
Singhal et al., 1992	66	0	None mentioned	tachypnea (7), bradycardia (5), cardio-respiratory arrest (4), difficult cannulation of umbilical vein (3), anemia (17), hyplglycemia (7), septicemia (6), acidosis (5) and congestive heart failure (1)
Steiner et al., 2007	141	0	None mentioned	Catheter malfunction (4), seizures (3), necrotizing entercolitis (2), apnea (1), bradycardia (5), hyperkalemia (1), other (16), hypocalcemia (53), thrombocytopenia (53)
Watchko et al., 1994	4 (79 infants not treated with EcT)	1 (non-chronic bilirubin encephalopathy infant; bradycardia and metabolic acidosis; no clear cause of death determined)	3 infants with chronic bilirubin encephalopathy died; 1 of the 3 was treated with EcT, 2 managed with phototherapy alone. (bilirubin levels of 26 mg/dL, 11.3 mg/dL and 18.5 mg/dL)	Hyperkalemia, hypocalcemia, hypothermia, wide fluctuations in blood pressure, acidosis, bradycardia

Table 18 – Neurological and developmental outcomes for early symptomatic and presymptomatic treatment of neonatal hyperbilirubinemia

Study & design	Tests	Subjects at baseline	Treatment employed	Outcomes
Brainstem Auditory Evoked Potential and Developmental Assessments				
Agrawal et al., 1998 Cohort study	BAEP; Denver Developmental Screening Test (DENVER11)	30 neonates with >15mg/dL; mean level =22.4 mg/dL; mean age 4.2 days old Control group: 25 neonates with <12mg/dL; mean level =7.7 mg/dL; mean age 3.9 days old	14 with EcT 16 with phototherapy	-17/30 study neonates showed abnormal on initial BAEP pre treatment -Abnormalities in BAEP correlated significantly with bilirubin level -Post treatment abnormalities reverted back to normal in 10 cases, but persisted in 7 of the 17 initially abnormal BAEP -Developmental screening at 1 year was abnormal in 3 infants who also had an abnormal BAEP (two were exhibiting signs of bilirubin encephalopathy at study time)
Deorari et al., 1994 Cohort study	BAEP; development quotient	18 infants with >15 mg/dL Control group: 20 term neonates without hyperbilirubinemia	18 phototherapy If abnormal BAEP, used EcT also (7 cases)	-Abnormal initial BAEP only occurred in seven neonates, all with initial bilirubin concentrations above 22.8mg/dL -BAEP abnormalities reversed to normal in all seven neonates after EcT -Hearing and developmental quotient was normal for all neonates at 1 year of age -None of the study or control groups developed neurological sequelae as assessed at one year follow-up
Funato et al., 1996 Before and after	BAEP; development quotient; IQ	10 newborns with hyperbilirubinemia (≥20mg/dL)	All (10) with EcT	-2 infants showed initial clinical symptoms of bilirubin encephalopathy; One infant had sustained abnormal BAEP findings at 3 months of age -Two infants initial clinical symptoms of bilirubin encephalopathy recovered to normal BAEP at 1.5 and 5 years of age -Developmental quotient follow-up from 1.5 to 6 years was normal for all -Intelligence quotient was normal for all but one who had a borderline IQ at 6 years of age and had prolonged recovery of BAEP
Lee et al., 2002 Cohort study	BAEP; language/communication development milestone: infancy through school-age	20 term neonates with peak TSB ≥18.5mg/dL (within 5 days of age) or ≥20mg/dL (>5 days old) Control group: 14 healthy neonates	17 with phototherapy only 3 with both phototherapy + EcT	-BAEP wave latencies were not significantly different between the control group and phototherapy only group -13 infants in the phototherapy only group demonstrated normal language development at follow-up (ranging from 3 months to 5 year follow-up) -2 of the 3 phototherapy and EcT treated group had abnormal BAEP, and developed chronic bilirubin encephalopathy (bilirubin levels not clearly stated, but presumably ≥20mg/dL based on methods)

Wong et al., 2005 Case series	BAEP; physical, neurologic, visual and auditory evaluations	99 total infants (30 with mean bilirubin=18.9mg/dL; 63 with mean bilirubin=21.7mg/dL; 6 with mean bilirubin=26.9mg/dL)	All 99 with phototherapy 3 also treated with EcT	-9/99 had abnormal BAEP when initially assessed -Only 2/99 (both from 26.9mg/dL group) had abnormal BAEP at 2 years of age; all others normal -2/99 (one from 26.9 mg/dL, one from 21.7mg/dL group) had mild motor delay at 3 months of age, and both returned to normal before 1 year of age -No abnormal effects of phototherapy were found -No relationship between abnormal BAEP and abnormal neurodevelopmental status found
Neurodevelopmental Evaluations				
Chen and Wong, 2006 Case series	VEP; physical, neurologic, visual, and auditory evaluations	16 in group 1: bilirubin level 13.2-19.9 mg/dL 8 in group 2: bilirubin level ≥20 mg/dL	All (32) with phototherapy	-All infants had regular physical, neurologic, visual, and auditory evaluations until 3 years of age -4 had abnormal initial VEP between the two groups before 1 year -All but one had normal neurodevelopmental status by 3 years of age; one child from group 2 had motor delay, hypotonia and abnormal VEP
Hansen et al., 2009 Case series	Magnetic Resonance Imagining (MRI); follow-up evaluations	6 infants between 4-8 days of life with bilirubin levels >27.9mg/dL	All (6) with phototherapy 4 with EcT	-All presented with hyperbilirubinemia and symptoms of acute intermediate to advanced phase bilirubin encephalopathy neurological symptoms -2/4 with MRI imaging had increased signals in globus pallidus -2/6 were normal with speech delay at 2 years of age -All other 4 normal at follow-up at ages of 17 months, 4 years, 6 years and 9 years of age
Newman et al., 2006 Case-control study	Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R); Beery–Buktenica Developmental Test of Visual-Motor Integration, (VMI-4); standard neurological evaluations; Parent Evaluation of Developmental Status (PEDS); Child Behavior Checklist (CBCL)	140 infants with TSB ≥25mg/dL (130 with 25 and 29.9 mg/dL and 10 with >30mg/dL) Control group: 419 randomly selected infants	136 with phototherapy 5 with EcT	-No significant differences between the two groups in intelligence testing, cognitive tests, neurological testing or motor performance at greater than or equal to 2 years of age -There were no cases of chronic bilirubin encephalopathy. -The frequencies of parental concern and reported behavioral problems also were not significantly different between the two groups. -When treated with phototherapy or EcT, total serum bilirubin levels in the range included in this study were not associated with adverse neurodevelopmental outcomes in infants born at or near-term.
Scheidt et al., 1991 RCT	Wechsler Intelligence Scale for Children–Revised (WISC-R)	224 neonates weighing less than 2000g at birth	All (224) with EcT	-Examined neurological and developmental outcomes at 6 year follow-up, post EcT for hyperbilirubinemia -No association was evident between maximum bilirubin level and IQ -IQ not associated with mean bilirubin level, time and duration exposure to bilirubin

Wolf et al., 1999 Case series	Bayley Scales of Infant Development (BSID)	50 infants admitted with a TSB > 23.4mg/dL	7 with EcT	-4/6 surviving infants with EcT scored abnormal on BSID at 1 year of age -Overall, 11/43 surviving infants scored abnormal or suspect on the BSID at 1 year of age (2 with severe motor delay and 4 with moderate motor delay) -5/43 developed choreo-athetosis type of cerebral palsy -Infants with highest bilirubin levels scored lower on BSID at one year of age ($p<0.03$) -Correlation between BSID raw scores at 12 months and TSB levels was 0.59 (ANCOVA)

Table 19 – Quality assessment of abstracted literature pertaining to economics

Type of evidence	**Number of articles**
Economic	**5**
I. Evaluation of important alternative interventions comparing all clinically relevant outcomes against appropriate cost measurement and including a clinically sensible sensitivity analysis.	0
II. Evaluation of important alternative interventions comparing a limited number of outcomes against appropriate cost measurement, but including a clinically sensible sensitivity analysis.	1
III. Evaluation of important alternative interventions comparing all clinically relevant outcomes against inappropriate cost measurement, but including a clinically sensible sensitivity analysis.	4
IV. Evaluation without a clinically sensible sensitivity analysis	0
V. Expert opinion with no explicit critical appraisal, based on economic theory	0

Adapted from NHS Centre for Reviews and Dissemination Report 4, March 2001

Table 20 – Abstracted economic literature reported cost outcomes and major drawbacks

Author(s)	Title of Paper	Year	Study Type	Economic evaluation and annotated costs
Burgos,A. E.;Schmitt,S. K.;Stevenson,D. K.;Phibbs,C. S.	Readmission for neonatal jaundice in California, 1991-2000: trends and implications	2008	Cost analysis	• 10 years of data on newborn hospitalizations from CA using hospital discharge records • Charges converted to costs using charge-to-cost ratio • Mean cost of jaundice readmission $2764 in 2001$ • Sample: healthy infants ≥34 wks gestation and ≤42 wks • Mean LOS = 2.5 days • Mean cost per day = $991
Newman,T. B.;Easterling,M. J.;Goldman,E. S.;Stevenson,D. K.	Laboratory evaluation of jaundice in newborns. Frequency, cost, and yield	1990	Cost analysis	• Reports only charge and cost for recommended tests, bilirubin + blood tests ($125 charge, $80 reimbursement) • Data are very dated (1980-1982) and from only one hospital, UCSF • Unlikely that tests have remained the same since 1982
Petersen,J. R.;Okorodudu,A. O.;Mohammad,A. A.;Fernando,A.;Shattuck,K. E.	Association of transcutaneous bilirubin testing in hospital with decreased readmission rate for hyperbilirubinemia.	2005	6,603 newborns Pre-TcB testing group = (August 2002 - March 2003) TcB testing group = (May 2003 - Dec 2003)	• Charges for newborn hospitalizations from one hospital in TX • Reported as mean charges for hyperbilirubinemia-related readmission • Study was not designed to measure healthcare costs (from paper); no description in methods • Only charges reported, no adjustment for charge-to-cost • Conclusion is that there is an increase in charges associated with TcB testing and phototherapy despite lower readmission rates for hyperbilirubinemia
Prasarnphanich,T.;Somlaw,S.	The value of routine bilirubin screening to detect significant hyperbilirubinemia in Thai healthy term newborns.	2007	1983 healthy term neonates (March 2004 - November 2004)	• Cost of detecting one case of hyperbilirubinemia: 6.22 US$ • Cost of detecting one case of hyperbilirubinemia: 247.87 US$ • Due to differences in health care patterns and unit costs, it is not appropriate to apply Thai costs to US setting • More recent data from US setting available

Table 21 – Abstracted study elements for economic evaluation of alternative screening strategies for hyperbilirubinemia.

Study	Country	Strategies Evaluated	Perspective	List of conditions screened for	Time horizon of the analysis	Type of model	Health states included in model	Costing year	Target population	Type of analysis (CEA, BCA, other)
Suresh & Clark, Pediatrics, 2004.	US	1. Current management 2. Universal follow-up 1 to 2 days after early discharge 3. Routine predischarge serum bilirubin testing with selective follow-up and laboratory testing 4. Routine predischarge transcutaneous bilirubin with selective follow-up and laboratory testing	Modified societal (short-term caregiver costs excluded)	Hyperbilirubinemia & need for Phototherapy	Lifetime	Decision analytic (decision tree)	See Fig 1, include: - Home nurse visit - Office visit - Lab testing - Hospital phototherapy - Home phototherapy - Chronic bilirubin encephalopathy (although not shown in figure)	2002	2.8 million (annual US cohort of healthy newborns ≥37 wks)	Cost-effectiveness analysis

	Type of costs included:						
Main outcomes reported (e.g., $/LY, $/QALY, net benefits, other)	**Direct medical**	**Direct nonmedical**	**Opportunity/ time**	**Source(s) of costs**	**Source(s) of transition prob's**	**Quality adjustments if included**	**Source(s) of quality adjustments**
Total costs # cases chronic bilirubin encephalopathy prevented Main outcome: cost per case prevented	Home nurse visit Office visit Serum bilirubin Hemogram Blood typing Coombs test Transcutaneous bilirubin Hospitalizations Hospital phototherapy Home phototherapy Chronic bilirubin encephalopathy	Chronic bilirubin encephalopathy (e.g., lifetime costs of medical care, special education, lost productivity)	Not included	Charge data from one hospital in VT Bilirubinometer manufacturer Visiting nurse association "Talking to local pediatricians" Author assumptions Medical equipment supplier in VT Published data	Published data Expert opinion (interviews with 4 pediatricians) Author assumptions	Not included	N/A

XIII. Table of case reports

Table 23 – Case reports

Authors	Title	Year	Periodical
Alaql,F.;Osiovich,H.	A case of extreme unconjugated fetal hyperbilirubinemia.	2004	American Journal of Perinatology
Berardi,A.;Lugli,L.;Ferrari,F.; Gargano,G.;D'Apolito,M.;Marrone,A.;Iolascon,A.	Kernicterus associated with hereditary spherocytosis and UGT1A1 promoter polymorphism.	2006	Biology of the neonate
Bertini,G.;Dani,C.;Fonda,C.; Zorzi,C.;Rubaltelli,F. F.	Bronze baby syndrome and the risk of kernicterus.	2005	Acta Paediatrica
Centers for Disease Control and Prevention (CDC)	Kernicterus in full-term infants--United States, 1994-1998.	2001	Morbidity & Mortality Weekly Report
Moll M.; Goelz R.; Naegele T.; Wilke M.; Poets C.F.	Are recommended phototherapy thresholds safe enough for extremely low birth weight (ELBW) infants? A report on 2 ELBW infants with kernicterus despite only moderate hyperbilirubinemia	2011	Neonatology
Schroeder,L.L.;O'Connor,T. A.	Bilirubin encephalopathy in a term infant after planned home delivery.	1992	Missouri medicine
Siegfried,E. C.;Stone,M. S.;Madison,K. C.	Ultraviolet light burn: a cutaneous complication of visible light phototherapy of neonatal jaundice.	1992	Pediatric dermatology
Stanley,T. V.	A case of kernicterus in New Zealand: a predictable tragedy?.	1997	Journal of Paediatrics & Child Health

XIV. References

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XV. Appendix A: American Academy of Pediatrics Treatment Guidelines

Figure 2 – 1994 AAP Neonatal Hyperbilirubinemia Treatment Guidelines*

Table 2. Management of Hyperbilirubinemia in the Healthy Term Newborn*

Age, hours	TSB Level, mg/dL (μmol/L)			
	Consider Phototherapy†	Phototherapy	Exchange Transfusion if Intensive Phototherapy Fails‡	Exchange Transfusion and Intensive Phototherapy
≤24§	...	...	...	...
25–48	≥12 (170)	≥15 (260)	≥20 (340)	≥25 (430)
49–72	≥15 (260)	≥18 (310)	≥25 (430)	≥30 (510)
>72	≥17 (290)	≥20 (340)	≥25 (430)	≥30 (510)

* TSB indicates total serum bilirubin.
† Phototherapy at these TSB levels is a clinical option, meaning that the intervention is available and may be used *on the basis of individual clinical judgment*. For a more detailed description of phototherapy, see the Appendix.
‡ Intensive phototherapy (Appendix) should produce a decline of TSB of 1 to 2 mg/dL within 4 to 6 hours and the TSB level should continue to fall and remain below the threshold level for exchange transfusion. If this does not occur, it is considered a failure of phototherapy.
§ Term infants who are clinically jaundiced at ≤24 hours old are not considered healthy and require further evaluation (see text).

Figure 3 – 2004 AAP Neonatal Hyperbilirubinemia Management – Risk Nomogram*

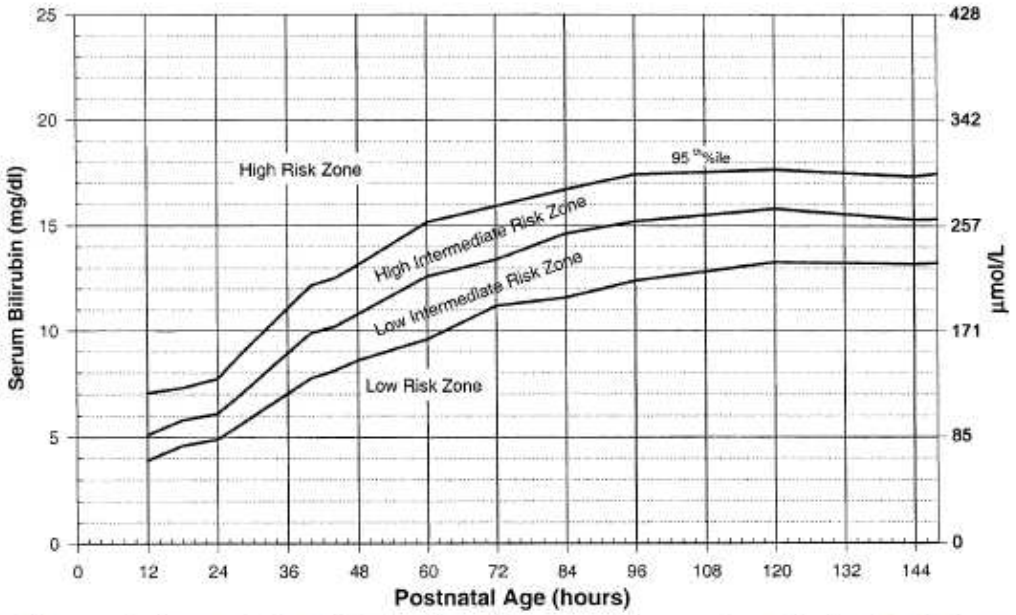

Fig 2. Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone) as shown in Appendix 1, Table 4. Used with permission from Bhutani et al.[21] See Appendix 1 for additional information about this nomogram, which should not be used to represent the natural history of neonatal hyperbilirubinemia.

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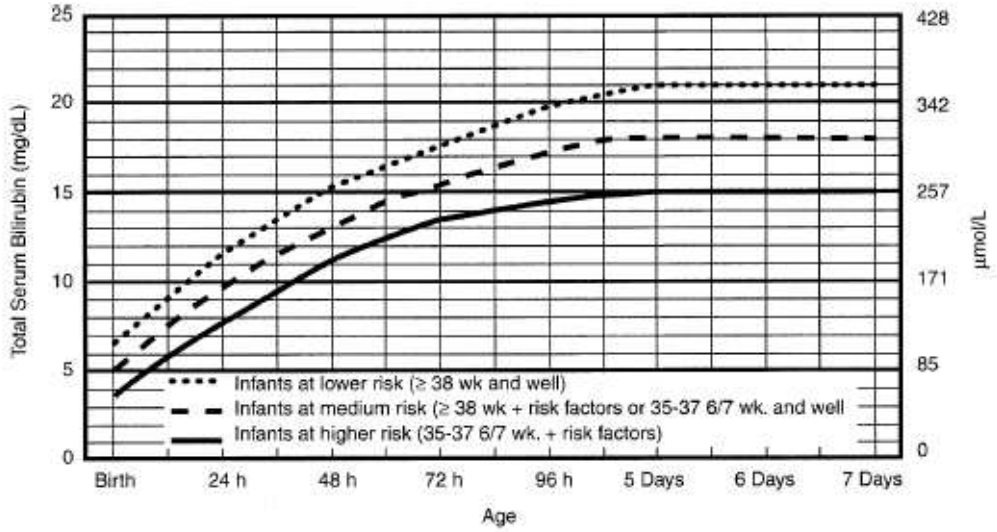
Figure 4 – 2004 AAP Neonatal Hyperbilirubinemia Treatment Guidelines - Phototherapy*



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Fig 3. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.

Note: These guidelines are based on limited evidence and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy which should be used when the TSB exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin,[45–47] the blood-brain barrier,[48] and the susceptibility of the brain cells to damage by bilirubin.[48]

"Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths of approximately 430–490 nm) of at least 30 μW/cm² per nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system.

See Appendix 2 for additional information on measuring the dose of phototherapy, a description of intensive phototherapy, and of light sources used. If total serum bilirubin levels approach or exceed the exchange transfusion line (Fig 4), the sides of the bassinet, incubator, or warmer should be lined with aluminum foil or white material.[50] This will increase the surface area of the infant exposed and increase the efficacy of phototherapy.[51]

If the total serum bilirubin does not decrease or continues to rise in an infant who is receiving intensive phototherapy, this strongly suggests the presence of hemolysis.

Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin level (cholestatic jaundice) may develop the bronze-baby syndrome. See Appendix 2 for the use of phototherapy in these infants.

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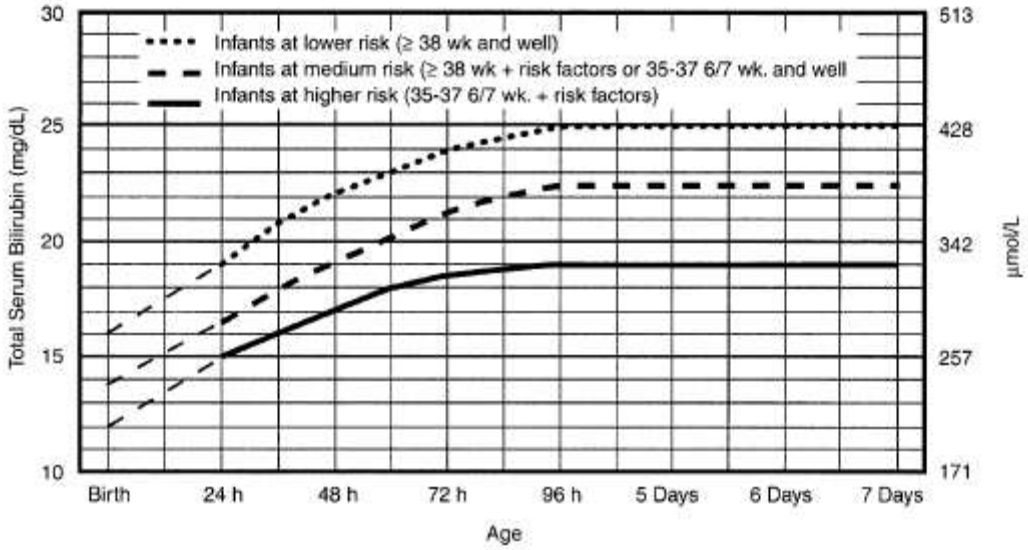
Figure 5 – 2004 AAP Neonatal Hyperbilirubinemia Treatment Guidelines – Exchange Transfusion*



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.
- Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (See legend)
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Fig 4. Guidelines for exchange transfusion in infants 35 or more weeks' gestation.
Note that these suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. See ref. 3 for risks and complications of exchange transfusion. During birth hospitalization, exchange transfusion is recommended if the TSB rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.
The following B/A ratios can be used together with but in not in lieu of the TSB level as an additional factor in determining the need for exchange transfusion[52]:

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XVI. Appendix B: Tables of abstracted literature

Table 24 – Abstracted literature pertaining to condition

Author(s)	Title of Paper	Year	Study Population Description	Condition Significant findings
AlOtaibi,S. F.;Blaser,S.;MacGregor,D. L.	Neurological complications of kernicterus.	2005	12 infants with severe neonatal jaundice and neurological sequelae secondary to bilirubin toxicity (January 1990 - May 2000)	• 12 infants with severe neonatal jaundice (>23.4mg/dL) and neurological sequelae secondary to bilirubin toxicity • 11/12 infants discharged home one day after birth and were readmitted with elevated bilirubin levels • Developmental follow-up (7 months – 6 years) - 3 patients developed normally, 2 were lost to follow-up, 7 had abnormal development (delayed gross motor, fine motor, and adaptive and social skills)
Baradaranfar, M. H.;Atighechi,S.;Dadgarnia,M. H.;Jafari,R.;Karimi,G.;Mollasadeghi,A.;Eslami, Z.;Baradarnfar, A.	Hearing status in neonatal hyperbilirubinemia by auditory brain stem evoked response and transient evoked otoacoustic emission	2011	70 total newborn babies 35 with TSB >20 mg/dL 35 non-elevated TSB control babies	• According to ABR, 26 (74.3%) of newborns with TSB >20 mg/dL had normal hearing; 4 (11.4%) had mild to moderate hearing loss and 5 (14.3%) had severe to profound hearing loss • Blood bilirubin levels in 4 infants with severe to profound hearing loss had TSB >30 mg/dL; 3 with mild to moderate hearing loss had TSB >30 mg/dL
Bhat,Y. R.;Rao,A.	Transcutaneous bilirubin in predicting hyperbilirubinemia in term neonates.	2008	461 healthy term newborns born between 37 and 42 weeks gestation (June 2003 - May 2005)	• 17.6% (81/461) healthy newborns were found to have subsequent hyperbilirubinemia (>17mg/dL) • TcB index of <5 at 24 hours of life and <8 at 48 hours put the infant at no measurable risk for developing hyperbilirubinemia • TcB index of >7 at 24 hours and >11 at 48 hours have a high chance of developing hyperbilirubinemia, these TcB values correlated with the high intermediate risk zone on the Bhutani nomogram
Bhutani, V.K. ;Johnson, L.	Kernicterus in late preterm infants cared for as term healthy infants.	2006	125 total eligible reported cases from the Pilot Kernicterus Registry 29 late preterm infants (34 0/7- 36 6/7 gestational age) 92 term infants (1992-2003)	• Severe squelae was more severe in late preterm infants • Gestational age, rather than just birth weight alone may be an additional significant risk factor for hyperbilirubinemia

Bjerre,J. V.;Petersen,J. R.;Ebbesen,F.	Surveillance of extreme hyperbilirubinemia in Denmark. A method to identify the newborn infants.	2008	249,308 infants born alive at term or near-term (January 2002 - December 2005)	• 113 infants with TSB >450 umol/L, or 45/100000 live births
Brooks,J.C.; Fisher-Owens,S.A.; Wu,Y.W.; Strauss, D.J.;Newman, T.B.	Evidence Suggests There Was Not a "Resurgence" of Kernicterus in the 1990s	2011	64,346 neonates born in California between 1988-1997 Infant (<1 year old) death certificate data (with an ICD-9 code for kernicterus) from the National Center for Health Statistics (1979-2006)	• Incidence estimates of kernicterus 1 in 200,000 California live births, 1 in 2,500 among children who received services from the Department of Developmental Services and 1 in 400 children with cerebral palsy • Both data sources suggest a flat incidence rate of less than 1 in 100,000 per year • In 1994, 3 reported infant deaths due to kernicterus, and 2 or fewer infants deaths due to kernicterus occurred each year for the other 28 years from 1979-2006 (0.28 deaths per million live births) in the United States
Burgos,A. E.;Schmitt,S. K.;Stevenson,D. K.;Phibbs,C. S.	Readmission for neonatal jaundice in California, 1991-2000: trends and implications	2008	4,440,866 healthy, routinely discharged infants between 34 and 42 weeks gestation (1991-2000)	• Factors most strongly associated with increased likelihood of readmission for jaundice were gestational age 34-37 weeks (OR: 2.33–3.18), gestational age 38 weeks (OR: 1.64), Medicaid or private insurance (OR: 1.45), Asian race (OR: 1.53). • The factors most strongly associated with a decreased likelihood of readmission for jaundice were cesarean delivery (OR: 0.44), black race (OR: 0.34).
Burke,B. L.;Robbins,J. M.;Bird,T. M.;Hobbs,C. A.;Nesmith,C.; Tilford,J. M.	Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988-2005.	2009	Neonatal discharges from 1988–2005 with ICD-9 codes for jaundice or chronic bilirubin encephalopathy (kernicterus) occurring within the first 30 days of life Jaundice diagnoses = 2,376,294 Chronic bilirubin encephalopathy (kernicterus) diagnoses = 1,395	• Hospitalizations for term and preterm newborn infants with jaundice treated with phototherapy increased after the publication of the 1994 AAP guidelines. • Term infant hospitalizations with a diagnosis of chronic bilirubin encephalopathy showed a decline before the publication of the 1994 AAP guidelines, the average incidence (1.5/100,000) remained the same from 1994–2005

Centers for Disease Control and Prevention	Kernicterus in full-term infants--United States, 1994-1998.	2001	Convenience sample of 4 children with kernicterus diagnosed since 1994 , born at >37 weeks gestational age and >2500g	• Hyperbilirubinemia in full-term otherwise healthy infants can lead to kernicterus • Peak TSB among the 4 infants ranged from 29.4-41.5 (mean 34.7 mg/dL)
Chen,W. X.;Wong,V.	Visual evoked potentials in neonatal hyperbilirubinemia.	2006	24 term neonates ≥37 weeks gestation with hyperbilirubinemia Moderate hyperbilirubinemia (serum bilirubin =225-341 umol/L) group = 16 Severe hyperbilirubinemia (serum bilirubin≥342 umol/L) group = 8 (1995-1996)	• No significant differences in either the latencies or amplitude of visual evoked potential between the moderate and severe hyperbilirubinemia groups, VEP of all infants returned to normal after 12 months of age • No significant differences in neurodevelopmental outcome up to 3 years between the moderate and severe hyperbilirubinemia groups • All subjects treated with phototherapy, did not find any effects of phototherapy on VEP • One term infant in severe hyperbilirubinemia group with ABO incompatibility had mild hypotonia and motor delay at 10 months, normal at 3 years
Chen,W. X.;Wong,V. C.;Wong,K. Y.	Neurodevelopmental outcome of severe neonatal hemolytic hyperbilirubinemia.	2006	128 term neonates with hyperbilirubinemia Hemolytic group = 29 Non-hemolytic group = 99 (1995 - 2000)	• No relationship between abnormal initial BAEP and the final neurodevelopmental outcome • The effect of hyperbilirubinemia on BAEP and neurodevelopmental status was transient • 5 subjects had abnormal neurodevelopmental outcome at 3 years, mild motor delay and hypotonia (3 in hemolytic group, 2 in non-hemolytic group)
Chen,Y. J.;Kang,W. M.	Effects of bilirubin on visual evoked potentials in term infants.	1995	94 infants 38-41 weeks gestation, within first week of life Controls = 22 Jaundice = 72 Low - 171-254 umol/l (n = 26) Moderate - 255-341 umol/l (n = 25) Severe - ≥342 umol/l (n = 21)	• At 1 year of age, none of the infants in the low and moderate groups showed any abnormality on the Denver Developmental Screen Test (DDST) and neurological examination • In the severe group, 4 /18 infants were abnormal in gross motor and fine motor skills of DDST • The results revealed that VEP may reflect severity of hyperbilirubinemia in the first 8 weeks of life
Ebbesen,F.;Ehrenstein,V.;Traeger,M.;Nielsen,G. L.	Neonatal non-hemolytic hyperbilirubinemia: a prevalence	2010	All male singletons born and registered in the Conscript District at age 18, n = 13,181	• 463 subjects in "exposed" group with history of neonatal hyperbilirubinemia within first two weeks of life • No evidence of increased risk of neuropsychiatric morbidity or worse cognitive performance among males exposed to hyperbilirubinemia as

	study of adult neuropsychiatric disability and cognitive function in 463 male Danish conscripts.		(1977 – 1983)	neonates • Level of neonatal non-hemolytic hyperbilirubinemia was no associated with cognitive performance at 18-20 years of age • No association between recorded neuropsychiatric disability and neonatal non-hemolytic hyperbilirubinemia as compared to controls
Ebbesen,F.;Andersson,C.;Verder,H.;Grytter,C.;Pedersen-Bjergaard,L.;Petersen,J. R.;Schaarup,J.	Extreme hyperbilirubinemia in term and near-term infants in Denmark.	2005	128,344 infants born alive at term or near-term (January 2000 - December 2001)	• 32 infants developed extreme hyperbilirubinemia (beyond EcT limit) (25 per 100 000) • Median maximum TSB concentration was 492 umol/l • 12 infants had signs and symptoms of CNS involvement (11 had ABE phase-1 and one had phase-2 symptoms) • 19 infants developed extreme hyperbilirubinemia during primary admission to the maternity ward or neonatal department; the others after having been discharged • Infants readmitted from home more often had signs and symptoms of CNS involvement
Engle,W. D.;Lai,S.;Ahmad,N.;Manning,M. D.;Jackson,G. L.	An hour-specific nomogram for transcutaneous bilirubin values in term and late preterm Hispanic neonates.	2009	2005 white Hispanic neonates with gestational age 35 weeks in well nursery (May 2006 - April 2007)	• TcB nomogram constructed for this exclusively Hispanic population, identifying the 5th, 25th, 50th, 75th, and 95th percentile values • 95th percentile values at 24, 48, and 72 hours were 7.6, 11.0, and 12.4 mg/dL • Hispanic neonates have significantly higher TcB values at the majority of time points analyzed compared to other studies
Fouzas,S.;Mantagou,L.;Skylogianni,E.;Mantagos,S.;Varvarigou,A.	Transcutaneous bilirubin levels for the first 120 postnatal hours in healthy neonates.	2010	2818 healthy neonates of gestational age ≥ 35 weeks (September 2005 - August 2008)	• TcB nomogram for first 120 postnatal hours • At 24 hours, 39.6% of TcB measurements from neonates who subsequently required phototherapy were below the 95th percentile and 9.1% were below the 75th percentile
Gale,R.;Seidman,D. S.;Dollberg,S.;Stevenson,D. K.	Epidemiology of neonatal jaundice in the Jerusalem population.	1990	10,122 term infants (≥37 weeks) Study group: 1,154 infants with bilirubin levels >12.9mg/dL Control group: 1,154 randomly selected infants with bilirubin levels ≤12.9mg/dL	• Interviews performed with mothers within 48 hours after delivery • High bilirubin level was significantly associated with male sex, maternal diabetes (chronic and gestational), pregnancy-induced hypertension, previous sibling with neonatal jaundice, delivery by cesarean section, vacuum use, forceps use, epidural anesthesia, mother with blood type O, first delivery, cephalohematoma, short gestation, lower birth weight, lower birth order, older maternal age, lower percentile for birth weight, and percentage of weight loss during

			(January 1984 - March 1988)	hospitalization
Gamaleldin,R.;Iskander,I.;Seoud,I.;Aboraya,H.;Aravkin,A.;Sampson,P. D.;Wennberg,R. P.	Risk factors for neurotoxicity in newborns with severe neonatal hyperbilirubinemia	2011	249 newborns ≤14 day old with TSB ≥ 25 mg/dL (average = 30.0 mg/dL; range = 25-76.4 mg/dL) (January 2008-December 2008)	• In absence of neurotoxicity risk factors, no cases of ABE below TSB level of 31.5 mg/dL • In absence of neurotoxicity risk factors, no evidence of ABE at discharge despite TSB levels >30 mg/dL in 25 infants • Risk factors for developing bilirubin neurotoxicity include Rh hemolytic disease, sepsis, low admission weight, ABO incompatibility • The threshold TSB level that identified 90% of infants with ABE was 25.4 mg/dL when neurotoxicity factors present • All 26 deaths associated with classic signs of Kernicterus (CBE) • Reason for variation in susceptibility of infants to a given TSB level unknown
Gkoltsiou,K.;Tzoufi,M.;Counsell,S.;Rutherford,M.;Cowan,F.	Serial brain MRI and ultrasound findings: relation to gestational age, bilirubin level, neonatal neurologic status and neurodevelopmental outcome in infants at risk of kernicterus.	2008	11 infants with unconjugated hyperbilirubinemia of >400 umol/L and/or neonatal or later neurological signs suggestive chronic bilirubin encephalopathy and with at least one cranial ultrasound and one MRI brain scan (April 1997 and May 2005)	• Neonatal neurological examination was abnormal in 8/10 • Cranial ultrasound showed increased basal ganglia in 4/9 , white matter echogenicity, lenticulostriate vasculopathy and caudothalamic hyperechogencity/cysts in 5/9 infants • MRI showed abnormal signal intensity in the globus pallidum in 1/2 preterm, 8/9 term and 9/11 later scans • 7 infants developed athetoid/dystonic cerebral palsy, 6 hearing loss • Adverse outcome was associated with abnormal basal ganglia on ultrasound and other MRI findings • Severe cerebral palsy occurred with relatively low TSB levels in preterm infants but only at high levels in full terms
Guaran,R. L.;Drew,J. H.;Watkins,A. M.	Jaundice: clinical practice in 88,000 liveborn infants.	1992	88,137 live-borns (1971-1989)	• 10,944/88,137 (12.4%) had hyperbilirubinemia (>154umol/L), incidence of documented cases increased during study period • 6,799 (62.1%) received no treatment, 4,126 (37.7%) received phototherapy, 248 (2.3%) received EcT (phototherapy and EcT not mutually exclusive) • Jaundice due to prematurity (no other cause identified and infants born before 37th week), most frequently identified cause of jaundice in this population - 2.0% had EcT, 75.3% had phototherapy, no death related to jaundice or treatment • Second most frequent cause was due to ABO erythroblastosis, 86% received phototherapy, 9.6% received phototherapy and EcT • Of the 248 infants who received EcT, 6 died - 2 of necrotizing enterocolitis, 1 of pulmonary

				hemorrhage and 3 possible attributable to the EcT. Nonfatal complications included - apnea, transient hypocalcemia and hypoglycemia, asymptomatic bacteraemia, perforated bowel, nonfatal necrotizing entercolitis, inspissated bile syndrome and disseminated intravascular coagulopathy • 4,126 infants received phototherapy, no deaths attributable to phototherapy were identified, infrequent complications included pyrexia and diarrhea
Hameed, N.N.; Na' ma, A.M.; Vilms, R.; Bhutani, V.K.	Severe Neonatal Hyperbilirubinemia and Adverse Short-Term Consequences in Baghdad, Iraq.	2011	162 total infants 1-23 days old admitted to the emergency room mean peak bilirubin level of 22.6 ± 6.3 mg/dL (October 2007-January 2008)	• 90% of infants 4-7 days old at 25-75th percentiles on nomogram at admission • Overall, 19/162 (12%) died; 34/162 (21%) developed bilirubin encephalopathy; 36/162 (22%) developed signs of ABE; and 109/162 (67%) had a normal clinical exam at <3 months • TSB levels and clinical outcomes of bilirubin encephalopathy or death: • <20 mg/dL: 1 bilirubin encephalopathy, 1 death (2/62 total; 3.2%) • 20.0-24.9 mg/dL: 7 bilirubin encephalopathy, 7 death (14/48 total; 29.2%) • 25.0-29.9 mg/dL: 12 bilirubin encephalopathy, 6 death (18/33 total; 54.6%) • 30.0-35 mg/dL: 7 bilirubin encephalopathy, 2 death (9/12 total; 75%) • >35mg/dL: 5 bilirubin encephalopathy, 2 death (7/7 total; 100%)
Harris,M. C.;Bernbaum,J. C.;Polin,J. R.;Zimmerman ,R.;Polin,R. A.	Developmental follow-up of breastfed term and near-term infants with marked hyperbilirubinemia.	2001	6 infants ≥36 weeks gestation, readmitted to the hospital in the first week of life due to hyperbilirubinemia >25 mg/dL (September 1993 - September 1996)	• 5/ 6 infants presented with abnormal neurologic signs • 3/4 of whom had MRIs showed increased signal intensity in the basal ganglia consistent with chronic bilirubin encephalopathy • 5/6 infants received EcTs and all were treated with phototherapy and intravenous fluids • Follow-up examinations between 3 months and 2 years showed resolution of clinical signs in all but 1 infant; 4 infants had a subsequent normal MRI and 1 had residual hearing impairment; 1 infant demonstrated severely abnormal developmental evaluations, as well as both an abnormal initial MRI and BAEPs; follow-up MRI showed evidence of encephalomalacia with changes not characteristic of chronic bilirubin encephalopathy
Jangaard,K. A.;Fell,D. B.;Dodds,L.;Allen,A. C.	Outcomes in a population of healthy term and near-term infants with serum	2008	56,019 newborns in the Perinatal Database with linkage to a registration file (January 1994 - December 2000):	• 3779/56,019 had TSB levels ≥13.5mg/dL • 348/56,019 had TSB levels greater than 19mg/dL (severe) • During study period, no reported cases of chronic bilirubin encephalopathy • Risk of cerebral palsy, abnormal hearing or abnormal vision not increased over no-

	bilirubin levels of >or=325 umol/L (>or=19 mg/dL) who were born in Nova Scotia, Canada, between 1994 and 2000.		Moderate hyperbilirubinemia group = 3431 with TSB 13.5-19mg/dL Severe hyperbilirubinemia group = 348 with TSB >19mg/dL No hyperbilirubinemia group = 52,240	hyperbilirubinemia group • Risk of developmental delay significantly increased in moderate hyperbilirubinemia group over no-hyperbilirubinemia group • Risk of ADHD significantly increased in severe hyperbilirubinemia group over no-hyperbilirubinemia group
Jiang,Z. D.;Chen,C.; Liu,T. T.; Wilkinson, A. R.	Changes in Brainstem Auditory Evoked Response Latencies in Term Neonates with Hyperbilirubinemia.	2007	Study group = 90 term neonates with TSB >10 mg/dL requiring Phototherapy or EcT Control group = 43 term neonates	• BAEP threshold in neonates with hyperbilirubinemia was significantly higher than in controls • 9/90 (10%) of neonates with hyperbilirubinemia had a BAEP threshold >20dB (normal hearing) • 14/90 (16%) of neonates with hyperbilirubinemia had a finding suggestive of peripheral auditory impairment • 16/90 (18%) of neonates with hyperbilirubinemia had a finding suggestive of central auditory impairment • In total, 25/90 (28%) of neonates with hyperbilirubinemia had BAEP abnormalities suggesting auditory impairment, occurring more frequently in those with a higher TSB level • BAEP abnormalities may recover quickly after treatment which may suggest transient auditory impairment
Johnson,L.;Bhutani,V. K.;Karp,K.;Sivieri,E. M.;Shapiro,S. M.	Clinical report from the pilot USA Kernicterus Registry (1992 to 2004).	2009	125 individuals born ≥35 weeks, discharged as healthy but subsequently developed chronic bilirubin encephalopathy , voluntarily reported to Pilot USA Kernicterus Registry (1992-2004)	• 7/125 were not reevaluated or treated for hyperbilirubinemia, remaining 118 all had bilirubin levels between >20mg/dL • Mortality rate was (6/125), 5 within first week of age, and all 6 within one year of age • Pre-discharge TcB or TSB was measured in 22/125, showing significant hyperbilirubinemia in all, TSB levels were either not interpreted on the basis of postnatal age or earlier/targeted follow-up was not considered • Study determined the underlying root cause of chronic bilirubin encephalopathy was systems failure of services by multiple providers and inability to identify at-risk infants • G6PD was one confounding risk factor for mortality and morbidity
Mah,M. P.;Clark,S. L.;Akhigbe,E.;Englebright,J.;Frye,D.	Reduction of severe hyperbilirubinemia after institution of	2010	1,028,817 infants Before routine screening group = 129,345 infants After routine	• Implementation of universal predischarge screening was associated with a statistically significant decline in the incidence of neonates with bilirubin levels between 25-29.9 mg/dL (extreme hyperbilirubinemia) and >30mg/dL

K.;Meyers,J. A.;Perlin,J. B.;Rodriguez, M.;Shepard,A.	predischarge bilirubin screening.		screening group = 899,472 infants (May 2004 - December 2008)	(hazardous hyperbilirubinemia) and was also associated with significant increase in phototherapy use • Incidence per 100,000 births - 1400 (severe), 140 (extreme) and 10 (hazardous)
Maimburg,R. D.;Bech,B. H.;Bjerre,J. V.;Olsen,J.;Moller-Madsen,B.	Obstetric outcome in Danish children with a validated diagnosis of kernicterus.	2009	9 children born at ≥35 weeks gestation with a valid diagnosis of chronic bilirubin encephalopathy (January 1994 - December 2003)	• 9 children with valid chronic bilirubin encephalopathy diagnosis lead to an incidence of 1.3/100,000 in the 10 year study period • 5/9 children had mental retardation, 4/9 had hearing impairment, 4/9 had cerebral palsy • 3/9 children died before the age of two (at the age of 2, 5, 19 months) • All maximum serum bilirubin in the newborn period was pathological, ranging from 531-745 umol/L, all bilirubin-induced neurological dysfunction (BIND) scores corresponding to moderate or advanced acute bilirubin encephalopathy
Maisels,M. J.;Kring,E.	Length of stay, jaundice, and hospital readmission.	1998	247 newborns readmitted to the hospital within 14 days	• Of the 247/29,934 newborn readmitted to the hospital within 14 days of life, 51% were readmitted for hyperbilirubinemia (14.5 - 28.9 mg/dL), for an incidence of 4.2/1,000 discharges • Of those readmitted for hyperbilirubinemia, 40/127 had >20 mg/dL and 4/127 had >25 mg/dL
Maisels,M. J.;Newman,T. B.	Kernicterus in otherwise healthy, breast-fed term newborns.	1995	6 described cases of chronic bilirubin encephalopathy (1979-1991)	• Very severe hyperbilirubinemia and chronic bilirubin encephalopathy can occur in term or near-term apparently healthy breastfed infants without apparent hemolysis
Manning,D.;Todd,P.;Maxwell, M.;Jane Platt,M.	Prospective surveillance study of severe hyperbilirubinemia in the newborn in the UK and Ireland.	2007	1,500,052 births Cases = 108 infants with severe hyperbilirubinemia in the first month of life (May 2003 - May 2005)	• Incidence in the UK of severe hyperbilirubinemia was found to be 7.1/100,000 live births • Incidence in the UK of bilirubin encephalopathy was found to be .9/100,000 live births • Range of peak serum bilirubin concentration timing was 1 - 9 days, mean of 4.3 days • 48/107 infants with severe hyperbilirubinemia treated with EcT • Of the 104 cases delivered in the hospital, 20 presented in the hospital, 84 readmitted • Of the 14 cases of bilirubin encephalopathy at one year follow-up - 3 had died, 2 lost to follow-up, 4 with sequelae of encephalopathy (hearing impairment, athetoid cerebral palsy), 2 incidental neurodevelopmental problems, 3 had reportedly normal development
Mansi,G.;De Maio,C.;Araimo,G.;Rotta,I.;Crivaro,V.;Sarno, M.;Raimondi,F. ;Paludetto,R.	Safe hyperbilirubinemia is associated with altered neonatal	2003	Study group = 28 jaundiced neonates with total bilirubin >13mg/dL not treated with	• Brazelton Neonatal Behavior Assessment Scale (BNBAS) at 4 days of age, controls performed significantly better than newborns with jaundice, mainly on social-interactive items

	behavior.		Phototherapy Control group = 28 matched neonates	
Mukhopadhyay,K.;Chowdhary,G.;Singh,P.;Kumar,P.;Narang,A.	Neurodevelopmental outcome of acute bilirubin encephalopathy.	2010	25 newborns ≥35 weeks gestation with TSB >20mg/dL and signs of ABE	• All subjects underwent double volume EcT and phototherapy • 15/25 (60%) follow-up data available up to 1 year, follow-up occurred at 3, 6, 9, and 12 months • At one year of age, 9/15 (60%) had abnormal Denver developmental screening test, 4/15 (27%) had neurological abnormality, 10/15 had abnormal BAER and 3/15 had no abnormal neurodevelopmental outcome • BAER abnormality had a significant relationship with abnormal outcome, MRI abnormality did not
Newman,T. B.;Escobar,G. J.;Gonzales,V. M.;Armstrong,M. A.;Gardner,M. N.;Folck,B. F.	Frequency of neonatal bilirubin testing and hyperbilirubinemia in a large health maintenance organization	1999	51,387 infants born at ≥36 weeks gestation and ≥2000g (1995 - 1996)	• Maximum TSB levels >20mg/dL identified in approximately 2.0% of births, >25mg/dL in .15% (1 in 650), >30mg/dL in .01% (1/10,000) • Gestational age, race, sex and maternal age were predictors of hyperbilirubinemia • Among the 11 hospitals, frequency of elevated TSB levels was not associated with the frequency of TSB testing
Newman,T. B.;Klebanoff,M. A.	Neonatal hyperbilirubinemia and long-term outcome: another look at the Collaborative Perinatal Project.	1993	41,324 singleton black and white infants with birth weight >2=500g who survived at least one year and had one bilirubin level recorded (1959-1974)	• Pregnancies occurring between 1959-1966 at which time phototherapy not in use and inconsistent use of EcT, exclusive breastfeeding rare in this cohort • No consistent association between peak serum bilirubin and IQ (at 7 yr follow-up) • Provides little evidence that higher bilirubin levels are associated with definitely abnormal neurologic examination results or hearing loss • Risk of abnormal or suspicious neurologic examination results increased in a stepwise fashion with increasing bilirubin level (mild and nonspecific motor abnormalities most often associated with bilirubin)
Newman,T. B.;Liljestrand,P.;Escobar,G. J.	Infants with bilirubin levels of 30 mg/dL or more in a large managed care organization.	2003	11 infants with TSB ≥30mg/dL within first 30 days of life out of birth cohort of 111,009 (1995 - 1998)	• Observed incidence of peak TSB >30mg/dL was approximately 1/10,000 • 2/11 received phototherapy during birth hospitalization, 9/11 discharged on 2nd day of life and received phototherapy later • Maximum TSB levels ranged from 30.7mg/dL - 45.5mg/dL, mean of 34.9mg/dL • 10/11 infants showed no signs of ABE, 1/11 had a questionable sign (brief cyanotic episode) • 3/11 cases demonstrated a clear departure from AAP guidelines for management of hyperbilirubinemia

				• 8/11 available for follow-up (one died of apparent sudden infant death syndrome, 2 lost to follow-up), no serious neurodevelopmental sequelae observed
Newman,T. B.;Liljestrand,P.;Jeremy,R. J.;Ferriero,D. M.;Wu,Y. W.;Hudes,E. S.;Escobar,G. J.;Jaundice and Infant Feeding Study,Team	Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more.	2006	Birth cohort 106,627 term and near-term infants Cases = 140 infants with TSB ≥25mg/dL Control group = 419 randomly selected infants (1995 - 1998)	• Follow-up data available at ≥2 years of age in 89% of the control group and 94% of the hyperbilirubinemia group • No significant differences between cases and controls in intelligence testing, neurological testing or motor performance • 90/140 with hyperbilirubinemia had a maximum TSB between 25-26.9mg/dL, 40 had a max TSB of 27-29.9mg/dL and 10 had a TSB >30mg/dL • 131/140 received phototherapy alone, 5 received phototherapy and EcT, 4 had only observation/follow-up • Neither the degree nor the duration of hyperbilirubinemia had a significant effect on outcomes • Results suggest the level at which the benefits of EcT exceed the risks will be more than 25mg/dL • Results suggest even elevated serum bilirubin levels >25mg/dL in the range observed in this study are not likely to result in long-term adverse effects on neurodevelopment if treated promptly
Nickisch,A.;Massinger,C.;Ertl-Wagner,B.;von Voss,H.	Pedaudiologic findings after severe neonatal hyperbilirubinemia.	2009	Study group = 15 children with neonatal bilirubin >20mg/dL and/or diagnosed bilirubin encephalopathy by MRI Control group = 15 randomly selected matched controls with neonatal bilirubin 12.5-19.5mg/dL (2002 - 2006)	• Long-term disorders of hearing in 13/15 children with severe neonatal hyperbilirubinemia compared to 2/15 with moderate hyperbilirubinemia • Auditory neuropathy was found in a total of 8 children (53%) with neonatal hyperbilirubinemia
Ogun,B.;Serbetcioglu,B.;Duman,N.;Ozkan,H.;Kirkim,G.	Long-term outcome of neonatal hyperbilirubinemia: subjective and objective audiological measures.	2003	60 infants Cases = 30 infants 24-72 months of age treated with Phototherapy during neonatal period for 20-24mg/dL bilirubin level Control group = 30 age-matched infants	• Comparison between study and control groups reveal no differences between groups in regards to auditory brainstem response (BAEP), oto-accoustic emission and subjective-speech-language-communication parameters • No correlation between TSB levels and BAEP latencies or thresholds was found

Paludetto,R.;Mansi,G.;Raimondi,F.;Romano, A.;Crivaro,V.;Bussi,M.;D'Ambrosio,G.	Moderate hyperbilirubinemia induces a transient alteration of neonatal behavior.	2002	100 neonates Cases = 50 term neonates with bilirubin levels of 13.2-20mg/dL Control group = 50 age matched neonates with bilirubin levels of 5.3-12mg/dL (January 1999 - December 2000)	• At first assessment, Brazelton Neonatal Behavioral Scale visual and auditory capabilities of hyperbilirubinemia group were especially compromised, also showed a higher frequency of tremors at first assessment • At 3 weeks of age, study and control groups did not show significant differences • Untreated moderate hyperbilirubinemia is associated with transient and reversible alteration of neonatal behavior
Saluja,S.;Agarwal,A.;Kler,N.;Amin,S.	Auditory neuropathy spectrum disorder in late preterm and term infants with severe jaundice.	2010	13 late preterm and term neonates with peak TSB 23.4-30mg/dL	• Otoacoustic emission and BAER performed on all neonates • 6/13 (46%) had acute auditory neuropathy spectrum disorder, 2 of whom had clinical signs and symptoms of ABE • Peak TSB not associated with auditory neuropathy spectrum disorder (95% CI)
Schedle,A.;Fricker,H. S.	Impact of hyperbilirubinemia and transient mother-child separation in the neonatal period on mother-child attachment in the 1st year of life.	1990	107 healthy infants between 38-42 weeks gestation and their mothers Hyperbilirubinemia and Phototherapy group = 29 infants with mean peak TSB of 271uMol/l Mild hyperbilirubinemia and no Phototherapy group= 40 infants with mean peak TSB of 209uMol/l Control group = 38 infants with no apparent jaundice (September 1986 - August 1987)	• Hyperbilirubinemia, with and without phototherapy, does not affect the quality of mother-child attachment • Frequency of minor medical problems and illnesses in the first year of life was not increased in the children with hyperbilirubinemia • Developmental screening (Denver test) showed no impairments in the children with hyperbilirubinemia • Hyperbilirubinemia and phototherapy do not seem to negatively affect the quality of attachment • Analysis of additional aspects showed that maternal coping and her perception of the child appear to be more important antecedents of the quality of attachment after the 1st year of life
Seidman,D. S.;Paz,I.;Stevenson,D. K.;Laor,A.;Danon,Y. L.;Gale,R.	Neonatal hyperbilirubinemia and physical and cognitive performance at 17 years of age.	1991	1948 total records matched to military draft medical records 17 years later (November 1970 - December 1971)	• 308 (15.8%) had moderate hyperbilirubinemia (peaked 13-20mg/dL) and 144 (7.4%) had severe hyperbilirubinemia (peaked >20mg/dL) • Risk for low IQ test scores (<85) was found to be significantly higher among full term males with TSB levels above 20mg/dL • No direct linear association shown between neonatal hyperbilirubinemia levels and

				intelligence test scores or school achievement at 17 years of age
Sgro,M.;Campbell,D.;Shah,V.	Incidence and causes of severe neonatal hyperbilirubinemia in Canada.	2006	367 clinically reported cases of severe neonatal hyperbilirubinemia 258 met inclusion criteria and confirmed to be severe neonatal hyperbilirubinemia (>37 weeks gestation and bilirubin levels >425umol/L) (July 2002-June 2004)	• Estimated incidence of severe neonatal hyperbilirubinemia of 1 /2480 live births
Sgro,M.;Campbell,D.;Barozzino,T.;Shah,V.	Acute neurological findings in a national cohort of neonates with severe neonatal hyperbilirubinemia	2011	258 total infants with TSB >25 mg/dL (July 2002-June 2004)	• Findings suggest a 1 in 20,000 incidence of ABE and 1.8 per 100,000 incidence of advanced ABE • Of the 258 infants, 32 (12.4%) identified to have neurological abnormalities consistent with ABE, and 6 of the 32 with intermediate to advanced ABE • Infants in the highest peak bilirubin level group (>32 mg/dL) had the greatest risk of acute neurological abnormalities consistent with ABE • The mid range (26-32 mg/dL) and lowest level (≤ 26 mg/dL) groups were less likely to have abnormalities (odds ratio (OR=0.174; P=0.0013 and 0.402; P=0.0613, respectively) • Exchange transfusion and presentation within the first 2 days of age were positively associated with abnormal neurological findings in infants (OR=3.332, P=0.003 and OR=2.572, P<0.0001, respectively)
Singhal,P. K.;Singh,M.;Paul,V. K.;Deorari,A. K.;Ghorpade, M. G.	Spectrum of neonatal hyperbilirubinemia: an analysis of 454 cases.	1992	7680 live births clinically suspected to have hyperbilirubinemia (January 1986-December 1989)	• 454/7680 (5.9%) developed hyperbilirubinemia (>12mg/dL) • Group 1 (Mild) included non-hemolytic causes: idiopathic (34.4%), bacterial infections (5.7%), intrauterine infections and others (2.9%) • Group 2 (Moderate) comprised of hemolytic and non-hemolytic causes: prematurity (16.7%), administration of oxytocin (9.9%), and bruising/cephalhematoma (2.9%) • Group 3 (Severe) included only hemolytic causes: blood group incompatibility between mother and baby (22.4%), and G6PD deficiency (5.1%) • 66/454 required ECT, 80.3% of which belonged to group 3; no deaths were attributable to ECT procedure • Early complications of ECT included: tachypnea ,

				bradycardia, cardio-respiratory arrest, difficult cannulation of umbilical vein • Delayed complications of ECT comprised of: anemia, hypoglycemia, septicemia, acidosis and congestive heart failure
Soorani-Lunsing,I.;Woltil,H. A.;Hadders-Algra,M.	Are moderate degrees of hyperbilirubinemia in healthy term neonates really safe for the brain?	2001	40 neonates Hyperbilirubinemia (TSB>220umol/L) group = 20 neonates Control group = 20 healthy matched neonates	• Minor neurological dysfunction was present in newborn period for 14/20 hyperbilirubinemia infants, and 5/20 control infants • At 12 months of age, 10/20 hyperbilirubinemia infants still affected; 2/20 were affected in the control group • Moderate hyperbilirubinemia (233-444umol/L) associated with minor neurological dysfunction throughout the first year of life with a dose-response relationship between the degree of hyperbilirubinemia and severity of neurological dysfunction
Vohr,B. R.;Karp,D.;O'Dea,C.;Darrow,D.;Coll,C. G.;Lester,B. M.;Brown,L.;Oh,W.;Cashore,W.	Behavioral changes correlated with brain-stem auditory evoked responses in term infants with moderate hyperbilirubinemia.	1990	50 infants Moderate TSB 10-20mg/dL group = 23 infants Low TSB <8mg/dL group = 27 infants	• Moderate hyperbilirubinemia (10-20mg/dL) affects BAEP central conduction time and specific characteristics of the Brazelton scores (orientation and range)
Watchko,J. F.;Claassen,D.	Kernicterus in premature infants: current prevalence and relationship to NICHD Phototherapy Study exchange criteria.	1994	81 infants autopsied who were <34 weeks gestation and lived at least 48 hours (January 1984 - June 1993)	• Chronic bilirubin encephalopathy observed in 3/81 autopsied infants (prevalence of 4%) • Bilirubin levels in babies with chronic bilirubin encephalopathy were 11.3 mg/dL, 18.5mg/dL and 26mg/dL • 1 infant without chronic bilirubin encephalopathy died during ECT, presumably due to the procedure • Of the 78 other infants, bilirubin levels ranged from 3.6-22.5 mg/dL
Wolf,M. J.;Wolf,B.;Beunen,G.;Casaer,P.	Neurodevelopmental outcome at 1 year in Zimbabwean neonates with extreme hyperbilirubinemia.	1999	50 infants admitted with a TSB > 23.4mg/dL 26/50 were preterm (<37 weeks gestation) (July 1991 - June 1992)	• Incidence of extreme jaundice (TSB>23.4mg/dL) is 4.8/1000 live births • Infants requiring phototherapy found to be 21.5/1000 live births in the special baby care unit • 2/50 died due to unknown causes, 5 lost to follow-up • 7/50 received EcTs • 4/6 surviving infants with EcT scored abnormal on Bayley Scales of Infant Development (BSID) at 1 year of age

				• Overall, 11/43 surviving infants scored abnormal or suspect on the BSID at 1 year of age (2 with severe motor delay and 4 with moderate motor delay) • 5/43 developed choreo-athetosis type of cerebral palsy • Infants with highest bilirubin levels scored lower on BSID at one year of age

Table 25 – Abstracted literature pertaining to screening

Author(s)	Title of Paper	Year	Study Population Description	Screening Test Characteristics Significant findings
Agarwal,R.;Kaushal,M.;Aggarwal,R.;Paul,V. K.;Deorari,A. K.	Early neonatal hyperbilirubinemia using first day serum bilirubin level.	2002	220 infants ≥35 weeks gestation (May - September 2001)	• 164/220 (77%) had clinically detectable jaundice, 10.3% had hyperbilirubinemia (TSB ≥17) • 1 infant with a TCB value of 6 developed hyperbilirubinemia • Predictive value of TSB 6 mg/dL at 24± 6 hours - Sensitivity 95%, Specificity 70.6%, PPV 27.2%, NPV 99.3%
Ahmed,M.;Mostafa,S.;Fisher,G.;Reynolds, T. M.	Comparison between transcutaneous bilirubinometry and total serum bilirubin measurements in preterm infants <35 weeks gestation.	2010	57 infants <35 weeks gestation admitted to neonatal unit (July 2007 - June 2008)	• TcB tends to have a higher screen positive rate than TSB • TcB meets the acceptability criteria for safety because the threshold for phototherapy is lowered, lowering the risk of causing brain injury by inaction • Reduction in blood sampling for TSB is an advantage because it reduces trauma and the likelihood of developing anemia
Alpay,F.;Saricis,S. U.;Tosuncuk,H. D.;Serdar,M. A.;Inanc,N.;Gokcay,E.	The value of first-day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns.	2000	498 healthy term newborns ≥38 weeks gestation (December 1997 - May 1998)	• No newborns had a serum total bilirubin level of ≥17 mg/dL in the first 72 hours of life • 60/498 cases (12.05%) had significant hyperbilirubinemia after 72 hours of life • Of the 206 newborns who had a serum bilirubin level of ≥6 mg/dL in the first 24 hours, 54 (26.21%) developed significant hyperbilirubinemia, whereas only 6 of the 292 newborns (2.05%) who had a serum bilirubin level of <6 mg/dL on the first day developed significant hyperbilirubinemia. • A mean serum bilirubin level of ≥6 mg/dL on the first day had the highest sensitivity (90%), NPV (97.9%) and a low PPV (26.2%).
Bhat,Y. R.;Rao,A.	Transcutaneous bilirubin in predicting hyperbilirubinemia in term neonates.	2008	461 healthy term newborns born between 37 and 42 weeks gestation (June 2003 - May 2005)	• 17.6% (81/461) healthy newborns were found to have subsequent hyperbilirubinemia (>17mg/dL) • TcB index of <5 at 24 hours of life and <8 at 48 hours put the infant at no measurable risk for developing hyperbilirubinemia • TcB index of >7 at 24 hours and >11 at 48 hours have a high chance of developing hyperbilirubinemia, these TcB values correlated with the high intermediate risk zone on the Bhuntani nomogram
Bhutani,V. K.;Gourley,G. R.;Adler,S.;Kreamer,B.;Dalin,	Noninvasive measurement of total serum bilirubin in a	2000	490 term and near-term newborns at discharge from	• Correlation between multiple simultaneous TcB and TSB measurements was linear and significant (r=0.91, r2=.83)

C.;Johnson,L. H.	multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia.		well nursery (March 1998-October 1998)	• TcB 75th percentile: NPV 100%, sensitivity 100%, specificity 88.1%, PPV 32.86%
Bhutani,V. K.;Johnson,L.; Sivieri,E. M.	Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns.	1999	13,003 term and near-term infants discharged from well nursery (1993 - 1997)	• Development of an hour-specific TSB nomogram for prediction of high, intermediate or low risk for developing clinically significant hyperbilirubinemia in newborns • Predischarge, 6.1% of the study population (172/2840) had TSB values in the high-risk zone (>95th percentile) at 18 to 72 hours • Predischarge, 32.1% of the population (912/2840) had TSB values in the intermediate-risk zone • Predischarge, 61.8% of the newborns (1756/2840) were in the low-risk zone (<40th percentile) and there was no measurable risk for significant hyperbilirubinemia
Boo,N. Y.;Ishak,S.	Prediction of severe hyperbilirubinaemia using the Bilicheck transcutaneous bilirubinometer.	2007	345 healthy term neonates with hyperbilirubinemia (January 2003 and January 2005)	• At TcB cut off of 200umol/L, BiliCheck detected TSB ≥300 umol/L with sensitivity 100%, specificity 33.6%
Briscoe,L.;Clark,S.;Yoxall,C. W.	Can transcutaneous bilirubinometry reduce the need for blood tests in jaundiced full term babies?.	2002	303 infants >34 weeks gestation having blood drawn in first week of life	• TcB can help determine the need for blood sampling for TSB but cannot measure TSB accurately
Carbonell,X.;Botet,F.;Figueras,J.;Riu-Godo,A.	Prediction of hyperbilirubinaemia in the healthy term newborn.	2001	2004 healthy term newborns of 37-42 weeks gestational age (April - Sep 1998; January - December 1999)	• The overall correlation between serum bilirubin and transcutaneous bilirubin is high • There is a better correlation between transcutaneous and serum bilirubin with the sternum measurement than with the forehead
Dai,J.;Krahn,J.; Parry,D. M.	Clinical impact of transcutaneous bilirubinometr	1996	1952 neonates cared for in a six month period (April 1995 - September 1995)	• A TcB cutoff of 17 was shown to have a sensitivity of 100%, specificity of 68% for hyperbilirubinemia • Use of TcB screening may provide a 20% reduction in TSB tests

	y as an adjunctive screen for hyperbilirubinemia.		Study population for jaundice meter = 45 healthy term infants	
Dalal,S. S.;Mishra,S.;Agarwal,R.;Deorari,A. K.;Paul,V.	Does measuring the changes in TcB value offer better prediction of Hyperbilirubinemia in healthy neonates?.	2009	358 neonates born at ≥ 35 weeks of gestation (October 2006 - April 2007)	• 48/325 (14.9%) of neonates developed hyperbilirubinemia by 5 days of age • Gestational age, TcB risk zone and change in TcB levels were found to be independent predictors of subsequent hyperbilirubinemia • Single TcB measurements at 30 to 48 hours predict hyperbilirubinemia with a reasonably high degree of accuracy, changes in TcB levels do not offer any added clinical benefit
De Luca,D.;Zecca, E.;Zuppa,A. A.;Romagnoli, C.	The joint use of human and electronic eye: visual assessment of jaundice and transcutaneous bilirubinometry.	2008	n = 517 white infants undergoing TSB for any reason (2005)	• Visual assessment alone underestimated TSB in 16.7-40.4% of newborns and overestimated in 4.9-35.7% • Adding TcB significantly reduced under and overestimating when the estimated bilirubin level was <8mg/dL and significantly decreased underestimating when the estimated bilirubin level was 8.1-12.mg/dL • Both sensitivity and specificity increased when added TcB to visual assessment, in all three TSB ranges: 6-8, 8.1-12, 12.1-15mg/dL
Eggert,L. D.;Wiedmeier, S. E.;Wilson,J.;Christensen,R. D.	The effect of instituting a prehospital-discharge newborn bilirubin screening program in an 18-hospital health system.	2006	101,272 neonates delivered at ≥35 weeks' gestation: Period 1 = 48,789 (March 2001 - Dec 2002) Period 2 = 52,483 (January 2003 - December 2004)	• After initiating the screening program, the incidence fell from 1/77 to 1/ 142 and the number of neonates with a level >25 mg/dL fell from 1/1522 to 1/4037 after • The rate of hospital readmission with a primary diagnosis of jaundice fell from 0.55% in period 1 to 0.43%
Engle,W. D.;Lai,S.;Ahmad,N.;Manning, M. D.;Jackson,G. L.	An hour-specific nomogram for transcutaneous bilirubin values in term and late preterm Hispanic neonates.	2009	2005 white Hispanic neonates with gestational age 35 weeks in well nursery (May 2006 - April 2007)	• TcB nomogram constructed for this exclusively Hispanic population, identifying the 5th, 25th, 50th, 75th, and 95th percentile values • 95th percentile values at 24, 48, and 72 hours were 7.6, 11.0, and 12.4 mg/dL Hispanic neonates have significantly higher TcB values at the majority of time points analyzed compared to other studies
Facchini,F. P.;Mezzacappa,M. A.;Rosa,I. R.;Mezzacappa Filho,F.;Aranh	Follow-up of neonatal jaundice in term and late premature newborns.	2007	11,259 newborns with birth weight ≥ 2,000g and gestational age of ≥35 weeks Study group =	• 2,452 (21.8%) of the birth cohort were referred to the follow-up based on predischarge bilirubin levels, 87.2% (2,140) complied • 80/2,140 were readmitted for phototherapy, two newborn infants had levels ≥25 mg/dL and none ≥30 mg/dL

a-Netto,A.;Marba,S. T.			2,452 neonates referred for follow-up (April 2001 - August 2005)	
Fouzas,S.;Karatza,A. A.;Skylogianni,E.;Mantagou,L.;Varvarigou,A.	Transcutaneous bilirubin levels in late preterm neonates.	2010	793 healthy late-preterm neonates (34-36 weeks gestation) (2006-2009)	• Developed a TcB nomogram designated for hour-specific evaluation of hyperbilirubinemia in neonates born between 34-36 weeks gestation • 64/793 (8.1%) had significant hyperbilirubinemia TcB measurements found to be accurate and correlated with paired TSB measurements • Neonates born <35 weeks gestation found to have 3 fold greater risk of developing significant hyperbilirubinemia
Fouzas,S.;Mantagou,L.;Skylogianni,E.;Mantagos,S.;Varvarigou,A.	Transcutaneous bilirubin levels for the first 120 postnatal hours in healthy neonates.	2010	2818 healthy neonates of gestational age ≥ 35 weeks (September 2005 - August 2008)	• TcB nomogram for first 120 postnatal hours • At 24 hours, 39.6% of TcB measurements from neonates who subsequently required phototherapy were below the 95th percentile and 9.1% were below the 75th percentile
Goncalves,A.;Costa,S.;Lopes,A.;Rocha,G.;Guedes,M. B.;Centeno,M. J.;Silva,J.;Silva,M. G.;Severo,M.;Guimaraes,H.	Prospective validation of a novel strategy for assessing risk of significant hyperbilirubinemia.	2011	463 well newborns ≥35 weeks and ≥2500g or ≥36 weeks and ≥2000g	• 396/463 with adequate data available • 44/396 infants developed significant hyperbilirubinemia • Risks for developing significant hyperbilirubinemia were 1.3% (95% CI) for very low risk group (n=230), 3.4% (95% CI) for the low risk group (n=86), 47.5% (95% CI) for the high risk group (n=80) • Predischarge bilirubin nomogram percentile was the strongest predictor of developing significant hyperbilirubinemia, however combining with gestational age increased the predictive ability • Study validated combining predischarge bilirubin level and gestational age as a method for significant hyperbilirubinemia risk assessment
Grohmann,K.;Roser,M.;Rolinski,B.;Kadow,I.;Muller,C.;Goerlach-Graw,A.;Nauck,M.;Kuster,H.	Bilirubin measurement for neonates: comparison of 9 frequently used methods.	2006	122 term and near-term infants (July 2003 - February 2004)	• A total of 124 samples were obtained from 122 term or near-term infants • Skin test devices had correlation coefficients between 0.961 and 0.966, and the nonchemical photometric devices between 0.980 and 0.994 • All skin test devices and 1 nonchemical photometric device underestimated bilirubin levels, particularly at high concentrations
Kaplan,M.;Shchors,I.;Algur,N.;Bromiker,R.;Schimmel,M. S.;Hammerman,C.	Visual screening versus transcutaneous bilirubinometry for	2008	346 well neonates ≥35 weeks gestation (November 2006)	• Prior to discharge, neonates were screened by visual assessment for jaundice and TcB predictive of subsequent hyperbilirubinemia • 83/346 (24%) had TSB based on visual assessment, 25% of these had PTB >75th percentile • 49/346 (14%) had TSB based on TcB value, 37%

	predischarge jaundice assessment.			of these had PTB >75th percentile • 25/346 neonates with PTB >75th percentile were identified by either method, 4 were missed by visual assessment alone, 7 were missed by TcB alone • Visual screening method required more PTB determinations to identify a comparable number of high intermediate risk neonates than TcB, however neonates in this range were missed by both methods
Karon,B. S.;Teske,A.;Santrach,P. J.;Cook,W. J.	Evaluation of the BiliChek noninvasive bilirubin analyzer for prediction of serum bilirubin and risk of hyperbilirubinemia.	2008	177 neonates in the well-baby nursery with TSB drawn (August 2006 - July 2007)	• TcB for predicting high (>95th percentile for age) TSB by diazo - sensitivity 100%, specificity 30% • 49/177 (27.7%) would be spared a blood draw for TSB by diazo if using TcB to predict risk zone • TcB for predicting high (>95th percentile for age) TSB by Viatros - sensitivity 100%, specificity 34% • 99/131 (29.8%) would be spared a blood draw for TSB by Viatros if using to predict risk zone • Relationship between TcB and TSB will likely be institution specific and will effect safety and efficacy of TcB screening
Keren,R.;Bhutani,V. K.;Luan,X.;Nihtianova,S.;Cnaan,A.;Schwartz,J. S.	Identifying newborns at risk of significant hyperbilirubinaemia: a comparison of two recommended approaches.	2005	996 full or near-term newborns in a hospital discharge follow-up program (1993-1997)	• Factors found to be associated with developing significant hyperbilirubinemia (>95th percentile) - gestational age <38wks and >40weeks, large for gestational age, higher pre-discharge TSB risk zone, higher birth weight, breast feeding, combined breast feeding and bottle feeding, maternal diabetes, vacuum extraction, prolonged rupture of members and oxytocin use • TSB risk zone was superior to a clinical risk factor score for predicting risk of developing significant neonatal hyperbilirubinemia, although both strategies could not maintain a sensitivity of >98% without low sensitivity
Keren,R.;Tremont,K.;Luan,X.;Cnaan,A.	Visual assessment of jaundice in term and late preterm infants.	2009	522 well term and late preterm newborns (September 2004 - October 2005)	• Jaundice measurement by the Kramer scale moderately correlated to bilirubin levels, did not accurately predict absolute bilirubin level or risk of developing significant hyperbilirubinemia • No significant difference in jaundice correlating to bilirubin values between black infants (i.e. more darkly pigmented) and non-black infants • Jaundice correlated poorly with bilirubin value in late preterm infants • Complete absence of jaundice was clinically informative of a low-risk for developing significant hyperbilirubinemia
Kuzniewicz,M. W.;Escobar,G. J.;Newman,T.	Impact of universal bilirubin	2009	358,086 infants born at gestational age	• From 1995-2007, proportion of infants undergoing TSB measurements increased and the proportion with maximal TSB levels of >25mg/dL

B.	screening on severe hyperbilirubinemia and phototherapy use.		≥35 weeks Before universal screening group = 319,904 After universal screening group = 38,182 (January 1995 - June 2007)	decreased • After implementation of universal screening there was a 62% reduction in incidence of maximum TSB levels above exchange guidelines (.45% to .17%), 74% reduction in maximum TSB levels between 25-29.9mg/dL (.12% to .031%), 56% increase in incidence of maximum TSB levels between 15-19.9mg/dL (9.59% to 14.94%) • Phototherapy use increased after 2001, dramatically increased from 2003-2005, increase in infants treated with phototherapy with TSB levels below the AAP recommended guidelines for treatment
Laeeq,A.;Yasin,M.;Chaudhry, A. R.	Transcutaneous bilirubinometry: clinical application.	1993	105 full term healthy jaundiced infants >37 weeks, not receiving phototherapy or EcT (November 1991 - March 1992)	• Sensitivity, specificity and positive predictive value were calculated for TcB at low (6mg/dL) high (15mg/dL) and mean serum bilirubin in this population (9.92mg/dL), at the mean TSB in the population, sensitivity was 90.5%, specificity 78% and positive predictive value of 64% • Results imply that TcB can strongly indicate whether infant has high serum bilirubin or not
Leite,M. G.;Granato Vde,A.;Facchini,F. P.;Marba,S. T.	Comparison of transcutaneous and plasma bilirubin measurement.	2007	200 newborns	• Gestational age, birth weight, race or phototherapy exposure did not significantly influence TcB measurements • TcB measurements taken at postnatal age <3 days were significantly higher than TSB • A TCB cutoff point of 14mg/dL was determined, below which TcB can be used safely to estimate TSB
Mah,M. P.;Clark,S. L.;Akhigbe,E.;Englebright,J.;Frye,D. K.;Meyers,J. A.;Perlin,J. B.;Rodriguez, M.;Shepard,A.	Reduction of severe hyperbilirubinemia after institution of predischarge bilirubin screening.	2010	1,028,817 infants born Before routine screening group = 129,345 infants After routine screening group = 899,472 infants (May 2004 - December 2008)	• Implementation of universal predischarge screening was associated with a statistically significant decline in the incidence of neonates with bilirubin levels between 25-29.9 mg/dL (extreme hyperbilirubinemia) and >30mg/dL (hazardous hyperbilirubinemia) and was also associated with significant increase in phototherapy use • Incidence per 100,000 births - 1400 (severe), 140 (extreme) and 10 (hazardous) • Incidence/100,000 births - 1400 (severe), 140 (extreme) and 10 (hazardous)
Maisels,M. J.;Deridder,J. M.;Kring,E. A.;Balasubramaniam,M.	Routine transcutaneous bilirubin measurements combined with clinical risk factors improve the prediction of subsequent	2009	11,456 infants discharged from well baby nursery Study group = 75 newborns readmitted with hyperbilirubinemia (TSB ≥ 17mg/dL) Control group =	• Three clinical factors were significant for predicting risk of hyperbilirubinemia - max predischarge TcB value/risk category, exclusive breast feeding and gestational age • Prediction of hyperbilirubinemia using these three variables was significantly better than each alone • Adding gestational age and breast feeding to the predischarge TcB value improves prediction of subsequent hyperbilirubinemia

	hyperbilirubinemia.		75 randomly selected (February 2005 - February 2007)	
Mishra,S.;Chawla,D.;Agarwal,R.;Deorari,A. K.;Paul,V. K.;Bhutani,V. K.	Transcutaneous bilirubinometry reduces the need for blood sampling in neonates with visible jaundice.	2009	617 infants ≥35 weeks gestation who developed clinical jaundice from 25-168 hours of age TcB group = 314 randomized infants Visual assessment group = 303 randomized infants (November 2006 - July 2007)	• Significant reduction of 34% in the need for blood sampling for TSB when screened with TcB vs. systematic visual assessment of jaundice • TcB reduced the need for blood sampling for TSB by 34% in the first week of life
Moyer,V. A.;Ahn,C.;Sneed,S.	Accuracy of clinical judgment in neonatal jaundice.	2000	122 healthy term newborns >2000g and >36 weeks gestation	• Agreement between experienced examiners regarding neonatal jaundice in otherwise healthy newborns is not much better than would be predicted by chance • Infants with no jaundice below the middle of the chest had a bilirubin values less than 12mg/dL, however jaundice below the middle of the chest did not reliably predict which infants would have a bilirubin level >12mg/dL • More difficult to predict elevated versus low bilirubin levels by appearance of jaundice
Newman,T. B.;Escobar,G. J.;Gonzales,V. M.;Armstrong,M. A.;Gardner,M. N.;Folck,B. F.	Frequency of neonatal bilirubin testing and hyperbilirubinemia in a large health maintenance organization	1999	51,387 infants born at ≥36 weeks gestation and ≥2000g (1995 - 1996)	• Maximum TSB levels >20mg/dL identified in approximately 2.0% of births, >25mg/dL in .15% (1 in 650), >30mg/dL in .01% (1/10,000) • Gestational age, race, sex and maternal age were predictors of hyperbilirubinemia • Among the 11 hospitals, frequency of elevated TSB levels was not associated with the frequency of TSB testing
Newman,T. B.;Liljestrand,P.;Escobar,G. J.	Combining clinical risk factors with serum bilirubin levels to predict hyperbilirubinemia in newborns.	2005	5706 newborns ≥2000g and ≥36 weeks gestation discharged at less than 48 hours of birth with a TSB level measured before 48 hours (1995 - 1998)	• 270/5706 developed TSB >20mg/dL post-discharge, of whom 94% were at the 75th percentile or higher based on the pre-discharge TSB level • Clinical risk factors such as gestational age significantly improved prediction of developing hyperbilirubinemia over the hour-specific TSB percentile, especially for newborns whose initial TSB level was in the 75th percentile or higher • Risk of developing hyperbilirubinemia was low among those whose initial TSB was below the 75th percentile, even in the presence of clinical

				risk factors
Petersen,J. R.;Okorodudu ,A. O.;Mohamma d,A. A.;Fernando,A .;Shattuck,K. E.	Association of transcutaneou s bilirubin testing in hospital with decreased readmission rate for hyperbilirubin emia.	2005	6,603 newborns Pre-TcB testing group (August 2002 - March 2003) TcB testing group (May 2003 - December 2003)	• 446 (6.8%) infants required phototherapy • The number of TSB measurements ordered and length of stay in hospital for newborns did not change for pre-TcB testing and post initiation of screening • Number of readmissions per 1000 newborns per month decreased from 4.5 to 1.8 after TcB screening was initiated
Prasarnphanic h,T.;Somlaw,S .	The value of routine bilirubin screening to detect significant hyperbilirubin emia in Thai healthy term newborns.	2007	1983 healthy term neonates (March 2004 - November 2004)	• 469 (23.7%) newborns had hyperbilirubinemia prediscarge (≥5mg/dL at 24 hours of age, ≥10 mg/dL at 25-48 hours, and ≥13mg/dL at 49-72 hours) • 12 newborns had severe hyperbilirubinemia (≥20mg/dL) but all were less than 25mg/dL • 279 (14.07%) of newborns with hyperbilirubinemia were detected by NBS • 448 treated with phototherapy (22.6%); 9 treated with ECT (0.5%) • Total cost calculated at $0.87 per one TSB, $6.22 for unexpected hyperbilirubinemia, and $247.87 per newborn with severe hyperbilirubinemia; authors determined it was cost effective to screen for hyperbilirubinemia
Riskin,A.;Aben d-Weinger,M.;B ader,D.	How accurate are neonatologist s in identifying clinical jaundice in newborns?.	2003	371 infants with a mean gestational age of 39.2± 2 weeks	• Compared clinician diagnosis of jaundice versus TSB values obtained at a mean of 67.3± 14.2 hours of life to determine which method detects elevated bilirubin levels • Study verified ability of experienced neonatologists to identify clinical jaundice at bilirubin levels below those required for intervention • Degree of jaundice was not determined by clinician impression, only by TSB values
Sanpavat,S.;N uchprayoon,I.	Transcutaneo us bilirubin in the pre-term infants.	2007	196 premature infants less than 38 weeks gestation with visually observed jaundice (September 2004 - August 2005)	• Correlation coefficient between TcB and TSB was significant at r=0.79 and p<0.0001 • TSB ranged from 4.5-17.6mg/dL and TcB ranged from 4.1-17.7mg/dL • Screening with TcB first would eliminate blood draws for TSB by 40% in the preterm population
Sarici,S. U.;Serdar,M. A.;Korkmaz,A. ;Erdem,G.;Ora n,O.;Tekinalp, G.;Yurdakok, M.;Yigit,S.	Incidence, course, and prediction of hyperbilirubin emia in near-term and term newborns	2004	365 newborns; 219 term (38+ weeks gestation) and 146 near-term (35-37 weeks gestation) (November 2001-May 2004)	• TSB measurements were made at 6 hours of age, and repeated daily for the next 4 days; last measurement was on the 7th day of life (150th hour) • 23 term (10.5%) and 37 near-term (25.3%) had significant hyperbilirubinemia • Near-term babies should not be treated as term newborns in the approach to managing

				hyperbilirubinemia
Schmidt,E. T.;Wheeler,C. A.;Jackson,G. L.;Engle,W. D.	Evaluation of transcutaneous bilirubinometry in preterm neonates.	2009	90 pre-term neonates ≤34 weeks gestational age (June 2007 - June 2008)	• TcB and TSB values were compared and interobserver precision for TcB measurements was assessed in preterm infants • TcB and TSB significantly correlates in preterm infants and ranged from 0.79 to 0.92 • Increased TcB use may decrease blood sampling in the preterm population • Sensitivity, specificity and NPV ranged from 0.67-1.0, 0.29-0.81, and 0.60-1.0, respectively
Seidman,D. S.;Ergaz,Z.;Paz,I.;Laor,A.;Revel-Vilk,S.;Stevenson,D. K.;Gale,R.	Predicting the risk of jaundice in full-term healthy newborns: a prospective population-based study.	1999	1177 healthy term newborns (October 1995 - December 1995)	• Attempted to predict severe hyperbilirubinemia development in full term healthy newborns based on multiple logistic regression model versus prediction by only first day of life (8-24 hours) TSB value • 60/1177 infants developed neonatal jaundice • Prediction by all model variables (included: day 1 TSB, change of TSB from day 1 to day 2, maternal age, education, blood type 0 and full breastfeeding): sensitivity=81.8%; specificity=82.9%; FP rate= 80.2%; FN rate= 1.1% • Prediction of development of severe hyperbilirubinemia by day 1 TSB levels alone: sensitivity=63.1%; specificity=94.2%; FP rate= 54.7%; FN rate= 2.8%
Stevenson,D. K.;Fanaroff,A. A.;Maisels,M. J.;Young,B. W.;Wong,R. J.;Vreman,H. J.;MacMahon, J. R.;Yeung,C. Y.;Seidman,D. S.;Gale,R.;Oh, W.;Bhutani,V. K.;Johnson,L. H.;Kaplan,M.; Hammerman, C.;Nakamura, H.	Prediction of hyperbilirubinemia in near-term and term infants.	2001	1370 infants ≥35 weeks gestation (February 1998 - February 1999)	• Measurement of TSB and end-tidal carbon monoxide corrected for ambient carbon monoxide (ETCOc) provides insight into processes that contribute to the condition; such as increased bilirubin production or decreased bilirubin production • Total of 120/1370 enrolled infants developed hyperbilirubinemia • Combination of TSB and ETCOc at 30±6 hours had 6.4% PPV and 99.0% NPV • ETCOc alone: TP=92; FN=28; FP=615; TN=635; sensitivity=76.7%; specificity=50.8%; PPV=13.0%; NPV=95.8%
Usatin,D.;Liljestrand,P.;Kuzniewicz,M. W.;Escobar,G. J.;Newman,T. B.	Effect of neonatal jaundice and phototherapy on the frequency of first-year outpatient visits	2010	136,959 infants Group 1 had a TSB of ≥12mg/dL = 128,417 infants Group 2 had a TSB of ≥17mg/dL - <23mg/dL = 6,777 infants Group 3 had same TSB as Group 2, but was	• Compared infants who never had bilirubin >12mg/dL to infants with bilirubin levels of 17-22.9 mg/dL and found that a higher bilirubin level group averaged only 0.36 extra first year visits when they were not treated with phototherapy, and an extra 0.73 visits when they were treated • Only a small increase in first year outpatient visits was seen, which is a mild or infrequent contribution to vulnerable child syndrome

			treated with Phototherapy = 1,765 infants (1995-2004)	
Varvarigou,A.;Fouzas,S.;Skyllogianni,E.;Mantagou,L.;Bougioukou,D.;Mantagos,S.	Transcutaneous bilirubin nomogram for prediction of significant neonatal hyperbilirubinemia.	2009	2039 healthy neonates ≥35 weeks gestation (September 2005 - December 2007)	• Developed predictive nomogram based on TcB from 12-72 hours of life • Proposed risk demarcations were calculated by using positive and negative likelihood ratios (LR) instead of TcB percentiles • When TSB nomogram was applied to the same population, 111 more measurements at 24 hours of life and 220 more measurements at 48 hours of life, respectively, were classified into the high and intermediate risk zones • At 24 hours of life, high-risk zone of TcB nomogram had 73.9% sensitivity and a positive LR of 12.1 in predicting significant hyperbilirubinemia; low-risk zone had 97.7% sensitivity and a negative LR of 0.02 • At 48 hours of life, high-risk zone of TcB nomogram had 90% sensitivity and a positive LR of 12.1 in predicting significant hyperbilirubinemia; low-risk zone had 98.8% sensitivity and a negative LR of 0.02

Table 26 – Abstracted literature pertaining to treatment

Author(s)	Title of Paper	Year	Study Population Description	Treatment Significant findings
Abrol,P.;Sankarasubramanian,R.	Effect of phototherapy on behaviour of jaundiced neonates.	1998	30 full term newborns with jaundice (15 study, 15 control) Study group = 15 newborns with bilirubin 12.1-15mg/dL who received phototherapy Control group = 15 newborns with bilirubin 8-12mg/dL who did not receive phototherapy Gestational age btw 37-40 weeks Birth Weight 10-90th percentile	• Initial and follow-up Brazelton's neonatal behavior assessments showed significant difference between study and control group in visual inanimate, visual animate and visual and auditory animate processes of the BNBAS, attributed to maternal separation factor
Abu-Ekteish,F.;Daoud,A.;Rimawi,H.;Kakish,K.;Abu-Heija,A.	Neonatal exchange transfusion: a Jordanian experience.	2000	336 neonates who underwent EcTs (January 1993 - December 1998)	• 0.46% of live births underwent EcT • Most common cause ABO incompatibility in term infants, G6PD deficiency in preterm infants • Complications in 51 cases (15%), most common anemia (18 cases), chronic bilirubin encephalopathy (2 cases) • Mortality in one case
Agrawal,V. K.;Shukla,R.;Misra,P. K.;Kapoor,R. K.;Malik,G. K.	Brainstem auditory evoked response in newborns with hyperbilirubinemia.	1998	Cases = 30 neonates with TSB >15mg/dL Controls = 25 controls with peak serum bilirubin <12 mg/dL (August 1995 - April 1996)	• BAEP detects subclinical bilirubin encephalopathy even before appearance of symptoms of chronic bilirubin encephalopathy • Group A (TSB 15-20): 1/9 with bilateral abnormal BAEP • Group B (TSB 21-25): 10/15 with bilateral abnormal BAEP • Group C (>25): 6/6 with bilateral abnormal BAEP • Screening by Denver Development Screening Test (Denver II) at 1 year of age revealed that neurological development was normal in all the neonates of Group A, 88.9% of Group B, and 66.7% of Group C • All the 3 infants who showed abnormal development on Denver II also had abnormal BAEP
Brewster,D. H.;Tucker,J. S.;Fleming,M.;Morris,C.;Stoc	Risk of skin cancer after neonatal phototherapy:	2010	Medical records from 77,518 neonates born (1976-1990)	• 5868/77,518 subjects received neonatal phototherapy • 2/5868 treated neonates developed melanoma,

kton,D. L.;Lloyd,D. J.;Bhattachary a,S.;Chalmers, J. W.	retrospective cohort study.			compared to 16/71,650 (median follow-up period of 24 years) • No significant evidence of an excess risk of skin cancer (melanoma or non-melanoma) following neonatal phototherapy
Chen,W. X.;Wong,V.	Visual evoked potentials in neonatal hyperbilirubin emia.	2006	24 term neonates ≥37 weeks gestation with hyperbilirubinemi a Moderate hyperbilirubinemi a (serum bilirubin =225-341 umol/L) group = 16 Severe hyperbilirubinemi a (serum bilirubin≥342 umol/L) group = 8 (1995-1996)	• No significant differences in either the latencies or amplitude of visual evoked potential between the moderate and severe hyperbilirubinemia groups, VEP of all infants returned to normal after 12 months of age • No significant differences in neurodevelopmental outcome up to 3 years between the moderate and severe hyperbilirubinemia groups • All subjects treated with phototherapy, did not find any effects of phototherapy on VEP • One term infant in severe hyperbilirubinemia group with ABO incompatibility had mild hypotonia and motor delay at 10 months, normal at 3 years
Csoma,Z.;Toth - Molnar,E.;Bal ogh,K.;Polyan ka,H.;Orvos,H. ;Ocsai,H.;Kem eny,L.;Szell,M. ;Olah,J.	Neonatal blue light phototherapy and melanocytic nevi: a twin study	2011	119 total subjects 58 sets of twins and 1 set of triplets; 3 to 30 years of age One twin member received neonatal phototherapy (January 2008-April 2008)	• Blue light phototherapy associated with higher prevalence of both cutaneous and uveal melanocytic lesions (P=0.005) • Neonatal blue light phototherapy may be a risk factor for melanocytic nevus development
de Carvalho,M.; Mochdece,C. C.;Sa,C. A.;Moreira,M. E.	High-intensity phototherapy for the treatment of severe nonhaemolyti c neonatal hyperbilirubin emia	2011	116 total newborn infants (mean age 6.8±2.9 days; range 1-16 days old) with TSB ≥ 20 mg/dL (mean 22.4± 2.4 mg/dL; range 20-29 mg/dL) (January 2000-December 2008)	• No patients had bilirubin-induced neurological dysfunction upon admission • Decreases in TSB after 2, 4, 6, 12, 18 and 24 hour of phototherapy were 9.4%, 16%, 23%, 40%, 44% and 50%, respectively • After 24 hours of treatment with phototherapy, 64% of patients already out of phototherapy • No infant was treated with exchange transfusion • BAER was performed in 100% of the patients, and in three of them, this examination was altered. When repeated 3 months later, all BAER examinations were normal • Neurological examination was normal in all patients • Phototherapy is effective in decreasing levels of TSB in newborn infants and decreases the need for exchange transfusion
Deorari,A. K.;Singh,M.;A huja,G.	One year outcome of babies with	1994	Study group: 18 term neonates who developed	• 7/18 neonates with hyperbilirubinemia had abnormal BAEP • Abnormalities in BAEP reversed to normal in all 7

K.;Bisht,M. S.;Verma,A.;P aul,V. K.;Tandon,D. A.	severe neonatal hyperbilirubin emia and reversible abnormality in brainstem auditory evoked responses.		hyperbilirubinemi a (>15mg/dL) Control group: 20 term neonates without clinical jaundice (April 1988 - May 1989)	neonates after exchange blood transfusion indicating transient nature of bilirubin toxicity to the brain • All neonates in the study and control group had normal hearing, development quotient and were free of neurological sequelae on follow-up for one year
Duman,N.;Ozk an,H.;Serbetci oglu,B.;Ogun, B.;Kumral,A.;A vci,M.	Long-term follow-up of otherwise healthy term infants with marked hyperbilirubin aemia: should the limits of exchange transfusion be changed in Turkey?.	2004	Study group = 30 children, aged 2–6 y with indirect hyperbilirubinemi a (20–24mg/dL) during the newborn period and treated without EcT because phototherapy was successful Control group = 30 children of the same age group without clinical jaundice in the newborn period (January 1995 - December 1998)	• There was no difference between the groups with regard to mean BAEP latencies and developmental scores • None of the infants had hearing loss, developmental delay or abnormal neurological findings
Funato,M.;Ter aoka,S.;Tamai, H.;Shimida,S.	Follow-up study of auditory brainstem responses in hyperbilirubin emic newborns treated with exchange transfusion.	1996	10 newborns with hyperbilirubinemi a (≥20mg/dL) undergoing EcT with BAEP values available	• Significant reduction of BAEP peripheral conduction time after EcT • Results suggest the central bilirubin damage occurred in association with the peripheral neurotoxicity before EcT and the recovery was delayed in spite of the EcT • Hyperbilirubinemia may affect both the peripheral and central auditory pathways and the more central the damage is, the more the recovery might be delayed • 2/9 infants followed up with at 3 months of age had abnormal BAEP results
Guaran,R. L.;Drew,J. H.;Watkins,A. M.	Jaundice: clinical practice in 88,000 liveborn infants.	1992	88,137 live-borns (1971-1989)	• 10,944/88,137 (12.4%) had hyperbilirubinemia (>154umol/L), incidence of documented cases increased during study period • 6,799 (62.1%) received no treatment, 4,126 (37.7%) received phototherapy, 248 (2.3%) received EcT (phototherapy and EcT not mutually exclusive) • Jaundice due to prematurity (no other cause identified and infants born before 37th week), most frequently identified cause of jaundice in

				this population - 2.0% had EcT, 75.3% had phototherapy, no death related to jaundice or treatment • Second most frequent cause was due to ABO erythroblastosis, 86% received phototherapy, 9.6% received phototherapy and EcT • Of the 248 infants who received EcT, 6 died - 2 of necrotizing enterocolitis, 1 of pulmonary hemorrhage and 3 possible attributable to the EcT. Nonfatal complications included - apnea, transient hypocalcemia and hypoglycemia, asymptomatic bacteraemia, perforated bowel, nonfatal necrotizing entercolitis, inspissated bile syndrome and disseminated intravascular coagulopathy • 4,126 infants received phototherapy, no deaths attributable to phototherapy were identified, infrequent complications included pyrexia and diarrhea
Hansen,T. W.;Nietsch,L.; Norman,E.;Bjerre,J. V.;Hascoet,J. M.;Mreihil,K.; Ebbesen,F.	Reversibility of acute intermediate phase bilirubin encephalopathy.	2009	6 infants who presented with extreme jaundice and symptoms of acute intermediate to advanced phase bilirubin encephalopathy	• 6 infants who exhibited signs of intermediate to advanced ABE • Follow-up has shown normal neurological development
Jackson,J. C.	Adverse events associated with exchange transfusion in healthy and ill newborns.	1997	15,000 NICU admissions 106 = patients who underwent EcT (81 healthy other than jaundice, 25 ill) (1980-1995)	• Severe complications (defined as death or permanent serious sequelae) occurred in 12% of the ill infants (3/25) and 1.2% of healthy infants (1/81) • In the healthy (jaundice only) infants, mortality rate well below 1%, rate of permanent serious sequelae approximately 1% • In the ill infants, procedure-related complications leading to death occurred at a rate of 8% and permanent serious sequelae 12% • Serious morbidities of EcT identified in the group of 106 infants included symptomatic hypocalcemia, bleeding from thrombocytopenia, catheter-related complications, and apnea and bradycardia with cyanosis requiring resuscitation
Kuzniewicz,M. W.;Escobar,G. J.;Newman,T. B.	Impact of universal bilirubin screening on severe hyperbilirubinemia and phototherapy use.	2009	358,086 infants born at gestational age ≥35 weeks Before universal screening group = 319,904 After universal screening group =	• From 1995-2007, proportion of infants undergoing TSB measurements increased and the proportion with maximal TSB levels of >25mg/dL decreased • After implementation of universal screening there was a 62% reduction in incidence of maximum TSB levels above exchange guidelines (.45% to .17%), 74% reduction in maximum TSB levels between 25-29.9mg/dL (.12% to .031%),

			38,182 (January 1995 - June 2007)	56% increase in incidence of maximum TSB levels between 15-19.9mg/dL (9.59% to 14.94%) • Phototherapy use increased after 2001, dramatically increased from 2003-2005, increase in infants treated with phototherapy with TSB levels below the AAP recommended guidelines for treatment
Lazar,L.;Litwin,A.;Merlob,P.	Phototherapy for neonatal nonhemolytic hyperbilirubinemia. Analysis of rebound and indications for discontinuing therapy.	1993	58 infants requiring Phototherapy for nonhemolytic hyperbilirubinemia (28 full term, 30 preterm) (1988-1989)	• Phototherapy was arbitrarily discontinued at 13mg/dL in full term and 10.7mg/dL in preterm infants, discontinuation at these levels appear harmless • Bilirubin rebound occurred within 24 hours following termination of therapy with spontaneous decline, no infant in this study required reinstitution of therapy • The researchers conclude infants can be sent home earlier than 24 hours after discontinuation of therapy
Lee,C. Y.;Chen,S. J.;Tang,R. B.	Reevaluation of recent criteria for blood exchange transfusion in term infants with hyperbilirubinemia.	2002	Hyperbilirubinemia group = 20 term neonates with peak TSB ≥18.5mg/dL (within 5 days of age) or ≥20mg/dL (older than 5 days) (17 Phototherapy only, 3 Phototherapy + EcT) Control group = 14 healthy neonates (January 1998 - December 2000)	• BAEP wave V latencies were not significantly different between the control group and phototherapy only group • 13 infants in the phototherapy only group demonstrated normal language development at follow-up (ranging from 3 months to 5 year follow-up), 4 infants lost to follow-up • 16/17 (94%) had a peak serum total bilirubin concentration qualifying them for EcT by previous standards and received phototherapy only, BAEP results normal, 12/12 with language development follow-up were normal • For the 3 infants receiving phototherapy and EcT, 2 infants developed chronic bilirubin encephalopathy • Factors other than peak serum total bilirubin concentration such as anemia, duration of hyperbilirubinemia, and decline rate of hyperbilirubinemia in response to phototherapy should be taken into consideration when treating hyperbilirubinemia
Newman,T. B.;Kuzniewicz,M. W.;Liljestrand,P.;Wi,S.;McCulloch,C.;Escobar,G. J.	Numbers needed to treat with phototherapy according to American Academy of Pediatrics guidelines.	2009	22,547 live-borns ≥35 weeks and ≥2000g with a TSB level within 3mg/dL of AAP guidelines for treatment (January 1995 - December 2004)	• 6960/22,547 (30.9%) had a hospital admission for phototherapy • For those who had phototherapy, 75.4% began within 8 hours of the qualifying TSB level (within 3mg/dL of the AAP recommended phototherapy threshold) • 354/22,547 (1.6%) exceeded the AAP threshold for EcT, 53% within 48 hours of the qualifying TSB level, 3 infants received EcT • Phototherapy appeared less effective in infants with a positive direct antiglobulin test result (DAT) • The study calculated approximately 84% efficacy

				for hospital phototherapy in newborns who were not DAT positive • For infants who were not DAT positive, with qualifying TSB levels 0 to .9mg/dL above the AAP threshold for phototherapy, the mean time of the qualifying TSB level was 63 hours • Estimated number needed to treat from this study was 222 for boys and 339 for girls to prevent one infant from developing a bilirubin level at which the AAP recommends EcT
Newman,T. B.;Liljestrand, P.;Jeremy,R. J.;Ferriero,D. M.;Wu,Y. W.;Hudes,E. S.;Escobar,G. J.;Jaundice and Infant Feeding Study,Team	Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more.	2006	Birth cohort 106,627 term and near-term infants Cases = 140 infants with TSB ≥25mg/dL Control group = 419 randomly selected infants (1995 - 1998)	• Follow-up data available at ≥2 years of age in 89% of the control group and 94% of the hyperbilirubinemia group • No significant differences between cases and controls in intelligence testing, neurological testing or motor performance • 90/140 with hyperbilirubinemia had a maximum TSB between 25-26.9mg/dL, 40 had a max TSB of 27-29.9mg/dL and 10 had a TSB >30mg/dL • 131/140 received phototherapy alone, 5 received phototherapy and EcT, 4 had only observation/follow-up • Neither the degree nor the duration of hyperbilirubinemia had a significant effect on outcomes • Results suggest the level at which the benefits of EcT exceed the risks will be more than 25mg/dL • Results suggest even elevated serum bilirubin levels >25mg/dL in the range observed in this study are not likely to result in long-term adverse effects on neurodevelopment if treated promptly
Patra,K.;Storfer-Isser,A.;Siner, B.;Moore,J.;Hack,M.	Adverse events associated with neonatal exchange transfusion in the 1990s.	2004	55 neonates underwent 66 ECTs (January 1992 - July 2002)	• 34/55 (62%) of neonates had evidence of morbidity prior to ECT (primarily respiratory distress and sepsis) • Overall, 74% of ECTs associated with an adverse event; most common, thrombocytopenia (44%), hypocalcemia (29%) and metabolic acidosis (24%) • Two serious adverse events occurred, 1 death of an infant and seizures in 1 infant • No cases of sepsis, necrotizing entercolitis or cardiac arrest • Adverse events more common in preterm infants, or those with comorbidities • Adverse events due to ECT are high, although majority are asymptomatic and treatable
Sanpavat,S.	Exchange transfusion and its morbidity in ten-year period at King Chulalongkorn	2005	165 neonates underwent 183 episodes of EcT (1994 - 2003)	• Overall morbidity rate was 15.3%, of which, 67% were infection associated conditions • No mortality or chronic bilirubin encephalopathy was present in study • ECT remains an invasive procedure and should be considered only when benefits outweigh the

	Hospital.			complications associated with the procedure
Schedle,A.;Fricker,H. S.	Impact of hyperbilirubinaemia and transient mother-child separation in the neonatal period on mother-child attachment in the 1st year of life.	1990	107 healthy infants between 38-42 weeks gestation and their mothers Hyperbilirubinemia and phototherapy group = 29 infants with mean peak TSB of 271uMol/l Mild hyperbilirubinemia and no phototherapy group= 40 infants with mean peak TSB of 209uMol/l Control group = 38 infants with no apparent jaundice (September 1986 – August 1987)	• Hyperbilirubinemia, with and without phototherapy, does not affect the quality of mother-child attachment • Frequency of minor medical problems and illnesses in the first year of life was not increased in the children with hyperbilirubinemia • Developmental screening (Denver test) showed no impairments in the children with hyperbilirubinemia • Hyperbilirubinemia and phototherapy do not seem to negatively affect the quality of attachment • Analysis of additional aspects showed that maternal coping and her perception of the child appear to be more important antecedents of the quality of attachment after the 1st year
Scheidt,P. C.;Bryla,D. A.;Nelson,K. B.;Hirtz,D. G.;Hoffman,H. J.	Phototherapy for neonatal hyperbilirubinemia: six-year follow-up of the National Institute of Child Health and Human Development clinical trial.	1990	1339 newborns with hyperbilirubinemia (>10 mg/dL within first 96 hours after birth) randomized to receive ECT (control) or phototherapy treatment (1974-1976)	• 1205 subjects survived to 1 year of age (10% died), 83% followed up and had neurological and developmental examinations • 62% followed-up at 6 years of age and had neurological and developmental examinations (4 patients died between 1-6 years) • All follow-up rates similar for both ECT and phototherapy groups • The two groups did not differ at either time point in mortality or diagnosed medical condition • Two groups overall had similar rates of cerebral palsy (5.8% versus 5.9%), other motor abnormalities (11.1% versus 11.4%) and sensorineural hearing loss (1.8% versus 1.9%); intelligence not significantly different • Phototherapy effectively controlled neonatal hyperbilirubinemia without evidence of adverse outcomes at 6 years of age and is at least as effective as management with ECT alone
Scheidt,P. C.;Graubard,B. I.;Nelson,K. B.;Hirtz,D. G.;Hoffman,H. J.;Gartner,L. M.;Bryla,D. A.	Intelligence at six years in relation to neonatal bilirubin levels: follow-up of the	1991	1339 newborns with hyperbilirubinemia (>10 mg/dL within first 96 hours after birth) randomized to	• Examined neurological and developmental outcomes at 6 year follow-up, post ECT for hyperbilirubinemia • No association was evident between maximum bilirubin level and IQ • IQ not associated with mean bilirubin level, time and duration exposure to bilirubin or measures

	National Institute of Child Health and Human Development Clinical Trial of Phototherapy.		receive ECT or phototherapy treatment Study group = 224 neonates treated with ECT only and weighed less than 2000g at birth (1974-1976)	of bilirubin-albumin binding • No evidence of bilirubin toxicity to central nervous system at levels permitted in the clinical trial (bilirubin levels for performing ECT ranged from 10-20mg/dL
Seidman,D. S.;Paz,I.;Armon,Y.;Ergaz,Z.;Stevenson,D. K.;Gale,R.	Effect of publication of the "Practice Parameter for the management of hyperbilirubinemia" on treatment of neonatal jaundice.	2001	16,140 infants born between two 15-month study periods Pre-AAP guidelines period = 6988 infants (June 1992 - September 1993) Post-AAP guidelines period = 9152 infants (June 1995 - September 1996)	• Assessed rates for phototherapy and ECT pre and post implementation of AAP practice parameter guidelines for hyperbilirubinemia • Rate of phototherapy decreased in second study period from 7.9% (514/6499) to 2.9% (251/8650) ($p<0.0001$) for term infants and 20.9% (102/489) to 9.4% (47/502) ($p<0.0001$) in near-term infants • ECT was significantly higher in first period of study than second period: 0.2% (15/6499) versus 0.03% (3/8650) ($p<0.001$)
Seidman,D. S.;Paz,I.;Stevenson,D. K.;Laor,A.;Danon,Y. L.;Gale,R.	Effect of phototherapy for neonatal jaundice on cognitive performance.	1994	1948 total records matched to military draft medical records 17 years later (November 1970 - December 1971)	• Compared IQ test scores at 17 years of age to subjects born 4 months before and 10 months after the introduction of phototherapy • Intelligence quotient score at 17 years of for 84 subjects with severe hyperbilirubinemia was 108± 2 for those treated with phototherapy and 107± 2 for matched controls • Phototherapy found to have no beneficial or adverse independent effect on IQ scores or intellectual ability after adjustment for confounding factors in late adolescence
Siegfried,E.C.; Stone,M.S.; Madison,K.C.	Ultraviolet light burn: a cutaneous complication of visible light phototherapy of neonatal jaundice.	1992	2 premature infants who had phototherapy and experienced ultraviolet light burns	• Plexiglass shields should always be used with phototherapy units to prevent ultraviolet light burn • Premature infants may be more susceptible to UVA-induced erythema
Singhal,P. K.;Singh,M.;Paul,V. K.;Deorari,A. K.;Ghorpade, M. G.	Spectrum of neonatal hyperbilirubinemia: an analysis of 454 cases.	1992	7680 live births clinically suspected to have hyperbilirubinemia (January 1986-December 1989)	• 454/7680 (5.9%) developed hyperbilirubinemia (>12mg/dL) • Group 1 (Mild) included non-hemolytic causes: idiopathic (34.4%), bacterial infections (5.7%), intrauterine infections and others (2.9%) • Group 2 (Moderate) comprised of hemolytic and non-hemolytic causes: prematurity (16.7%), administration of oxytocin (9.9%), and bruising/cephalhematoma (2.9%)

				• Group 3 (Severe) included only hemolytic causes: blood group incompatibility between mother and baby (22.4%), and G6PD deficiency (5.1%)
Steiner,L. A.;Bizzarro,M. J.;Ehrenkranz, R. A.;Gallagher,P . G.	A decline in the frequency of neonatal exchange transfusions and its effect on exchange-related morbidity and mortality.	2007	107 infants undergoing 141 total ECTs (1986-2006)	• Decline in frequency of EcTs per 1000 newborns in special care unit over 21 year study period (r2=0.30; p=0.010) • From 1986-2006, a lower proportion of patients experienced an adverse event related to EcT • No deaths were related to EcT during the study period • ECT-related complications were defined as follows: severe thrombocytopenia (38%), hypocalcemia (38%), seizures (2%), bradycardia (4%), apnea (1%), catheter malfunction (3%), hypercalcemia (1%), and necrotizing entercolitis (1%)
Usatin,D.;Lilje strand,P.;Kuzn iewicz,M. W.;Escobar,G. J.;Newman,T. B.	Effect of neonatal jaundice and phototherapy on the frequency of first-year outpatient visits	2010	136,959 infants Group 1 had a TSB of ≥12mg/dL = 128,417 infants Group 2 had a TSB of ≥17mg/dL - <23mg/dL = 6,777 infants Group 3 had same TSB as Group 2, but was treated with phototherapy = 1,765 infants (1995-2004)	• Compared infants who never had bilirubin >12mg/dL to infants with bilirubin levels of 17-22.9 mg/dL and found that a higher bilirubin level group averaged only 0.36 extra first year visits when they were not treated with phototherapy, and an extra 0.73 visits when they were treated • Only a small increase in first year outpatient visits was seen, which is a mild or infrequent contribution to vulnerable child syndrome
Watchko,J. F.;Claassen,D.	Kernicterus in premature infants: current prevalence and relationship to NICHD Phototherapy Study exchange criteria.	1994	81 infants autopsied who were <34 weeks gestation and lived at least 48 hours (January 1984 - June 1993)	• Chronic bilirubin encephalopathy observed in 3/81 autopsied infants (prevalence of 4%) • Bilirubin levels in babies with chronic bilirubin encephalopathy were 11.3 mg/dL, 18.5mg/dL and 26mg/dL • 1 infant without chronic bilirubin encephalopathy died during ECT, presumably due to the procedure • Of the 78 other infants, bilirubin levels ranged from 3.6-22.5 mg/dL
Wolf,M. J.;Wolf,B.;Beu nen,G.;Casaer ,P.	Neurodevelop mental outcome at 1 year in Zimbabwean neonates with extreme hyperbilirubin	1999	50 infants admitted with a TSB > 23.4mg/dL 26/50 were preterm (<37 weeks gestation) (July 1991 - June 1992)	• Incidence of extreme jaundice (TSB>23.4mg/dL) is 4.8/1000 live births • Infants requiring phototherapy found to be 21.5/1000 live births in the special baby care unit • 2/50 died due to unknown causes, 5 lost to follow-up • 7/50 received EcTs • 4/6 surviving infants with EcT scored abnormal

	aemia.			on Bayley Scales of Infant Development (BSID) at 1 year of age • Overall, 11/43 surviving infants scored abnormal or suspect on the BSID at 1 year of age (2 with severe motor delay and 4 with moderate motor delay) • 5/43 developed choreo-athetosis type of cerebral palsy • Infants with highest bilirubin levels scored lower on BSID at one year of age
Wong,V.;Chen ,W. X.;Wong,K. Y.	Short- and long-term outcome of severe neonatal nonhemolytic hyperbilirubinemia.	2006	99 infants Moderate hyperbilirubinemia (mean max=18.9mg/dL) group = 30 infants Severe hyperbilirubinemia (mean max=21.7mg/dL) group = 63 infants Super hyperbilirubinemia (mean max=26.9mg/dL) group = 6 infants (1995 - 2000)	• 9/99 had abnormal BAEP when initially assessed • All 99 treated with phototherapy, 3 also with EcT • Physical, neurological, visual and auditory evaluations occurred every 3-6 months from birth until the age of 3 • Only 2/99 (both from severe group) had abnormal BAEP at 2 years of age; all others normal • 2/99 (one from severe, one from moderate group) had mild motor delay at 3 months of age, and both returned to normal before 1 year of age • No abnormal effects of phototherapy were found • No relationship between abnormal BAEP and abnormal neurodevelopmental status was found
Zainab,K.;Adlina,S.	Effectiveness of home versus hospital phototherapy for term infants with uncomplicated hyperbilirubinemia: a pilot study in Pahang, Malaysia.	2004	36 infants with hyperbilirubinemia (mean bilirubin level was 237.3 umol/L at start of phototherapy) Home phototherapy group = 18 infants Hospital phototherapy group = 18 infants (March 2002 - Aug 2002)	• Phototherapy complications reported included skin rash (n=3) and diarrhea (n=5); 28 reported no complications • Mean duration of treatment was significantly less for the home treatment group: hospital= 1.72 ± 0.73 days vs. home= 1.17 ± 0.37 days • Home phototherapy is feasible and a safe alternative way to treat when an infant has uncomplicated hyperbilirubinemia

Table 27 – Studies identified as reporting costs related to screening or treatment

Author(s)	Title of Paper	Year	Study Type	Economic evaluation Annotated Costs
Burgos,A. E.;Schmitt,S. K.;Stevenson, D. K.;Phibbs,C. S.	Readmission for neonatal jaundice in California, 1991-2000: trends and implications	2008	Cost analysis	• 10 years of data on newborn hospitalizations from CA using hospital discharge records • Charges converted to costs using charge-to-cost ratio • Mean cost of jaundice readmission $2764 in 2001$ • Sample: healthy infants ≥34 wks gestation and ≤42 wks • Mean LOS = 2.5 days • Mean cost per day = $991
Newman,T. B.;Easterling, M. J.;Goldman,E. S.;Stevenson, D. K.	Laboratory evaluation of jaundice in newborns. Frequency, cost, and yield	1990	Cost analysis	• Reports only charge and cost for recommended tests, bilirubin + blood tests ($125 charge, $80 reimbursement) • Data are very dated (1980-1982) and from only one hospital, UCSF • Unlikely that tests have remained the same since 1982
Petersen,J. R.;Okorodudu ,A. O.;Mohamma d,A. A.;Fernando,A .;Shattuck,K. E.	Association of transcutaneou s bilirubin testing in hospital with decreased readmission rate for hyperbilirubin emia.	2005	6,603 newborns Pre-TcB testing group (August 2002 - March 2003) TcB testing group (May 2003 - December 2003)	• Charges for newborn hospitalizations from one hospital in TX • Reported as mean charges for hyperbilirubinemia-related readmission • Study was not designed to measure healthcare costs (from paper); no description in methods • Only charges reported, no adjustment for charge-to-cost • Conclusion is that there is an increase in charges associated with TcB testing and phototherapy despite lower readmission rates for hyperbilirubinemia
Prasarnphanic h,T.;Somlaw,S .	The value of routine bilirubin screening to detect significant hyperbilirubin emia in Thai healthy term newborns.	2007	1983 healthy term neonates (March 2004 - November 2004)	• Cost of detecting one case of hyperbilirubinemia: 6.22 US$ • Cost of detecting one case of severe hyperbilirubinemia: 247.87 US$ • Due to differences in health care patterns and unit costs, it is not appropriate to apply Thai costs to US setting • More recent data from US setting available