

Universal Predischarge Screening for Neonatal Hyperbilirubinemia

Report from Evidence Review
*Secretary's Advisory Committee on Heritable
Disorders in Newborns and Children*
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Recent Progress and Activities

Critical Congenital Cyanotic Heart Disease

- Final review presented September 2010
- Paper in development

Neonatal Hyperbilirubinemia

- Preliminary (literature only) evidence review presented today

Publications

- Kemper AR, Knapp AA, Green NS, Comeau AM, Metterville DR, Perrin JM. Weighing the evidence for newborn screening for early-infantile Krabbe disease. *Genet Med.* 2010 Sep;12(9):539-43.
- Kemper AR, Knapp AA, Metterville DR, Green NS, Comeau AM, Perrin JM. Weighing the evidence for newborn screening for Hemoglobin H disease. *Journal of Pediatrics.* (in press; epub ahead of print)

Review of the Evidence Process (Calonge, Green, Kemper, Evidence team)

Workgroup Team Members

Key authors:

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- Anne Marie Comeau, PhD, New England Newborn Screening Program/UMass Medical School
- Nancy S. Green, MD, Columbia University
- Alex R. Kemper, MD, MPH, MS, Duke University
- Denise Queally, JD, Consumer, PKU Family Coalition

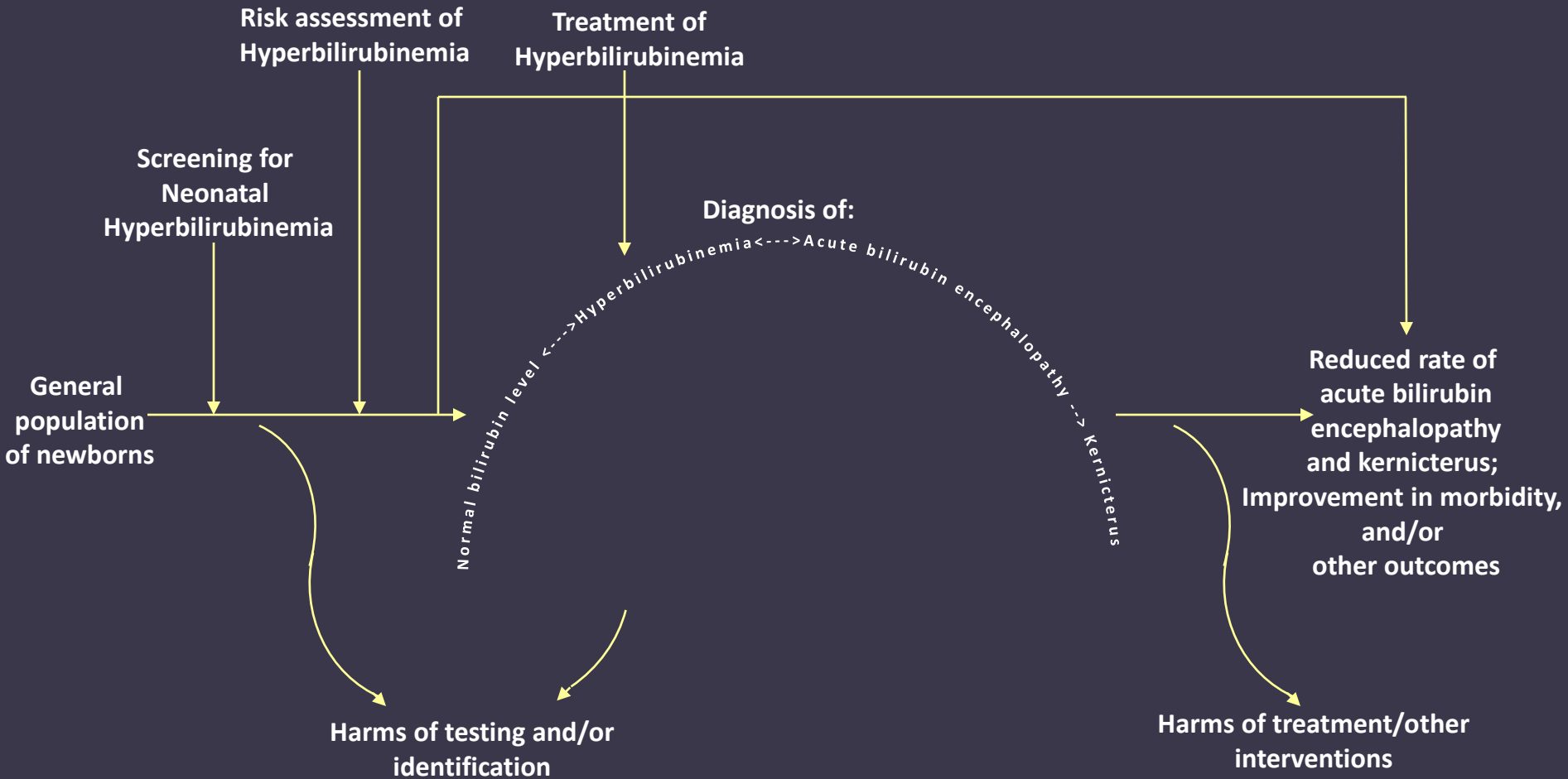
Materials Included in Preliminary Review

- Detailed literature review methods
- Summary of evidence from literature review
- Tables highlighting key data from abstracted articles
- Bibliography

Neonatal Hyperbilirubinemia Overview

- Elevated total bilirubin level in a newborn
- Multiple etiologies
- Detectable risk factor for acute bilirubin encephalopathy (ABE) and kernicterus
- Primary concern reflects potential for neurotoxic effects of severe hyperbilirubinemia

Conceptual Framework



Rationale for Review

1. Hyperbilirubinemia can lead to kernicterus, with permanent damage to the central nervous system (CNS) and death
2. Early identification of risk factors for kernicterus, including elevated serum bilirubin, may allow interventions to lower risk
3. TcB or TSB measurement widely available
4. Treatment is widely available to prevent severe neonatal hyperbilirubinemia (phototherapy, exchange transfusion (EcT))

Case Definition

- Technical Expert Panel helped to refine case definition

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Case Definition

Neonatal Hyperbilirubinemia

- Clinically significant hyperbilirubinemia in the neonatal period as indicated by TSB levels >95th percentile for age in hours, which may require follow-up and treatment.

Acute Bilirubin Encephalopathy (ABE)

- Variable acute manifestations of bilirubin toxicity present in the first weeks of life. Symptoms include neurological manifestations, somnolence, hypotonia, loss of the Moro reflex, followed by an irreversible stage characterized by hypertonia of the extensor muscle groups. Fever and/or a high-pitched cry may be present.

Chronic Bilirubin Encephalopathy (Kernicterus)

- Chronic and permanent brain damage caused by bilirubin toxicity and characterized by four clinical manifestations 1) movement disorder (athetosis, dystonia, spasticity, hypotonia), 2) auditory dysfunction, 3) oculomotor impairment and, 4) dental enamel hypoplasia.

Hyperbilirubinemia has been associated with other longer term neurologic dysfunction, and we will also address these associations in this review.

Methods for Evidence Review

- Preliminary report (today)
 - Systematic literature review to summarize evidence from published studies on the natural history, screening, treatment and economics of screening for neonatal hyperbilirubinemia
- Final report
 - Updated literature review
 - Consultation with multiple neonatal hyperbilirubinemia investigators and consumers, as well as assessment of unpublished data

Methods for Literature Search

- Searched MEDLINE for all relevant screening studies published over a 20 year period
- Completed searches combining the National Library of Medicine Medical Subject Heading (MeSH) “hyperbilirubinemia”, “bilirubin encephalopathy”, and “kernicterus”
- Reviewed references from nomination form and bibliography of review papers
- Three investigators (JPC, AAK, DRM) reviewed all abstracts and independently abstracted a subset of the articles (20% overlap)

Systematic Literature Review Findings

- January 1990 – September 2010
 - Medline, OVID In-Process and Other Non-Indexed Citations
 - English language only
 - Human studies only
 - In cases of duplicate publications, selected the most recent or complete versions
- 2,742 abstracts selected for preliminary review
- 172 articles selected for in-depth review
- 99 articles met all inclusion criteria for abstraction

Papers Meeting Review Criteria

Study Design

Number of papers

Experimental intervention	4
Cohort study	17
Case-control study	8
Case series	57
Sample size ≤ 10	6
Sample size 11 to 50	5
Sample size 51 to 100	4
Sample size 101 to 1000	19
Sample size ≥ 1001	23
Economic Evaluation	2
Cross-sectional study	11
Total studies	99

Key Questions - Condition

- Is severe neonatal hyperbilirubinemia well-defined? When does it appear clinically? What are the known risk factors, if any?
- What evidence is available regarding the relationship between severe neonatal hyperbilirubinemia and kernicterus?
- How well characterized is kernicterus? When does it appear clinically?

Hyperbilirubinemia Incidence

- Neonatal jaundice 10-15%
- Bilirubin > 25mg/dl .14%
- Bilirubin > 29mg/dl .01%
- Kernicterus .001-.002%
(1-2/100,000)

Changes in Incidence

- 1991-2000, California databases
 - Readmission rate for jaundice increased through 1998
 - Factors associated with increased likelihood of readmission included GA 34-39 weeks, birth weight <2500 g, male, Medicaid or private insurance and Asian race
- 1988-2005, USA databases
 - Rates of newborn jaundice diagnoses fell from 1988–1993 and increased from 1997-2005
 - Number of newborns with a diagnosis of kernicterus declined throughout this period, from ~5.1/100,000 in 1988 to ~1.5/100,000 from 1994-2005
- 1979-2002, Pilot USA Kernicterus Registry
 - Increase in voluntarily reported cases rose from 2 between 1979-1984 and peaking at 21 between 1993-1994 and again between 2001-2002

Risk Factors

Hyperbilirubinemia

- Prematurity
- Asian race
- Isoimmunization
- Hemolytic disease
- Low birth weight

Kernicterus

- Prematurity
- Asian race
- Early discharge
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Spectrum of Severity

- Studies describe spectrum of acute and chronic manifestations of neonatal hyperbilirubinemia
- **Differences in study design limit the ability to compare data**
- Summarized in Table 5 of evidence review

Acute Manifestations

- Acute manifestations
 - Abnormal VEP, BAEP and MRI findings
 - Symptoms of central nervous system involvement
 - Abnormal behavioral assessments
- Some studies show association between the severity of these symptoms and TSB level
- Some studies indicate symptoms are transient and resolve

Chronic Manifestations

- Neurodevelopmental issues
 - 7 studies show significantly increased risk of abnormal neurodevelopment (delayed gross motor, fine motor, and adaptive and social skills)
 - 6 studies suggest resolved or minor effects of hyperbilirubinemia on neurodevelopmental outcomes
- Auditory issues
 - 3 studies indicate a direct relationship between elevated TSB levels (>20 mg/dL) and risk of developing long-term hearing disorders

Kernicterus

- Kernicterus
 - 125 cases of kernicterus followed by the Pilot USA Kernicterus Registry - 6/125 infants died in the first year of life
 - Studies suggest characteristic changes on MRI
 - No evidence in the literature of a specific bilirubin level confirmed to lead to kernicterus
 - Kernicterus has been reported in apparently healthy term newborns without hemolysis

Kernicterus

- Pilot USA Kernicterus Registry data (n=125)
 - Contributing factors: G6PD deficiency (26/125), hemolysis (25/125), birth trauma (18/125)
 - Co-morbidities: sepsis, dehydration, infection
- Retrospective chart review, 1999-2000 (n=12)
 - G6PD deficiency (7/12), dehydration (3/12), sepsis (1/12)

Condition - Remaining Questions

- What evidence is available regarding the relationship between severe neonatal hyperbilirubinemia and kernicterus?
- When does kernicterus appear clinically?

Key Questions - Screening

- What methods exist to screen newborns for neonatal hyperbilirubinemia?
- 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 is the predictive validity of using the risk assessment nomogram to predict risk of developing hyperbilirubinemia?

Key Questions - Screening

- What are the recommended follow-up and monitoring procedures for newborns found to have an intermediate risk level by bilirubin screening?
- Do outpatient facilities have the capacity to handle follow-up visits for screen positive infants?
- Has there been population-based pilot screening?
- What are the potential harms or risks associated with screening?

Screening Methods

Bilirubin estimations/measurements

- Visual Assessment
- Transcutaneous bilirubin (TcB)
- Total serum bilirubin (TSB)

Risk prediction

- Hour specific nomogram

Screening - TSB

TSB screening for subsequent significant hyperbilirubinemia

Study	Population	Cutoff, Timing	Subsequent Hyperbilirubinemia	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Agarwal et al., 2002	220 infants ≥ 35 weeks gestation	$>6\text{mg/dL}$, 24 hours	$\geq 17\text{mg/dl}$ >24 hours of age	95	70.6	27.2	99.3
Alpay et al., 2000	498 healthy term newborns ≥ 38 weeks gestation	$\geq 6\text{mg/dL}$, 24 hours	$\geq 17\text{mg/dl}$ >24 hours of age	90	65.3	26.2	97.9
Carbonell et al., 2001	2004 healthy term newborns of 37-42 weeks gestational age	$\geq 6\text{mg/dL}$, 24 hours	$\geq 17\text{mg/dl}$ >72 hours of age	100	60	13	100
		$\geq 9\text{mg/dL}$, 48 hours		98	45	10	99.6
Prasarnphanich & Somlaw, 2007	1983 healthy term neonates	12mg/dL , 48-72 hours	$\geq 13\text{mg/dL}$ 49-72 hours of age, $\geq 15\text{mg/dL}$ >72 hours of age	36.6	87.9	15.3	95.9
Seidman et al., 1999	1177 healthy term newborns	$>5\text{mg/dL}$, 8-24 hours	$>10\text{ mg/dL}$ on day 2, $>14\text{ mg/dL}$ on day 3, $>17\text{ mg/dL}$ on days 4 and 5 of life	63.1	94.2	-	-

Screening - TcB

TcB screening for elevated TSB values

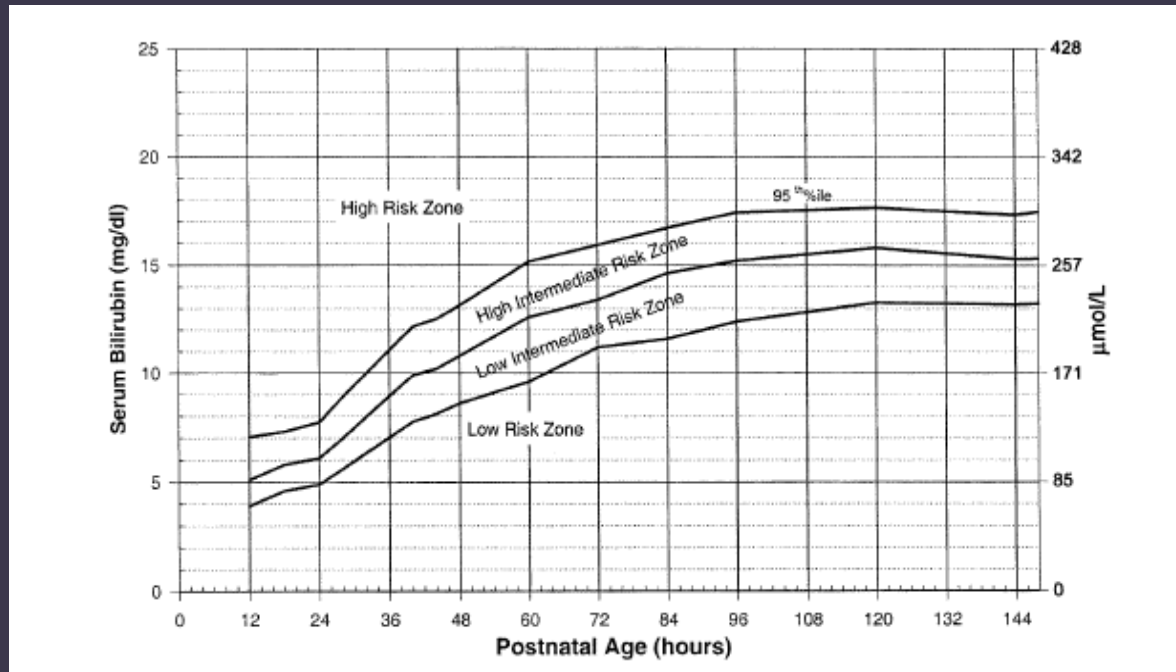
Study	Population	Cutoff, Timing, Placement	TSB comparison value	Sensitivity (%)	Specificity (%)
Boo & Ishak, 2007	345 healthy term neonates with hyperbilirubinemia	14.6 mg/dL, median 70 hours, forehead	>17.5 mg/dL	100	39.2
		11.7 mg/dL, median 70 hours, sternum	>17.5 mg/dL	100	33.6
Briscoe et al., 2002	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
Dai et al., 1996	45 healthy term infants	17 TcB value, >24 hours, forehead	>15.2 mg/dL	100	68
Sanpavat & Nuchprayoon, 2007	196 premature infants <38 weeks gestation with visually observed jaundice	TcB value 6, mean 4.5 days, forehead	≥6 mg/dL	97.8	40
		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	29
		>8mg/dL, mean 58.8 hours, sternum	>10mg/dL	93	74

Screening - TcB

TcB screening for subsequent significant hyperbilirubinemia

Study	Pop.	Cutoff, Timing	Subsequent hyperbilirubinemia	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Bhat & Rao, 2008	461 healthy term newborns born between 37 and 42 weeks gestation	>5 TcBI, 24 hours	≥17mg/dl at >72 hours of age	100	35.5	24.8	100
		>8 TcBI, 48 hours		100	52.6	31	100
		>7 TcBI, 24 hours		83.9	83.6	52.3	96
		>11 TcBI, 48 hours		44.4	95.5	67.9	88.9
Carbonell et al., 2001	2004 healthy term newborns of 37-42 weeks gestational age	>13, 48 hours, sternum	≥17mg/dl at >72 hours of age	98	32	8	99.6

Screening - Risk Nomogram



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Predictive characteristics of TSB risk zones on Bhutani nomogram for subsequent hyperbilirubinemia

Percentile	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Above 95 th	54	96.2	39.5	97.8
Above 75 th	90.5	84.7	21.6	99.5
Above 40 th	100	64.7	11.6	100

*From Bhutani et al, 1999

Screening - Risk Nomogram

Predictive characteristics of 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, >75 th	100	88.1	32.9	100
Dalal et al., 2009	358 neonates born at ≥35 weeks of gestation	30-48 hours, >75 th	82.6	79	41.2	95.1

Screening Summary

- Underestimation of TSB level was the most common diagnostic error using clinician's visual assessment alone
- In infants with jaundice, the visual assessment grading system did not prove accurate in approximating bilirubin level or risk of developing subsequent hyperbilirubinemia
- TcB screening studies agreed 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 NPV

Screening Summary

- Interpretation of risk of subsequent hyperbilirubinemia is possible with an hour-specific bilirubin nomogram based on TSB or TcB values
- 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

Screening - Remaining Questions

- What is the optimal approach for newborn screening for hyperbilirubinemia?
- Do risk factor assessments improve prediction of developing hyperbilirubinemia leading to kernicterus?
- What follow-up practices should be in place for newborns found to have an intermediate risk level by bilirubin screening?
- Do outpatient facilities have the capacity to handle follow-up visits for screen positive infants?
- What are the potential harms or risks associated with screening?
- Has there been population-based pilot screening?
- What would be the effect of taking bilirubin screening in its current form to state mandated newborn screening?
- What proportion of cases of kernicterus would be prevented by screening?

Key Questions - 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 kernicterus

Treatment - Methods

- Phototherapy
- Exchange transfusion

Treatment - Phototherapy

- Phototherapy effectively decreases levels of TSB in the neonatal period
- Effectiveness of phototherapy varies significantly depending on infant age, gender, and gestational age
- Indirect evidence of the wide availability of treatment
- Physical complications associated with phototherapy include fluid loss, temperature instability and corneal damage; two most common reported are skin rash and diarrhea
- No evidence of disruption in mother-child attachment after the first year of life

Treatment - Exchange Transfusion

- Adverse events common with EcT
- Mortality rate of EcT is approximately 0.53 per 100 patients and 0.3 per 100 procedures
- Morbidity rate 12-15.3%
- Bilirubin level to perform EcT remains controversial

Treatment - Outcomes

- Mixed results regarding the reversal of neurological and developmental symptoms after treatment
 - 3 studies suggest no or minimal resolution of neurological and developmental symptoms after treatment
 - 6 studies, including ones with longer follow up periods, show recovery from early acute clinical manifestations of hyperbilirubinemia after treatment
- Indirect evidence shows very early symptomatic and presymptomatic infants treated with phototherapy remain normal and prevents development of further clinical manifestations due to hyperbilirubinemia through all follow-up examinations

Treatment - Harms

Phototherapy

- Fluid loss
- Temperature instability
- Skin rash
- Diarrhea
- Corneal damage
- Bronze baby syndrome
- Behavioral changes (crying episodes, poorer scores in orientation items)

Exchange Transfusion

- Mortality rate has been calculated as 0.53/100 patients and 0.3/100 procedures
- Morbidity rate has been noted as 12-15.3%
- One study found 74% of EcTs were associated with an adverse event
- Summarized in Table 15 of evidence review

Treatment - Remaining Questions

- Does treating neonatal hyperbilirubinemia prevent kernicterus?
- What is the availability of treatment?

Key Questions - Economics

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

Economics

- Five papers identified as including cost and/or economic outcomes related to screening for hyperbilirubinemia
 - Four cost analyses only (no evaluation of outcomes)
 - Studies reported costs of jaundice readmission (1), test cost (1), cost of hyperbilirubinemia-related hospitalization (1) with varying levels of quality
 - One study reported data more than 20 years old
 - Other studies reported data from one institution
 - One study (jaundice admission) used statewide data (from CA)
 - One international study not applicable to US setting
- Economics articles reported limited cost data but did not evaluate the cost-effectiveness or cost-benefit of newborn screening for hyperbilirubinemia

Cost-Effectiveness Analysis

- One identified paper was a cost-effectiveness analysis of strategies to prevent kernicterus in newborns
 - Main outcome: Cost per case of kernicterus prevented
 - Results of Base Case Analysis: \$5,743,905 per case prevented using pre-discharge serum bilirubin testing
 - Sensitivity analysis: Screening strategies are unlikely to be cost-saving and will require an investment for health benefits associated with averted cases of kernicterus
 - Difficult to evaluate whether or not these screening strategies can be considered cost-effective without the use of QALYs as an outcome

Economics - Remaining Questions

- What are the costs associated with the screening test and follow-up for newborns found to have an intermediate risk level by bilirubin screening?
- What are the costs associated with confirmatory testing, and the failure to find at risk newborns in the pre-symptomatic period?
- What are the costs associated with treatment?
- What is the cost-effectiveness of newborn screening for neonatal hyperbilirubinemia?

Key Findings

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						Fair
22; 48,569	Case series	Good	Inconsistent	Direct	Imprecise	-
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	-
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 75 th percentile.						

Key Findings

Number of studies; subjects	Design	Risk of bias/study quality	Consistency	Directness	Precision	Strength of evidence
Specificity and sensitivity of risk assessment/ pre-discharge screening prediction						Moderate
7; 20,713	Prospective Cohort	Good	Inconsistent	Direct	Imprecise	-
<p>Summary: The specificity of the pre-discharge 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 kernicterus.</p>						
Screening for hyperbilirubinemia prevents kernicterus						Poor
0;0	N/A	N/A	N/A	N/A	N/A	-
<p>Summary: No data identified regarding whether screening for neonatal hyperbilirubinemia prevents kernicterus.</p>						

Key Findings

Number of studies; subjects	Design	Risk of bias/study quality	Consistency	Directness	Precision	Strength of evidence
Effectiveness of early intervention for hyperbilirubinemia						Moderate
11; 18,329	Prospective Cohort	Good	Inconsistent	Indirect	Imprecise	-
<p>Evidence Summary: Indirect evidence that early intervention is associated with improved outcomes for those with neonatal hyperbilirubinemia. Evidence indicates treatment lowers elevated bilirubin concentration levels, and lower bilirubin level is associated with less acute clinical manifestations. No evidence that treatment prevents kernicterus.</p>						

Next Steps

Experts and Advocates to Consult

Vinod Bhutani, MD, PhD

Coleen Boyle, PhD, MSH

Karen Dixon, PhD

Gabriel Escobar, MD

Thomas Hegyi, MD

Lois Johnson-Hamerman, MD

Michael Kaplan, MB, ChBM

Jeffrey Maisels, MD

Marie Mann, MD, MPH

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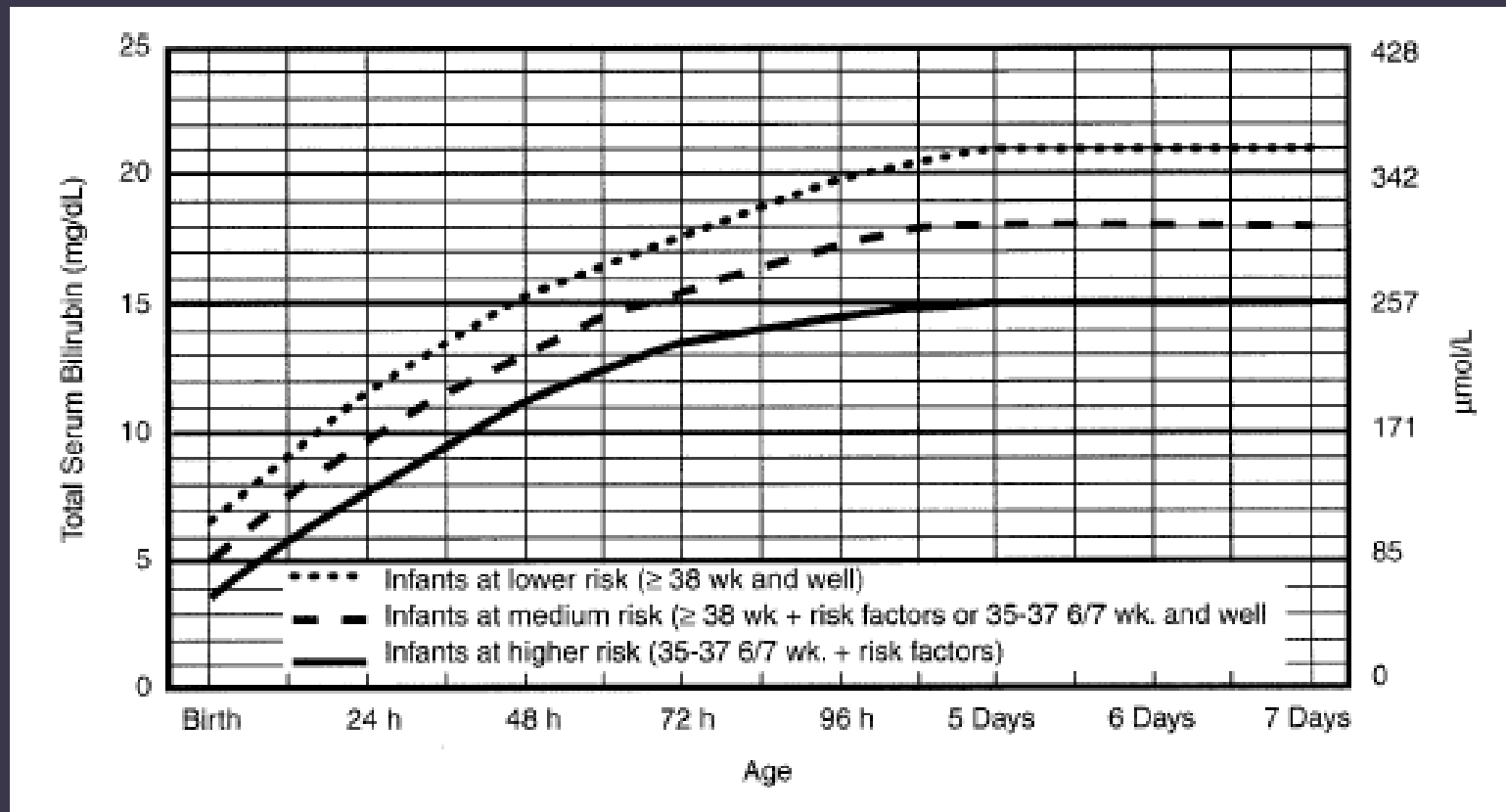
Recommendations of additional experts to contact are welcome

Questions for Experts

- How are infants at risk of subsequent hyperbilirubinemia, who do not require treatment, managed?
- What would be the effect of taking bilirubin screening in its current form to state mandated newborn screening?

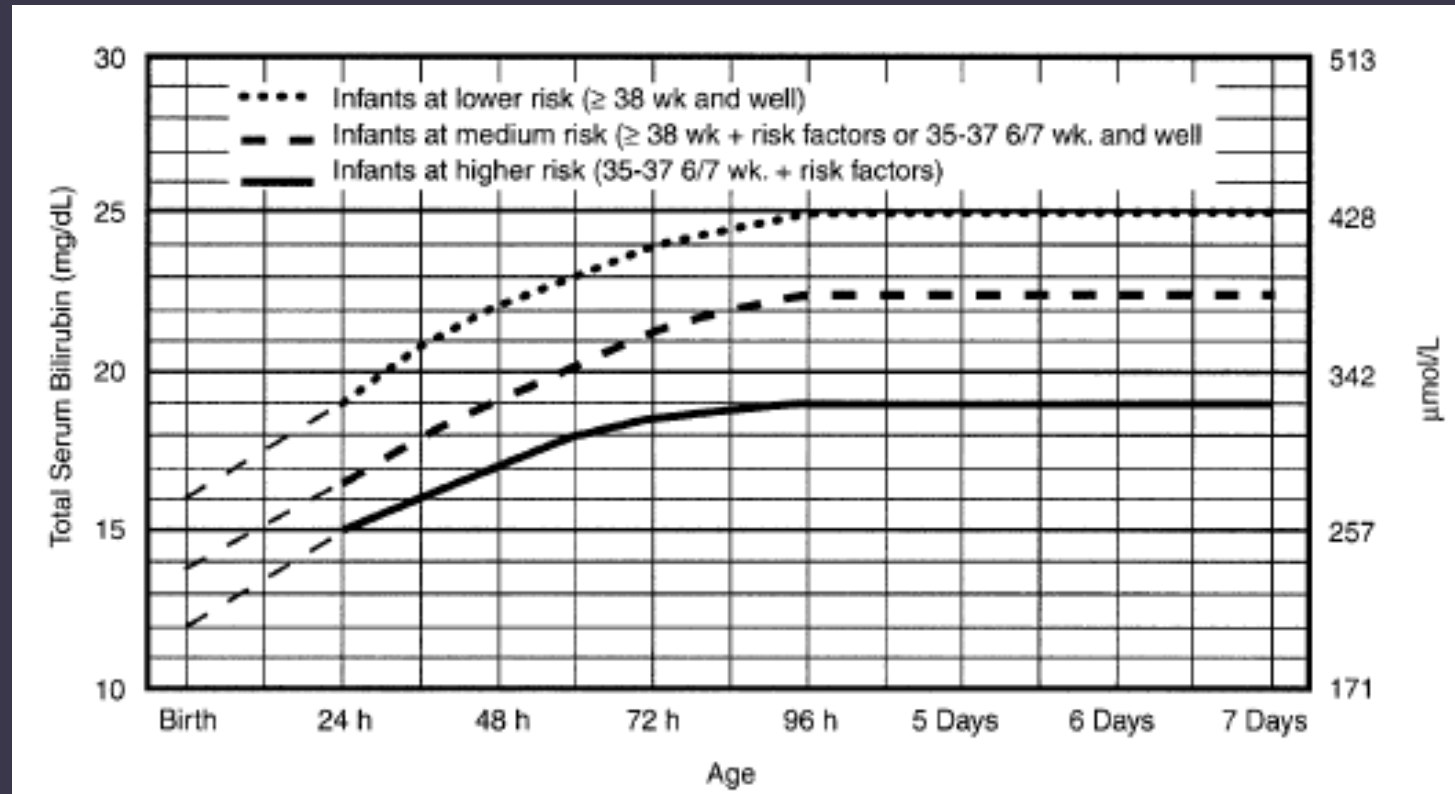
Thank you

2004 AAP Phototherapy Guidelines



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2004 AAP Exchange Transfusion Guidelines



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