

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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Neonatal Hyperbilirubinemia Overview

- Bilirubin elevations common in newborns
 - Multiple etiologies
- Detectable risk factor for acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy (kernicterus)
- Primary concern: preventing neurotoxic effects of hyperbilirubinemia
- Two previous key reports

American Academy of Pediatrics Clinical Practice Guidelines

- Prevention and management of hyperbilirubinemia in newborns ≥ 35 weeks' gestational age
- Published 2004 (2009 update with clarifications)
- Main recommendations
 - Promote and support successful breastfeeding
 - Systematic assessment before discharge: measurement of bilirubin level (with TSB or TcB) individually or in combination with clinical risk-factor assessment to help assess risk of subsequent hyperbilirubinemia
 - Early and focused follow-up based on risk assessment, based on pre-discharge TSB/TcB, gestational age, and other risk factors
 - When indicated, phototherapy or exchange transfusion to decrease serum bilirubin, prevent hyperbilirubinemia, and possibly bilirubin encephalopathy (kernicterus)

US Preventive Services Task Force (USPSTF) Report

- *Evidence review*: screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy in healthy newborns ≥ 35 weeks' gestational age
- *Release*: October 2009
- **Assessment**
 - Evidence re benefits and harms of screening newborn infants to prevent chronic bilirubin encephalopathy is lacking
- **Summary of Recommendation**
 - Evidence insufficient to recommend screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy

ACHDNC Case Definitions

Neonatal Hyperbilirubinemia

- TSB levels >95th percentile for age in hours in term and near term newborns, which require follow-up and treatment

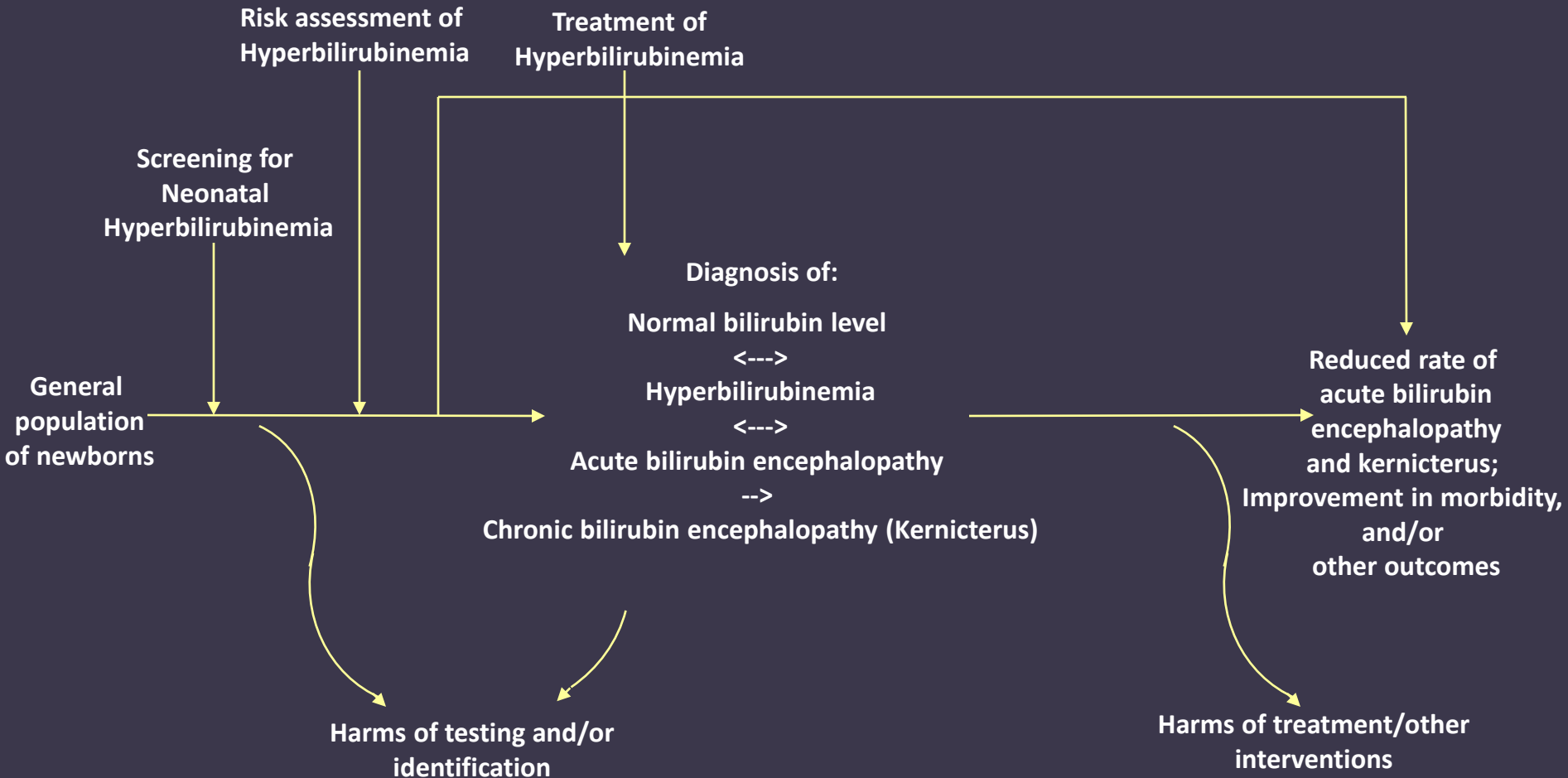
Acute Bilirubin Encephalopathy (ABE)

- Advanced manifestations of bilirubin toxicity in first weeks of life, loss of Moro, extensor hypertonia, high-pitched cry. [Some authors use ABE to describe less severe symptoms, such as somnolence, hypotonia, and fever – not considered ABE in this report.]

Chronic Bilirubin Encephalopathy (Kernicterus)

- Persistent and permanent brain damage from bilirubin toxicity, characterized by
 - movement disorder (athetosis, dystonia, spasticity, hypotonia)
 - auditory dysfunction
 - oculomotor impairment
 - dental enamel hypoplasia

Conceptual Framework



Systematic Literature Review

Findings

- Searched for all relevant studies published January 1990 – October 2011
 - MEDLINE, EMBASE, & OVID In-Process and Other Non-Indexed Citations
 - English language only
 - Human studies only
- 3,075 abstracts for preliminary review
- 201 articles selected for in-depth review
- 113 articles met all inclusion criteria for abstraction

Papers Meeting Review Criteria

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

Condition

- Reported incidence of bilirubin levels $>30\text{mg/dL}$ ranges from 3 to 12 per 100,000
- Estimated incidence of ABE is <1 per 200,000 live births
- Estimated incidence of CBE (kernicterus) ranges from 0.49 to 2.7 per 100,000
 - Most evidence indicates rates <1 per 100,000

Hyperbilirubinemia and ABE/CBE

- No specific bilirubin level associated with acute or chronic bilirubin encephalopathy, although in general
 - Higher levels of neonatal bilirubin are associated with higher occurrence of ABE and CBE manifestations
- Most cases of chronic bilirubin encephalopathy have TSB >30mg/dL
 - Rare cases occur below TSB of 25mg/dL with co-morbidities and/or significant risk factors
- Although some neonates develop less severe signs of hyperbilirubinemia (than ABE), large majority of studies indicate no long-term effects

Screening

- Three current forms of screening for hyperbilirubinemia:
 - Visual assessment
 - TcB
 - TSB
- TcB appears as valid screening tool for detecting significant hyperbilirubinemia requiring confirmatory follow-up with TSB
- An hour-specific bilirubin nomogram based on TSB values allows prediction of subsequent hyperbilirubinemia; can apply risk nomogram also to TcB values

Treatment

- RCT evidence that phototherapy effectively decreases levels of bilirubin in the neonatal period
- Indirect evidence that screening and phototherapy decrease rates of chronic bilirubin encephalopathy (kernicterus)
- Case series provide evidence that symptoms of ABE may resolve with treatment
- Direct evidence that earlier treatment with phototherapy effectively lowers serum bilirubin levels and diminishes the need for treatment with EcT
- Adverse events remain common after EcT, with mortality approximately 0.53 per 100 patients and 0.3 per 100 procedures

Economics

- Limited quantity and quality of economic evidence
- Limited evidence for costs of
 - jaundice readmission
 - phototherapy treatment
 - long-term outcomes
 - cost-effectiveness of strategies to prevent kernicterus (1 study)
- Estimated costs of TcB testing
 - Range: <\$1 to \$7.80
- Cost per case of kernicterus prevented:
 - TSB: \$5,743,905 (sensitivity analyses: range \$4 million to \$128 million)
 - TcB: \$9,191,352 (range \$6 million to \$195 million)

Harms and Benefits of Universal Predischarge Screening Program

Harms

- Risks of phototherapy include fluid loss, temperature instability, corneal damage, skin rash, diarrhea, delayed parenting/bonding (all minor risks)
- EcT (not screening) is associated with a mortality rate of ~0.53 per 100 patients and ~0.3 per 100 procedures; and morbidity ranging from 12-15.3%

Benefits

- Identifies newborns who will likely develop TSB >30mg/dL
- Lowering bilirubin level reduces the risk of newborn developing ABE and CBE
- Early identification and treatment with phototherapy may prevent need for EcT or readmission to hospital

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						Moderate
27; 49,276	Case Series (16), Case control (6), Cohort (4), Cross sectional (1)	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/predischarge screening prediction						Moderate
7; 20,713	Prospective Cohort	Good	Inconsistent	Direct	Imprecise	-
<p>Summary: Specificity of predischarge screening and risk assessment nomogram at and above the 75th risk percentile is high 84.7% for TSB, ≥79% for TcB). Sensitivity at and above the 75th risk percentile is also high (90.5% for TSB, >82% for TcB). At and above the 40th percentile, specificity is 64.7% (TSB) or 38.4% (TcB) and sensitivity is 100% (TSB) or 94.1% (TcB). 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
12; 18,445	Prospective Cohort	Good	Inconsistent	Indirect	Imprecise	-
<p>Evidence Summary: Indirect evidence that early intervention is associated with improved outcomes for those with neonatal hyperbilirubinemia. Direct 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>						

Key Findings Summary

- High total serum bilirubin concentration leads to acute clinical manifestations
 - Strength of evidence: **Moderate**
- Additional sensitivity of TcB over visual assessment for hyperbilirubinemia
 - Strength of evidence: **Fair**
- Specificity and sensitivity of risk assessment/predischarge screening prediction
 - Strength of evidence: **Moderate**
- Screening for hyperbilirubinemia prevents kernicterus
 - Strength of evidence: **Poor**
- Effectiveness of early intervention for hyperbilirubinemia
 - Strength of evidence: **Moderate**

Gaps in Evidence

- No clear connection between specific bilirubin levels and chronic bilirubin encephalopathy (kernicterus)
- No clear evidence that treating clinically significant neonatal hyperbilirubinemia prevents chronic bilirubin encephalopathy
 - How many cases of CBE could universal screening prevent?
- No evidence re universal predischarge bilirubin newborn screening logistics and large-scale screening impact
- Evidence lacks cost-effectiveness of universal predischarge bilirubin newborn screening

Decision Analysis

- Developed decision analytic model to project outcomes for universal pre-discharge screening for hyperbilirubinemia
- Conducted 3 meetings with 6 experts* to
 - confirm/revise model structure
 - identify key outcomes
 - cases of chronic bilirubin encephalopathy (CBE)
 - develop assumptions
 - Inputs based on 3 large-scale “pre-post” studies
 - Reduction in proportion of newborns with severe NHB will reduce cases of CBE
- Key Findings:
 - Confirmed lack of data for relationship between NHB and CBE
 - TcB screening in practice not fully described in literature

*Experts: Vinod Bhutani, MD; Lois Johnson-Hammerman, MD-FAAP; M. Jeffrey Maisels, MD; Thomas B. Newman, MD, MPH; Ann Stark, MD; & David Stevenson, MD

Decision Analysis, cont.

- Assumptions for projected impact of screening:
 - US birth cohort: 4 million
 - Incidence of CBE: 0.5-1.0 per 100,000
 - Impact of screening: 45-73% reduction
- Boundaries of benefits, using varying assumptions:
 - Range of projected annual cases of CBE before implementation of universal screening: 20-40
 - Range of cases of CBE potentially averted by screening: 8-29 per year (not all cases of CBE would likely be prevented by universal screening)

Thank you