MAYO CLINIC

Transcutaneous biliriubin screening

North Texas POC Webinar
February 6, 2014

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DISCLOSURE

Relevant Financial Relationship(s)

None

Off Label Usage

None

Outline

- Introduction
  - Risk of hyperbilirubinemia (kernicterus)
  - American Academy of Pediatrics, (AAP) recommendations
- Transcutaneous bilirubin screening
- Impact of universal TcB screening on TSB values and utilization of resources

Objectives

- Review current guidelines for management of neonatal jaundice
- Define variables that impact the relationship between transcutaneous and laboratory bilirubin
- Identify factors that may influence the effectiveness of transcutaneous bilirubin screening programs

Introduction

- Bilirubin levels increase in newborn period due to:
  - Lifespan/fragility of neonatal red blood cells
  - Immaturity of conjugation system in liver
  - Increased reabsorption via enterohepatic circulation
  - Nutritional factors (breast feeding)
  - Less protein to bind/excrete bilirubin
  - Other factors
- High unbound bilirubin levels are toxic to brain

Kernicterus

- Chronic form of Acute Bilirubin Encephalopathy (ABE)
  - Athetoid Cerebral Palsy
  - Auditory dysfunction
  - Dental-enamel dysplasia
  - Paralysis of upward gaze
  - Intellectual and other handicaps (less frequent)

Historical Information

- Prior to late 1960: Most kernicterus was due to Rh isoimmunization
- 1994 AAP practice parameter: Management of hyperbilirubinemia in the healthy term infant
- 1994-2004: Increasing case reports of Acute Bilirubin Encephalopathy (ABE)
- 2004 AAP practice parameter: Management of hyperbilirubinemia in the newborn infant 35 or more weeks gestation

Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks Gestation

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AAP clinical practice guidelines July 04

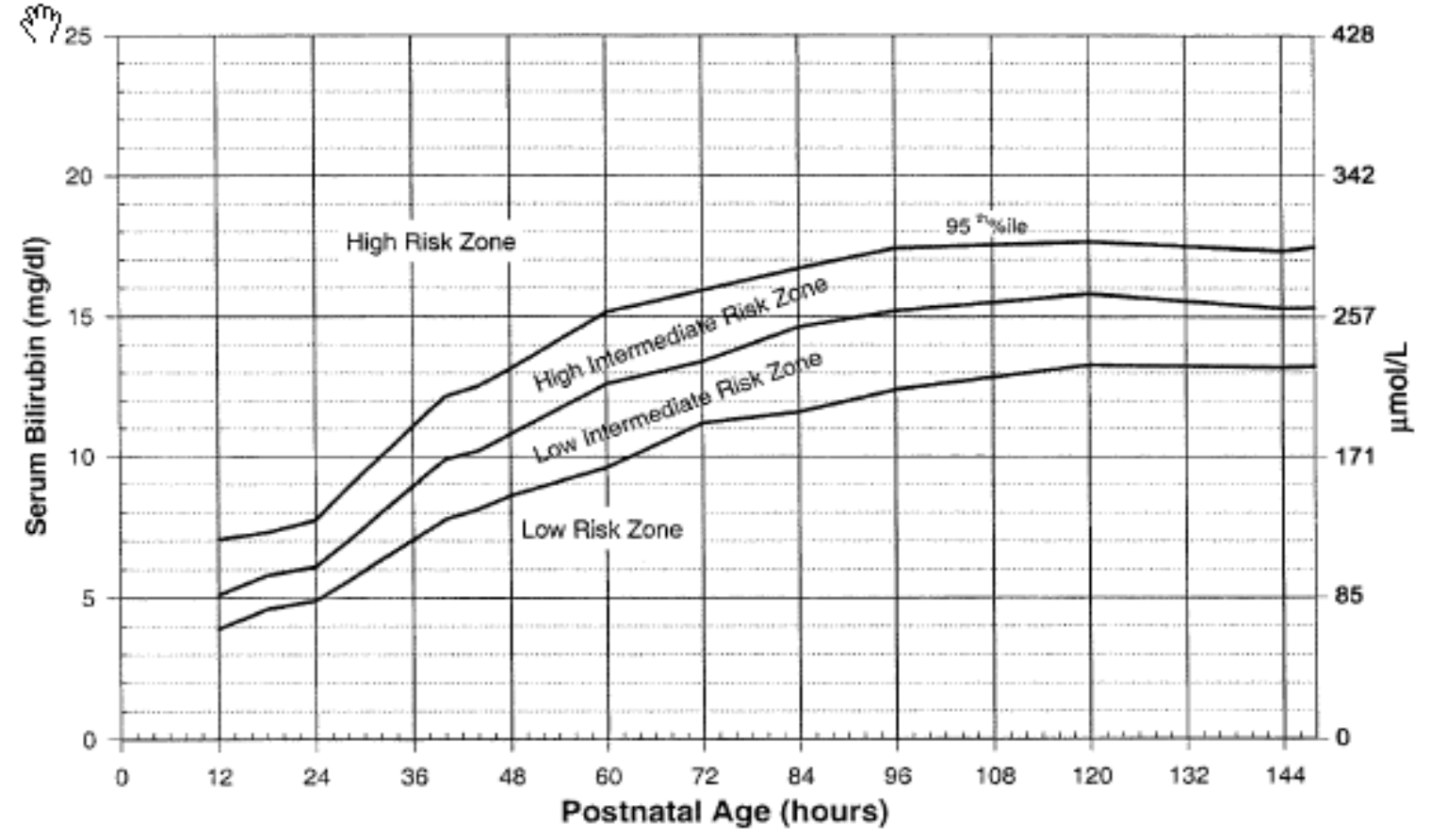
Focus of the Guideline

- Reduce frequency of severe hyperbilirubinemia and bilirubin encephalopathy
- Minimize the risk of unintended harm
  - Increased anxiety
  - Decreased breastfeeding
  - Unnecessary treatment and excessive cost

Key Elements to the Recommendation

- Interpret bilirubin levels according to postnatal age
- Assess all infants before D/C for risk of severe hyperbilirubinemia
  - Predischarge TSB or TcB interpreted according to age
  - Assess clinical risk factors
  - Visual assessment alone unreliable

Bilirubin (Bhutani) Nomogram



Bilirubin screening

- How can AAP recommendations for screening be met?
  - Universal (b/c discharge) serum bilirubin (TSB)
  - Universal (b/c discharge) transcutaneous bilirubin with or without reflex serum level (TcB)
  - Serum bilirubin for infants deemed at risk
  - Transcutaneous bilirubin for infants deemed at risk with or without reflex serum level

Controversies

- US Preventive Services Task Force (2009)
  - Evidence insufficient to assess net balance of benefit vs. harms in universal bilirubin screening of infants
  - Rate of kernicterus low and largely unknown
  - Large system-wide universal screening programs increase phototherapy usage and blood draws for bilirubin (cost)
- Expert opinion piece same issue Pediatrics
  - Perform TSB or TcB on all infants before discharge

Previous studies of TcB

Previous studies of TcB

- 4 studies concluded that BiliChek TcB underestimated serum bilirubin by 0.06-0.96 mg/dL
- 1 study concluded that BiliChek TcB overestimated serum bilirubin by ~ 1 mg/dL across a wide range of serum bilirubin values
- 2 studies found that BiliChek TcB slightly overestimates serum bilirubin at low concentrations, but significantly underestimates serum bilirubin at higher (> 12 mg/dL) levels
- Reasons for discrepancies?

Mayo study of TcB

- Can BiliChek TcB be used to predict risk of hyperbilirubinemia?
- If TcB level at X hours of life would suggest that infant is low or high risk for hyperbilirubinemia, how confident are we that serum bilirubin would fall in same risk zone?

Mayo study of TcB

- What we would like to know

  What is sensitivity and specificity of high risk TcB for predicting high risk TsB?

  If TcB is low risk, can we avoid blood draw (high sensitivity)?

  Can we avoid enough blood draws to make TcB measurement useful (high specificity)?

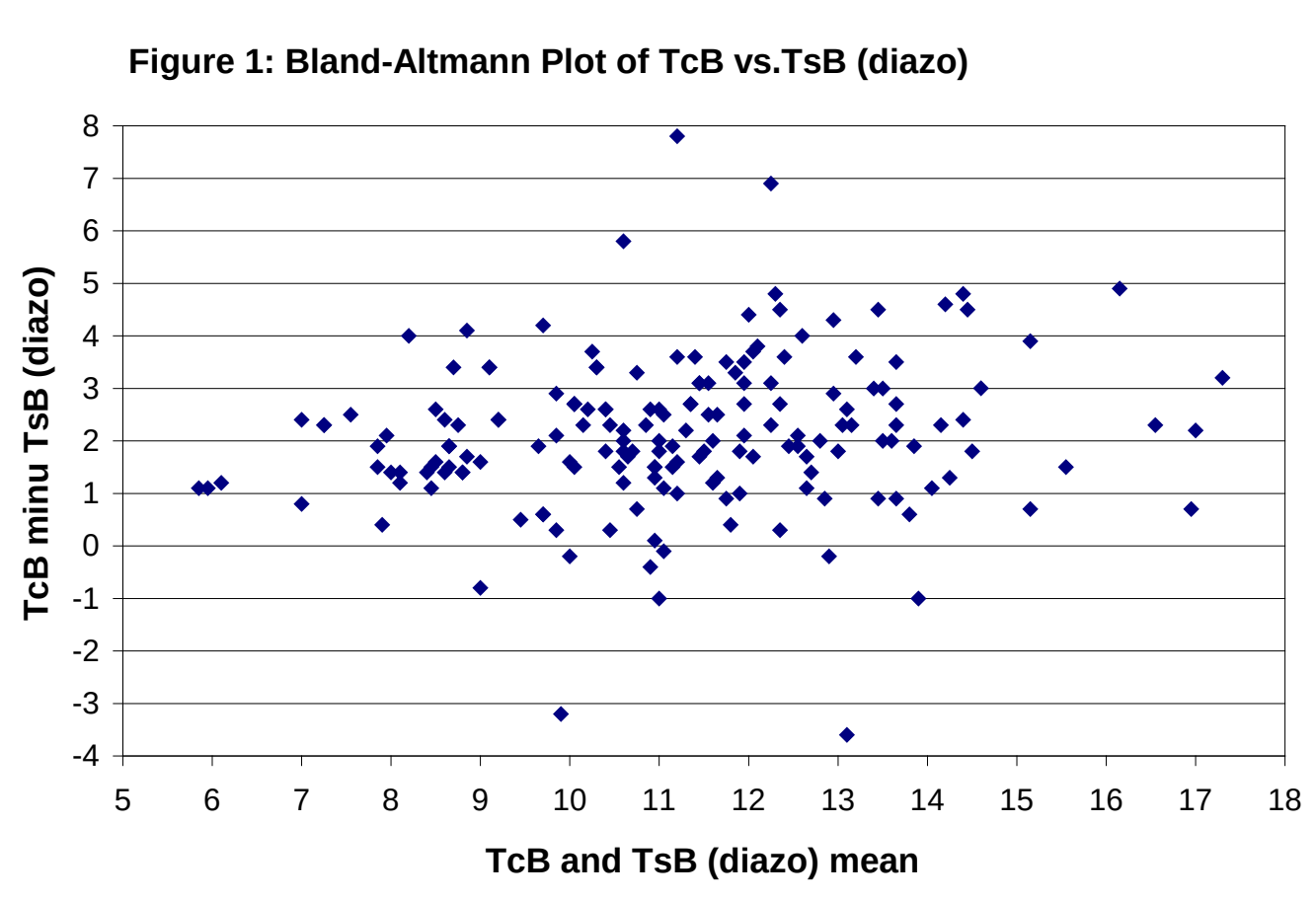
  What are the factors (clinical and lab) that impact correlation between TcB and TsB?

Mayo study of TcB

- Study design
  - 200 infants with clinical suspicion hyperbilirubinemia
  - Measure BiliChek TcB within 30 minutes of serum bilirubin drawn
  - Measure serum bilirubin diazo (current) method and direct photometric measurement of unconjugated bilirubin (Vitros)
  - Record gestational age, postnagal age (hours), mother's ethnicity for each infant
  - Record whether capillary or venipuncture, level of serum free hemoglobin for each specimen, and collect in both clear and amber tube types

Mayo study of TcB

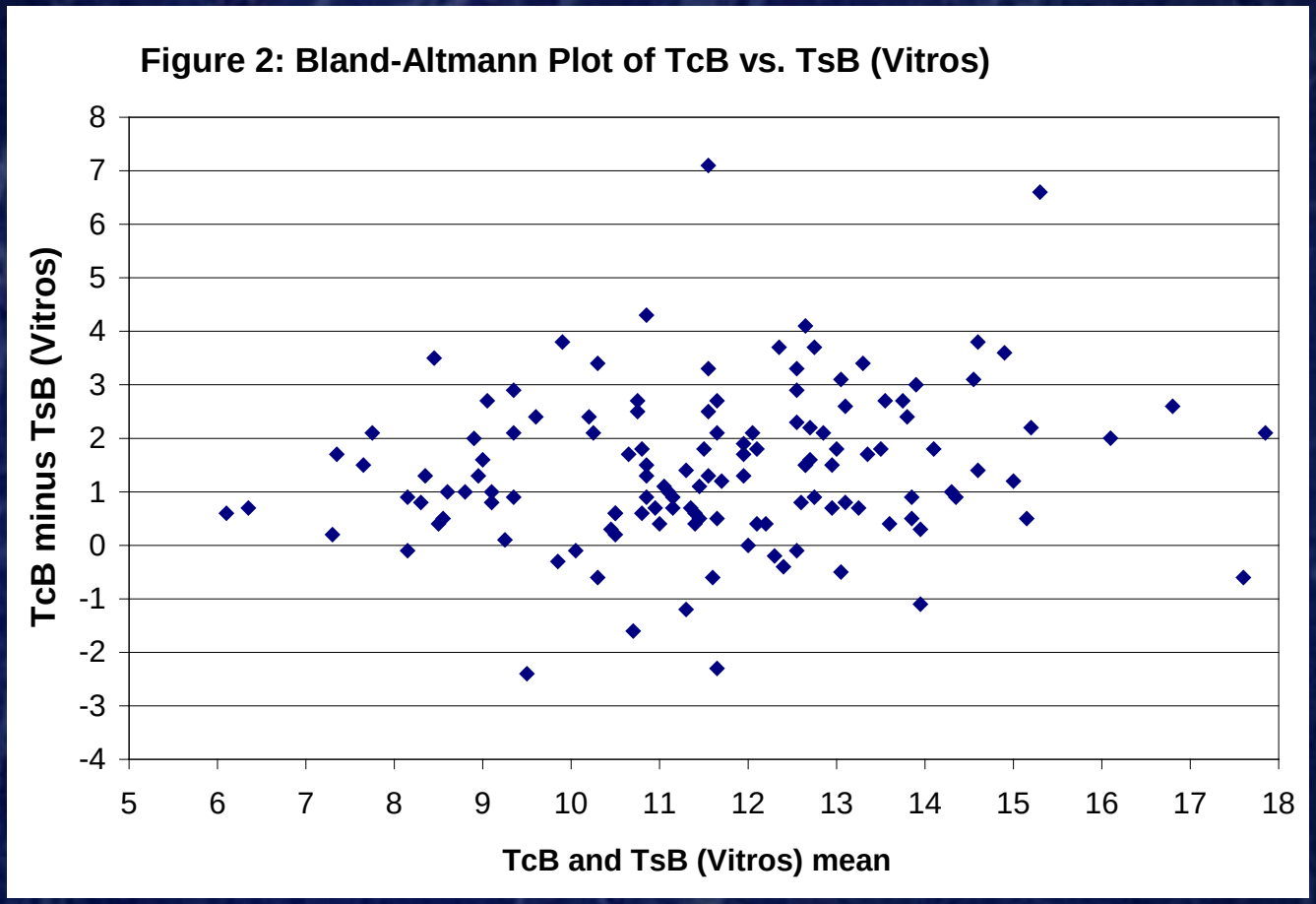
Results: TcB vs. diazo TsB



Median bias (TcB minus TsB) = 2.0 mg/dL

Mayo study of TcB

Results: TcB vs. Vitros TsB



Median bias (TcB minus TsB) = 1.3 mg/dL

Mayo study of TcB

What is the clinical impact of systematic overestimation of transcutaneous bilirubin?

Can TcB effectively be used to predict risk of hyperbilirubinemia?

Mayo study of TcB

- Each TcB and TsB value, combined with postnatal age in hours, used to determine risk zone (low, low-intermediate, high-intermediate, high risk)
- Sensitivity and specificity of high risk TcB for predicting high risk TsB was calculated

Mayo study of TcB

	Transcutaneous bilirubin		
Serum bilirubin (diazo)	Low or low-intermediate risk	High-intermediate or high risk	Total
Low or low-intermediate risk	48	77	125
High-intermediate or high risk	1	51	52
Total	49	128	177

51/52 (98%) sensitivity for predicting high risk diazo TsB

48/125 (38%) specificity for predicting low risk diazo TsB

Mayo study of TcB

	Transcutaneous bilirubin		
Serum bilirubin (Vitros)	Low or low-intermediate risk	High-intermediate or high risk	Total
Low or low-intermediate risk	35	29	64
High-intermediate or high risk	4	63	67
Total	39	92	131

63/67 (94%) sensitivity for predicting high risk Vitros TsB

35/64 (55%) specificity for predicting low risk Vitros TsB

Mayo study of TcB

TcB minus TsB bias not associated with:

Gestational age, postnatal age, mother's ethnicity, cap vs. venipuncture, free Hgb level

TcB minus TsB bias as a function of tube type:

Diazo TsB

Clear tube: Median bias 2.2 mg/dL

Amber tube: Median bias 2.0 mg/dL

p = 0.7437, NS

Vitros TsB

Clear tube: Median bias 1.7 mg/dL

Amber tube: Median bias 0.9 mg/dL

p = 0.0119

Mayo study of TcB

- Would use of TcB prevent blood draws?
  - TcB sensitive (94-98%) predictor of high risk serum bilirubin values
  - Infants with low risk TcB could safely forego blood draw for serum bilirubin
  - TcB vs. diazo TsB: 49/177 (28%) of TcB results were in low risk zone
  - TcB vs. Vitros TsB: 39/131 (30%) of TcB results were in low risk zone
- Conclusion: Use of TcB could avoid ~ 30% of blood draws

Mayo study of TcB

- Adjusted TcB values (TcB – 1 mg/dL)
- 95% sensitivity for prediction of high-intermediate risk (HIR) or high risk (HR) serum value
  - 100% sensitivity for prediction of HR values
- 63% specificity for prediction of HIR or HR serum value
- 45% blood draws avoided
- Subtracting 1.5 mg/dL missed HR infants

Mayo TcB screening protocol

- Feb 2010, universal TcB screening implemented
  - All infants get TcB (- 1 mg/dL)
  - Plot with postnatal age on Bhutani nomogram
  - If HIR or HR do serum bilirubin, treat accordingly
  - Pre-order follow-up TSB at outpatient visit 2-5 days after discharge
  - If low-intermediate risk (LIR) or low-risk (LR) no blood draw unless other risk factors

Impact of universal TcB screening on serum levels and utilization

- Several large system-wide studies showed that universal bilirubin screening:
  - Decreased rate/number high (> 20 mg/dL) neonatal bilirubin levels
  - Increased phototherapy usage
  - Increased or decreased blood draws for TSB
- None of the studies used 100% TcB screening
- None of the studies used age-adjusted interp of values based upon TcB bias

Impact of universal TcB screening on serum levels and utilization

- Mayo study 1 year before and after implementing universal TcB screening
  - Rate of TSB draws both inpatient and outpatient (follow up), and total
  - Rate of phototherapy both inpatient and outpatient, total
  - Distribution TSB values, both inpatient and outpatient
  - Did universal TcB screning impact utilization of phototherapy and lab services?
  - Did universal TcB screening change distribution bilirubin values for either inpatients or outpatients?

Impact of universal TcB screening on utilization

Bilirubin Newborn Screening Protocol Outcome Metric	Rate per 1000 infants, median (range)		p-value
	Pre-Protocol	Post-Protocol	
Inpatient TSB Blood Draw Rate	438 (266, 564)	411 (327, 508)	0.02
Outpatient TSB Blood Draw Rate	267 (103, 436)	309 (199, 494)	< 0.0001
Total (Inpatient + Outpatient) TSB Blood Draw Rate	717 (395, 1000)	713 (571, 975)	0.008
Pre-Discharge Phototherapy Rate	39 (17, 54)	17 (8, 50)	< 0.0001
Readmission Phototherapy Rate	18 (6, 36)	25 (0, 59)	0.04
Total (Pre-discharge + Readmission) Phototherapy Rate	59 (23, 74)	39 (17, 92)	< 0.0001

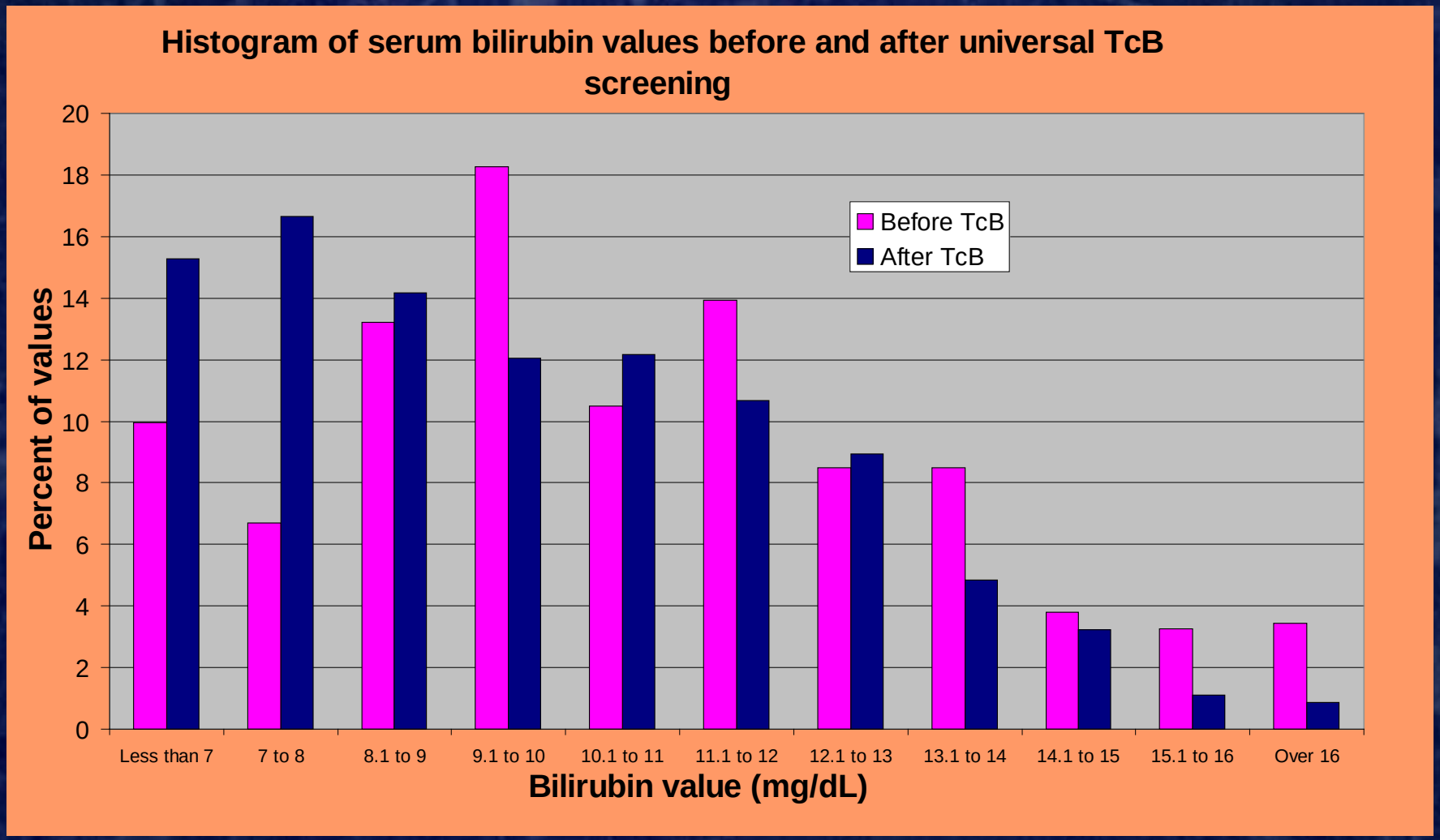
- **No major change rate of blood draws for TSB**

  Shift from inpatient to outpatient measurement

- **Decrease in rate of phototherapy**

  Shift from inpatient to (readmission) outpatient

Impact of universal TcB screening on serum bilirubin levels



Impact of universal TcB screening on serum bilirubin levels

- Median inpatient TSB decreased from 10.2 to 9.3 ($p < 0.0001$)
- Median outpatient TSB did not change
  - TcB on inpatients only
  - Preorder TSB on high risk infants
- Overall (inpatient plus outpatient) TSB decreased slightly from 11.6 to 11.1 mg/dL ($p=0.0009$)
- Number outpatient infants with TSB > 20 mg/dL decreased from 11/405 (3%) to 8/569 (1%)

Impact of universal TcB screening on serum levels and utilization

- Expected findings
  - Universal TcB screening shifts distribution inpatient TSB levels
  - Decreases number infants with TSB > 20 mg/dL

Impact of universal TcB screening on serum levels and utilization

- Unexpected findings
  - Universal TcB screening did not change rate blood draws for serum bilirubin
  - Universal TcB screening shifted blood draws from inpatient to outpatient
    - Part of protocol (pre-order outpatient TSB)
    - Provider confidence in screening program
  - TcB screening reduced rate of phototherapy
  - TcB shifted phototherapy from initial nursery admission to readmission
    - Provider confidence in screening program
    - Follow-up system must be robust

Conclusions

- Universal TcB screening of infants based upon observed relationship of TcB to TSB
- Protocol allows for age-adjusted TcB interpretation per AAP guidelines
- Universal TcB screening shifted distribution serum bilirubin values and reduced number infants with high TSB
- Protocol design (age-adjusted interp) did not result in increased utilization as measured by rate of blood draws or phototherapy

Acknowledgements

- Walt Cook, MD
- Andrea Wickremasinghe, MD