



MAYO CLINIC

# **Transcutaneous bilirubin screening**

**Ohio Point of Care Network  
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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**
- **2022 AAP major update to guidelines**

**Clinical Practice Guideline Revision:  
Management of hyperbilirubinemia in  
newborn infant 35 or more weeks of  
gestation**

**AAP clinical practice guidelines Sept 2022**



# Focus of the Guideline

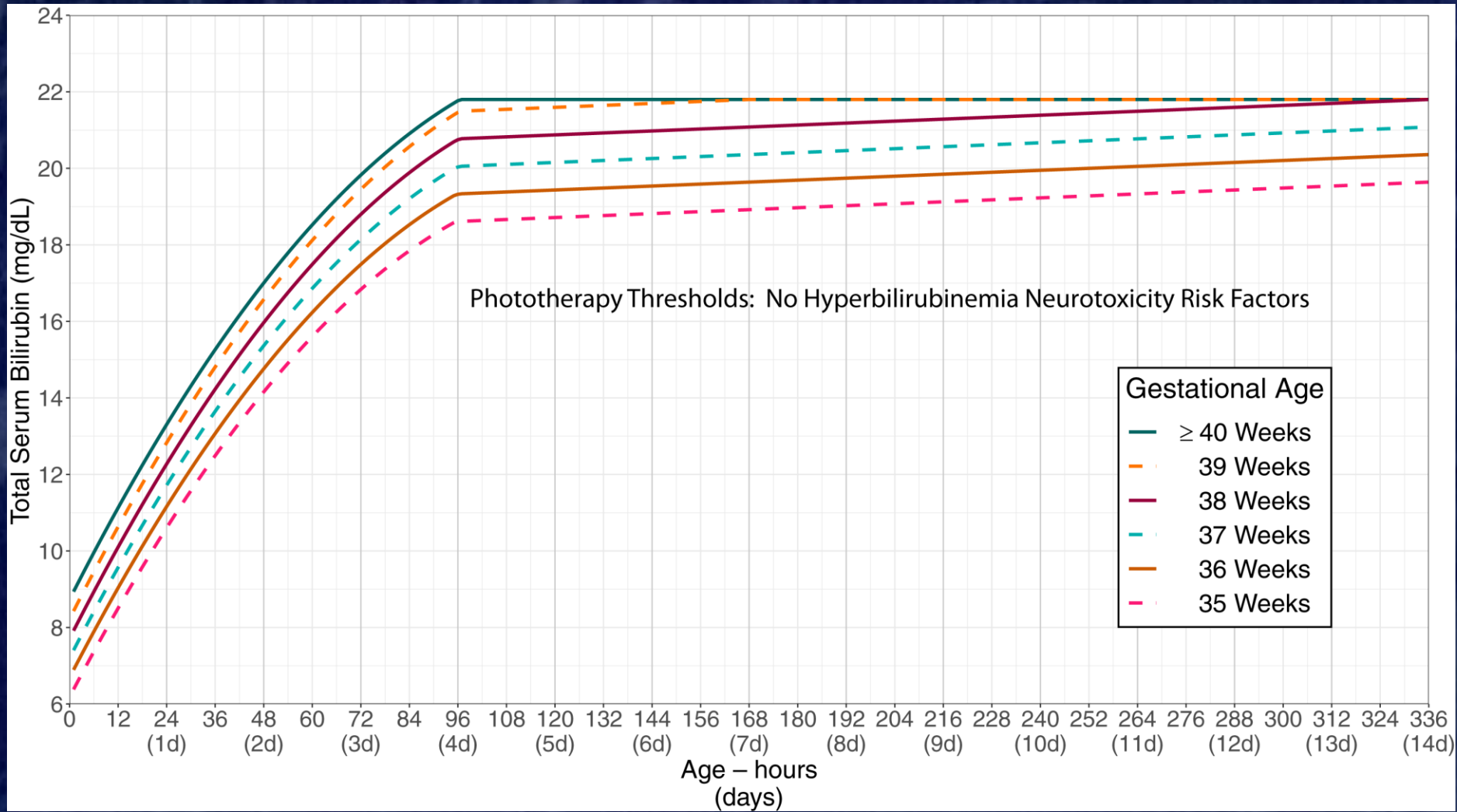
- **Reduce frequency of severe hyperbilirubinemia and bilirubin encephalopathy**
- **Minimize the risk of unintended harm**
  - Increased anxiety**
  - Decreased breastfeeding**
  - Unnecessary treatment and excessive cost**
  - Raised phototherapy thresholds slightly as risks of phototherapy (still infrequent) became known**
  - Balance use of resources/harm with risk of encephalopathy**

# Key Elements to the Recommendation

- Interpret bilirubin levels according to postnatal age in hours and gestational age (35-40 weeks)
- Measure serum (TSB) or transcutaneous (TCB) bilirubin infant visually jaundiced before 24 hours
- Measure TSB or TCB between 24-48 hours life, or before hospital discharge (if earlier)
- Bhutani nomogram no longer used to interpret age-adjusted risk of severe hyperbilirubinemia
- Consensus phototherapy threshold created by hour of life and gestational age (35-40+), +/- neurologic risk factors, similar exchange transfusion thresholds



# Phototherapy thresholds



# Bilirubin screening

- **Follow-up of infant at risk for hyperbilirubinemia**
- **If screening by TCB, obtain TSB and act on serum values if within 3 mg/dL of phototherapy threshold or  $\geq 15$  mg/dL**
- **Infants with hyperbilirubinemia risk factors require closer monitoring**

**Lower GA, jaundice within 24 hrs, predischage TSB or TSB close to phototherapy threshold, hemolysis any cause, phototherapy before discharge, family Hx RBC membrane disorder or requiring phototherapy/exchange transfusion, breastfeeding WITH SUBOPTIMAL INTAKE, scalp hematoma, Down syndrome, macrosomic infant diabetic mother**



# Bilirubin screening

- **Infants with neurotoxicity risk factors require closer follow-up and use separate phototherapy and exchange transfusion thresholds (still by age in hours and GA)**

**GA < 38 wk, albumin < 3.0 g/dL, isoimmune hemolytic dz or any other hemolysis, sepsis, significant clinical instability previous 24 hr**

- **Infants receiving phototherapy should have Hgb/Hct or CBC and DAT if mother antibody positive or type O**
- **Follow-up infant NOT receiving phototherapy**  
**Driven by phototherapy threshold minus TSB/TCB**  
**Anywhere from 4-24 hr to clinical judgement ( $\geq 5.5$  mg/dL below phototherapy threshold)**

# 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)**
  - **New guidelines support universal screening, don't address balance of harm vs benefit other than slight increase phototherapy thresholds**



# Laboratory reference ranges for total bilirubin first 14 days life

- Was very difficult when Bhutani nomogram was used for interpretation
- Essentially impossible now, need to consider
  - Gestational age, neurotoxicity risk factors, age of life in hours
- Direct providers to external or internal calculator that can define risk and direct appropriate action (e.g. [bilitool.org](http://bilitool.org))

# 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?**
  - Bhutani risk zones: Low, low intermediate, high intermediate, high risk by bilirubin conc and age in hrs**
- **Studies done to determine whether high-intermediate or high risk TCB value predicted high-intermediate or high risk serum value by Bhutani nomogram, which is no longer in AAP guidelines**



# 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**

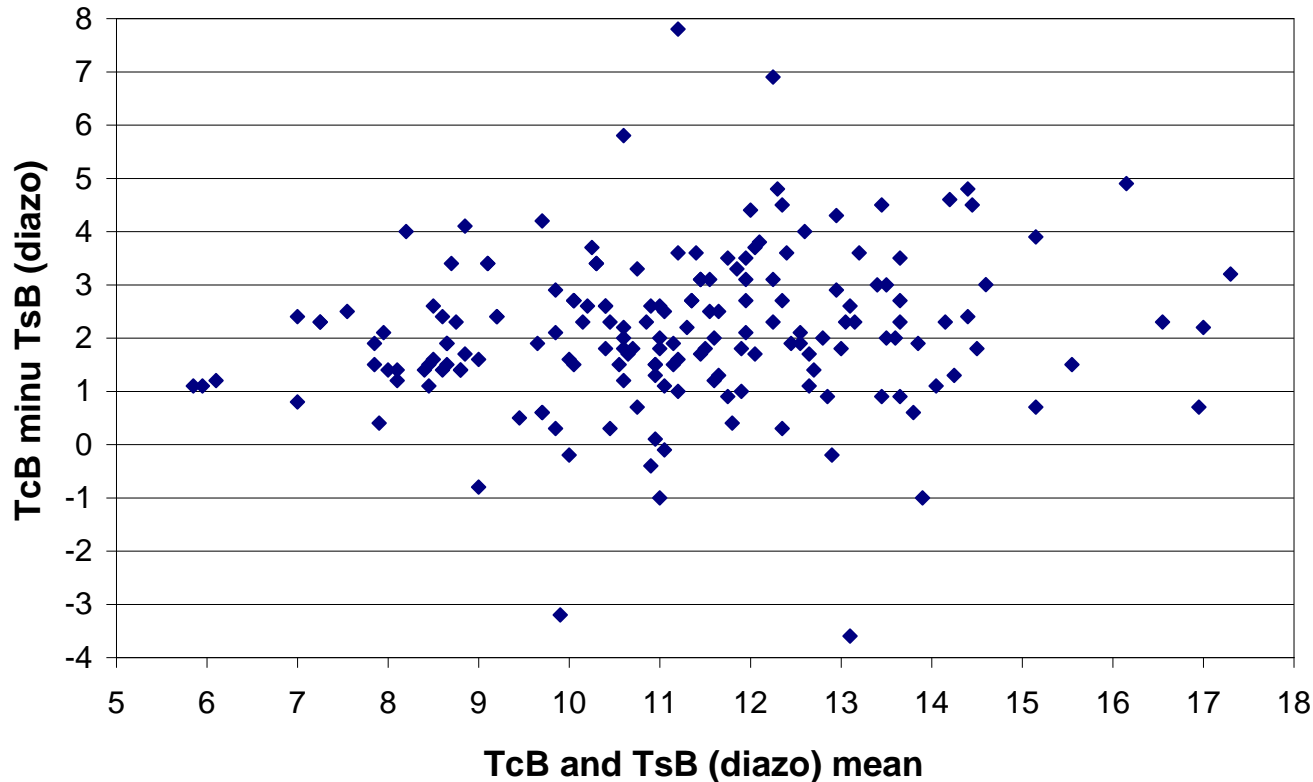
- **200 infants with clinical suspicion hyperbilirubinemia**
- **Measure BiliChek TcB within 30 minutes of serum bilirubin drawn**
- **Measure serum bilirubin diazo (current) method and direct photometric measurement of unconjugated bilirubin (Vitros)**
- **Record gestational age, postnatal age (hours), 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

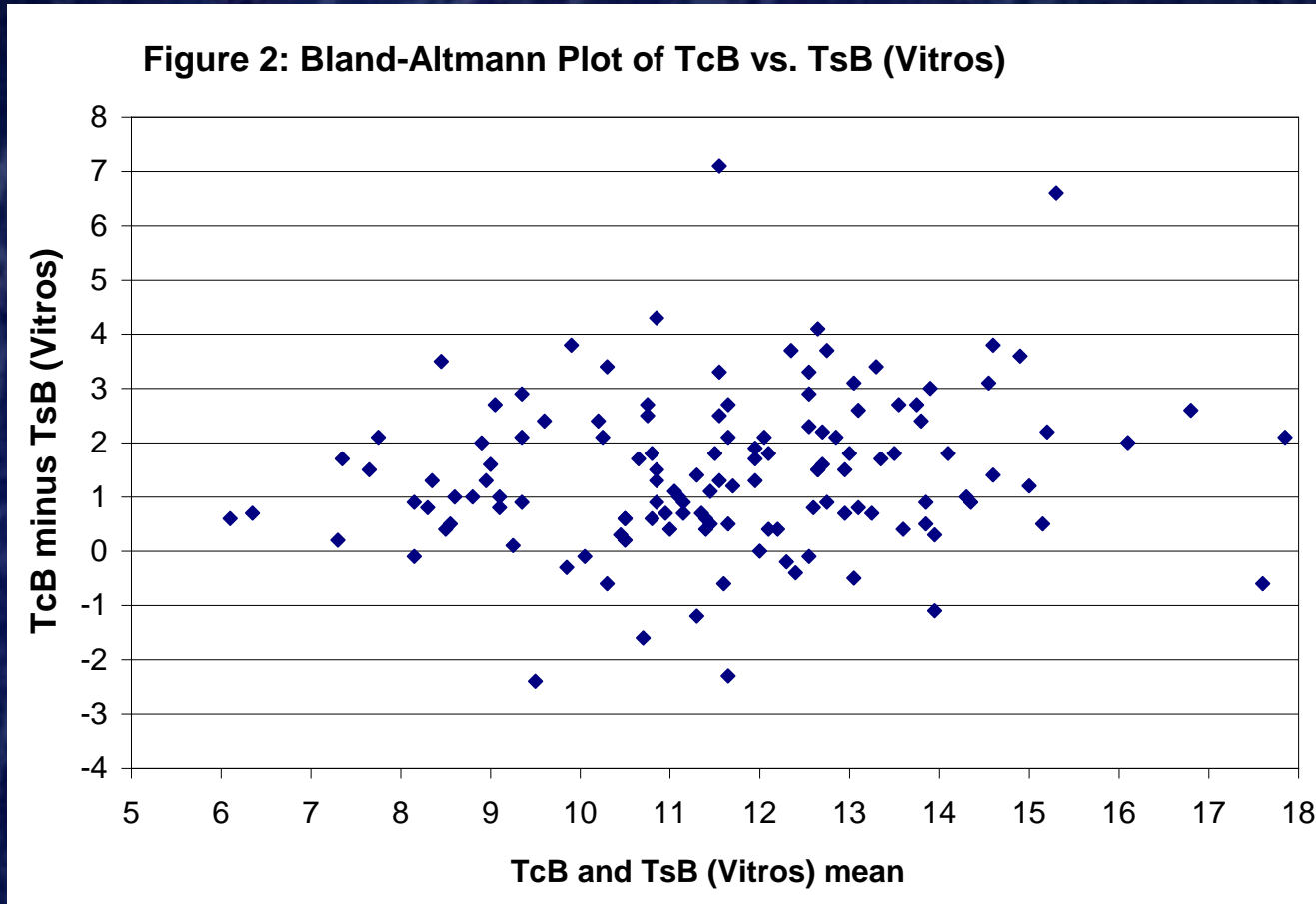
Figure 1: Bland-Altman Plot of TcB vs. TsB (diazo)



**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

Serum bilirubin (diazo)	Transcutaneous bilirubin		
	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

**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 age-adjusted interp of values based upon observed 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 screening 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

- 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



# Universal screening after 2022 AAP guidelines

- Two things have changed
- BiliChek device no longer manufactured
  - Our protocol based upon observed BiliChek minus Roche Tbili bias
- 2022 AAP guidelines
  - New consensus phototherapy thresholds by GA and age in hrs, follow-up decisions based upon how close to phototherapy threshold
  - Recommend TSB if TCB within 3 mg/dL phototherapy threshold or  $\geq 15$  mg/dL
  - Given allowable bias (3 mg/dL) likely very sensitive, how specific?

# Conclusions

- **Universal TcB screening of infants developed based upon observed bias between TcB to local TSB**
- **Protocol allows for age-adjusted TcB interpretation per 2004 AAP guidelines**
- **Universal TcB screening shifted distribution serum bilirubin values and reduced number infants with high TSB**
- **Protocol design (bias and age-adjusted interp) did not result in increased utilization as measured by rate of blood draws or phototherapy**
- **Need to study effect of new AAP guidelines on rate of blood draws, should not affect rate phototherapy as based upon TSB**



# Acknowledgements

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