

Neonatal Hyperbilirubinemia Updates



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DOERNBECHER
CHILDREN'S
Hospital

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- Ellen Laves, MD, Carrie Phillipi, MD, PhD, and Mina Tahai, MD (for many of the slides)
- Tom Newman, MD, MPH (for all the learnings)

Learning Objectives

1. Review the basic pathophysiology of neonatal hyperbilirubinemia
2. Understand the AAP's clinical practice guidelines for hyperbilirubinemia in newborns ≥ 35 weeks
3. Review outcomes of guidelines implementation and emerging data about the possible risks associated with phototherapy
4. Discuss Northern California Neonatal Consortium Consensus Guidelines for Screening & Management

Neonatal Jaundice

60% of healthy newborns will have clinical jaundice



Why Newborns?

- **Increased bilirubin production** (\uparrow Hgb & short RBC lifespan)
- **Limited bilirubin-binding capacity** (low serum albumin)
- **Decreased conjugation** (\downarrow glucuronosyl-transferase activity)
- **Decreased excretion** leading to reabsorption in the bowel (bowel flora, intestinal motility, stool frequency, caloric intake, and feeding frequency)

What's the significance?

Acute bilirubin encephalopathy:

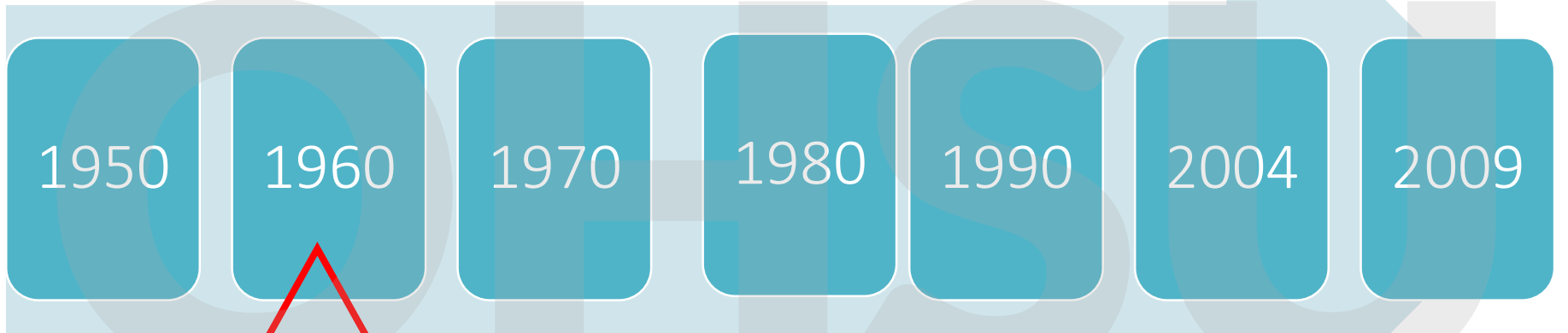
- Lethargy → stupor
- Hypotonia → hypertonia → retrocolis-opisthotonus
- Poor feeding, shrill cry

Kernicterus (chronic bilirubin encephalopathy):

- Extrapyrmidal signs (athetosis), severe delays/MR
- Sensorineural hearing loss
- Gaze palsies
- Dental dysplasia



20!



↓ BF rates

The Kinder, Gentler Era
↑ BF rates

Reduced <30
More phototherapy
Reduced kernicterus???

1950

1960

1970

1980

1990

2004

2009

Rhogam

Vigintiphobia

AAP Policy Shift
Universal
Screening

USPSTF
Statement

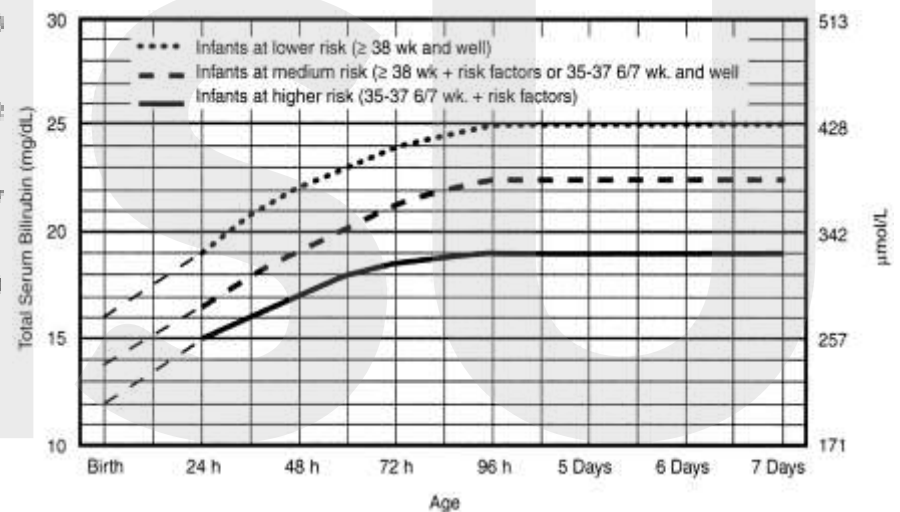
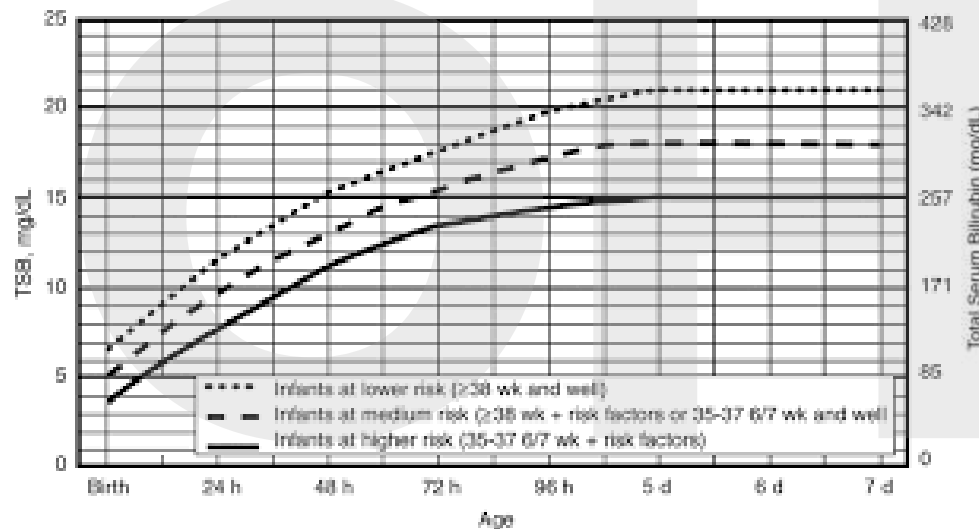
Exchange
Transfusions

Phototherapy

2004 AAP Guidelines

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant's age in hours.
6. Recognize that infants at less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

AAP Guideline Graphs



- 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 $\mu\text{mol/L}$) 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.

Effect of Universal Screening

[Kuzniewicz et al. 2009](#) 38,182 infants.

10.6% were born at facilities with universal bilirubin screening.

Compared with infants born at facilities that were NOT screening:

- 62% lower incidence of TsB levels over the AAP threshold (0.17% vs 0.45%; $P < .001$),
- Had twice the rate of inpatient phototherapy (9.1% vs 4.2%; $P < .001$), and
- Had slightly longer birth hospitalization lengths of stay (50.9 vs 48.7 hours; $P < .001$).

Effect of Universal Screening

- Only 56% of those who received phototherapy had TsB above threshold, compared with 70% in facilities without universal screening.

OHSU

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Is this the right approach?

Phototherapy NNT

Newman, et al 2009

281,898 AGA infants born ≥ 35 weeks' gestation at 12 Northern California Kaiser hospitals from 1995 to 2004.

- 22,547 with a TsB within 3 mg/dL of the AAP phototherapy threshold
- Used multiple logistic regression to estimate the efficacy of hospital phototherapy in preventing the bilirubin level from exceeding the 2004 guideline's exchange transfusion threshold within 48 hours.

NNTs (95% CI)

Gestational Age, wk	Age at Qualifying TSB: <24 h	Age at Qualifying TSB: 24 to <48 h	Age at Qualifying TSB: 48 to <72 h	Age at Qualifying TSB: ≥72 h
Boys				
35	14 (7–40)	26 (14–57)	83 (36–190)	171 (70–426)
36	10 (6–19)	19 (12–39)	59 (31–101)	122 (68–236)
37	16 (10–28)	29 (20–58)	95 (52–168)	196 (100–407)
38	35 (14–100)	67 (31–215)	222 (107–502)	460 (196–1352)
39	74 (31–244)	142 (62–554)	476 (197–1385)	989 (373–3607)
40	106 (44–256)	204 (98–487)	682 (367–1294)	1419 (634–3755)
≥41	148 (54–428)	284 (127–780)	953 (366–3017)	1983 (676–8408)
Girls				
35	21 (12–49)	40 (21–86)	126 (50–267)	261 (105–585)
36	15 (11–26)	28 (20–51)	90 (43–146)	186 (102–347)
37	23 (16–39)	44 (31–75)	145 (73–243)	300 (146–671)
38	53 (23–134)	102 (43–236)	339 (154–730)	705 (314–2016)
39	113 (58–342)	217 (103–713)	729 (272–1730)	1516 (614–4520)
40	162 (75–400)	312 (164–704)	1046 (491–2136)	2176 (922–6107)
≥41	226 (92–702)	435 (183–1140)	1461 (510–4842)	3041 (888–11096)

Table 4: Newman et al *Pediatrics*. 2009 May ; 123(5): 1352–1359. doi:10.1542/peds.2008-1635

In the Setting of Universal Screening, do Infants Exceed Exchange Transfusion Levels?

Flaherman et al., 2012 ~ 18,000 newborns (2005-2007) in the KP Northern California Hospitals after the implementation of universal screening

- 22 infants (14 infants <38 weeks) exceeded exchange transfusion threshold
- Only 1 received an ET
- **No documented sequelae**

In the Setting of Universal Screening, do Infants Exceed Exchange Transfusion Levels?

- Screening TsB was at least “high-intermediate risk” for all 22 infants and “high-risk” for all ≥ 38 weeks.
- 4 outcomes may be attributable to incomplete adherence to AAP guideline
- 13 might have been prevented by better adherence to AAP *follow-up* guideline

BUT...

- Re-testing would have required **2166** additional bilirubin tests to prevent (at most) 13 outcomes

Jaundice Outcomes

Wickremasinghe, et al 2015

- **SNHL**: Only bilirubin levels ≥ 10 mg/dl above exchange transfusion thresholds (or ≥ 35 mg/dl) were associated with a significantly increased risk

Wu, et al 2015

- **Cerebral Palsy** consistent with kernicterus occurred only in infants with 2+ risk factors for NT and TsB >5 mg/dl above exchange transfusion threshold

Vandborg, et al 2012

- No significant difference in **development** at age 1-5 years (ASQ) in infants with a peak serum bilirubin over 25mg/dl

Who Gets Kernicterus?

Kuzniewicz et al 2014: Kaiser Northern California.

525,409 infants ≥ 35 weeks gestation between 1995-2011

- 47 infants identified with TsB ≥ 30 (8.6 per 100,000 births)
- Median follow up 7.9 years

TABLE 3 Characteristics of Infants With CBE

Case no.	Gestational Age, wk	Peak TSB, mg/dL	Seizures	SNHL	CP	G6PD Activity, U/g Hb	Sepsis	Coombs Test
1	35	38.2	No	Yes	No	Not tested	No	Negative
2	38	40.7	Yes	Yes	No	0.8	No	Negative
3	36	49.1	Yes	Yes	Yes	7.6	Yes	Negative
4	36	48.5	Yes	Yes	Yes	6.6	No	Negative

Are there risks of
phototherapy?

OHHSU

Does Phototherapy affect Breastfeeding?

Waite, et al 2016: small reduction in breastfeeding rates at 12 months and in exclusivity at 1, 2, and 4 months

TABLE 2. RATES OF ANY BREASTFEEDING AND EXCLUSIVE BREASTFEEDING BY MONTH FOR PHOTOTHERAPY EXPOSED AND PHOTOTHERAPY UNEXPOSED INFANTS

	<i>Breastfeeding rate in phototherapy exposed, N= 220</i>	<i>Breastfeeding rate in phototherapy unexposed, N= 4,016</i>	<i>OR (95% CI)</i>
	<i>n (%)</i>	<i>n (%)</i>	
Any breastfeeding			
Month 1	186 (86.1)	1,813 (85.4)	1.14 (0.71–1.81)
Month 2	137 (75.3)	1,360 (74.8)	1.18 (0.78–1.78)
Month 4	108 (65.1)	1,069 (67.2)	1.03 (0.70–1.53)
Month 6	85 (54.5)	889 (59.9)	0.88 (0.60–1.27)
Month 9	66 (43.7)	695 (49.9)	0.80 (0.56–1.15)
Month 12	29 (20.7)	406 (31.4)	0.58 (0.37–0.91)
Exclusive Breastfeeding			
Month 1	81 (37.5)	1,022 (48.1)	0.69 (0.49–0.95)
Month 2	57 (31.3)	767 (42.2)	0.69 (0.48–0.99)
Month 4	29 (17.5)	462 (29.0)	0.57 (0.36–0.88)

ORs based on logistic regression adjusting for maternal age, race, maternal education, household income, gestational age, prenatal intention to breastfeed, supplemental formula use on day of life 1, and breastfeeding problems in the first 2 weeks of life.

OR, odds ratio.

Does Phototherapy lead to increased Seizure Risk?

Maimburg et al 2016

- Increased risk of epilepsy among children treated with phototherapy, the association was seen only in boys (adjusted HR 1.98, 95% CI: 1.40–2.78)

Newman, et al 2018

- Increased risk of epilepsy, adjusted hazard ratio (aHR) of 1.22 (95% CI: 1.05 to 1.42; P = 0.009)
- Boys were at higher risk of seizures overall (aHR = 1.18; 95% CI: 1.10 to 1.27) and had a higher aHR for phototherapy (1.33; 95% CI: 1.10 to 1.61)

Is Phototherapy linked to Childhood Cancer?

Newman et al 2016

Retrospective cohort study of 525,409 children born at ≥ 35 weeks' gestation between 1995-2011 at 15 KPNC hospitals

Exclusions: death, transfer, lost to follow-up at < 60 days, cancer dx before 60 days

- Initial crude IRRs were uniformly positive with low p-values.
- After adjusting for confounding were no longer significant

Upper limit of the hazard ratios is most concerning for infant's with Down syndrome with the NNH being 23 at the upper limit

Cancer Type

Hazard Ratio

Any Cancer ($N = 711$)

Crude IRR

Stepwise Cox

Restricted PS

Any Leukemia ($N = 223$)

Crude IRR

Stepwise Cox

Restricted PS

Lymph. Leukemia ($N = 169$)

Crude IRR

Stepwise Cox

Restricted PS

Nonlymph. Leukemia ($N = 54$)

Crude IRR

Stepwise Cox

Restricted PS

Kidney Cancer ($N = 26$)

Crude IRR

Stepwise Cox

Restricted PS

Bone Cancer ($N = 13$)

Crude IRR

Stepwise Cox

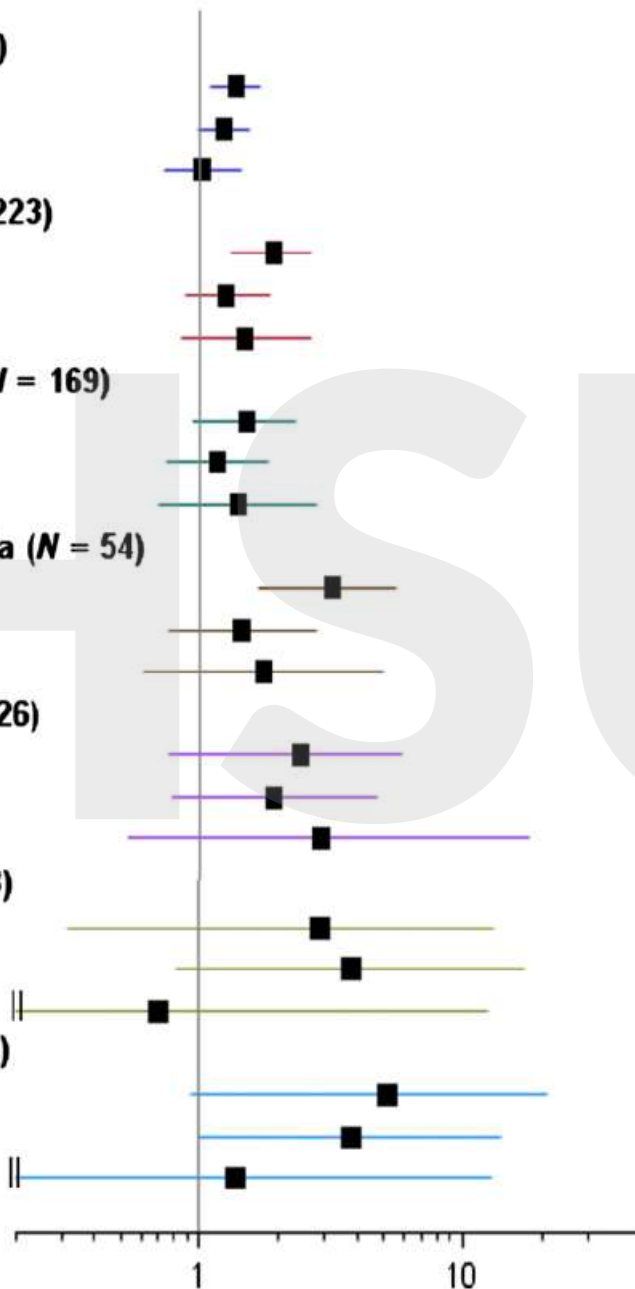
Restricted PS

Liver Cancer ($N = 12$)

Crude IRR

Stepwise Cox

Restricted PS



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Is phototherapy worth even a small risk?

Development of the NCNC Guidelines

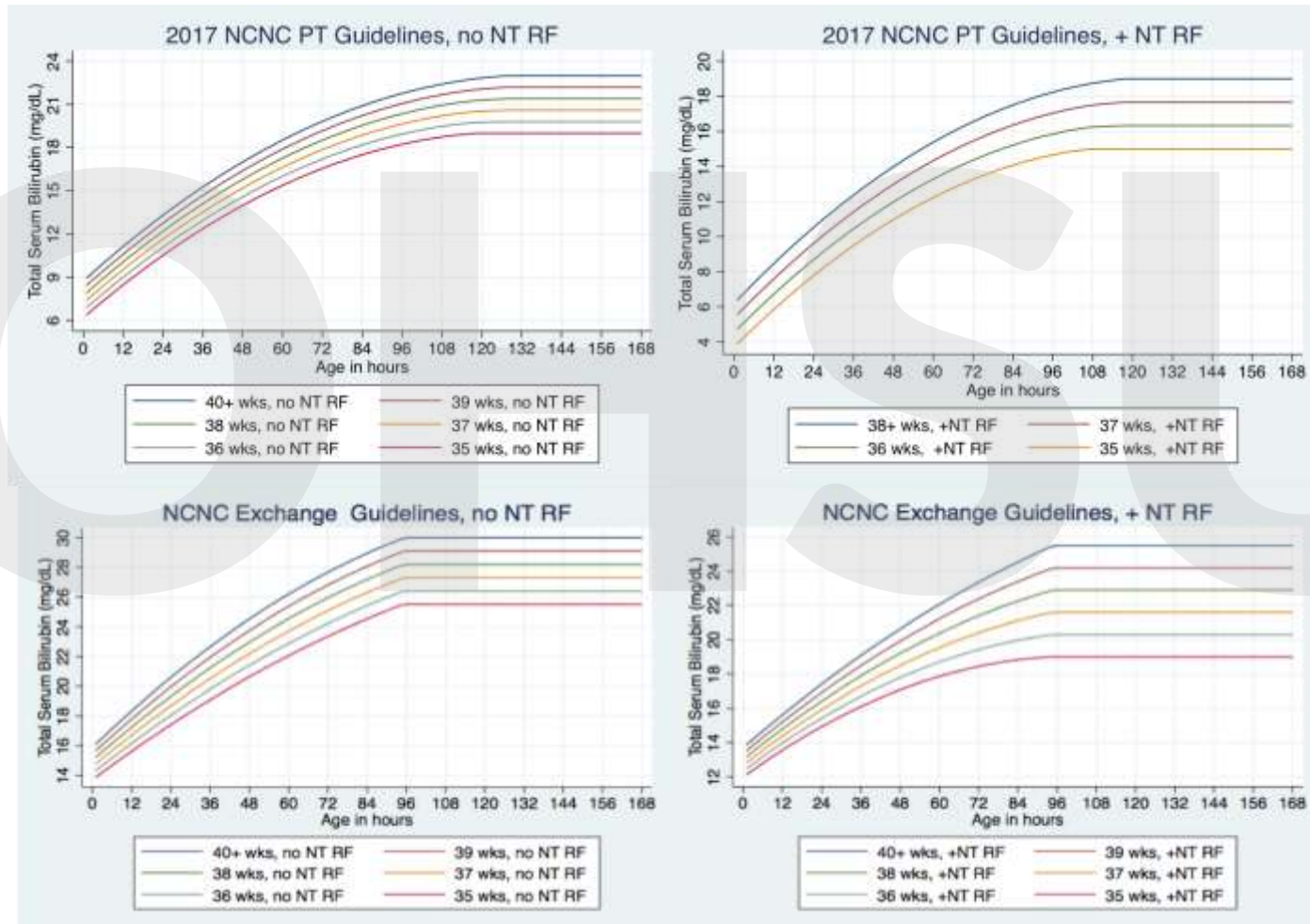
Based on concerns that the 2004 AAP Guideline was based on limited evidence, internally inconsistent and recommend a significant practice shift at 38 weeks gestation, the UCSF Northern California Neonatal Consortium members came together to:

- Update hyperbilirubinemia clinical practice based on recent research
- Draw on the KP Northern California experience with updated clinical practice guidelines

Full executive summary and recommendations:

http://www.phototherapyguidelines.com/NeoHyperbilirubinemiaGuidelineFINAL_2018-0209.docx

NCNC Graphs



www.phototherapyguidelines.com

NCNC Hyperbilirubinemia Treatment Guideline

This tool is designed to help guide phototherapy and other treatment decisions in newborns of at least 35 weeks gestational age. The treatment thresholds are based upon expert opinion of members of the [Northern CA Neonatal Consortium](#) (NCNC) and do not determine standard of care. The current (2004) treatment thresholds of the American Academy of Pediatrics (AAP) are provided as a comparison. (See the complete [NCNC Neonatal Hyperbilirubinemia Guideline](#) or [treatment guideline graphs](#).)

This calculator is intended to provide a user-friendly interface to the NCNC guidelines. Professional judgment should be used in applying the results in clinical settings.

Gestational Age

Weeks (35-42)

40 ▾

Days (0-6)

1 ▾

Total Serum Bilirubin Level

mg/dL (0-50)

21

Age at Collection

Hours (0-168)

168

OR

Get age from dates

Calculate

Clear

Calculated results for the data you entered:

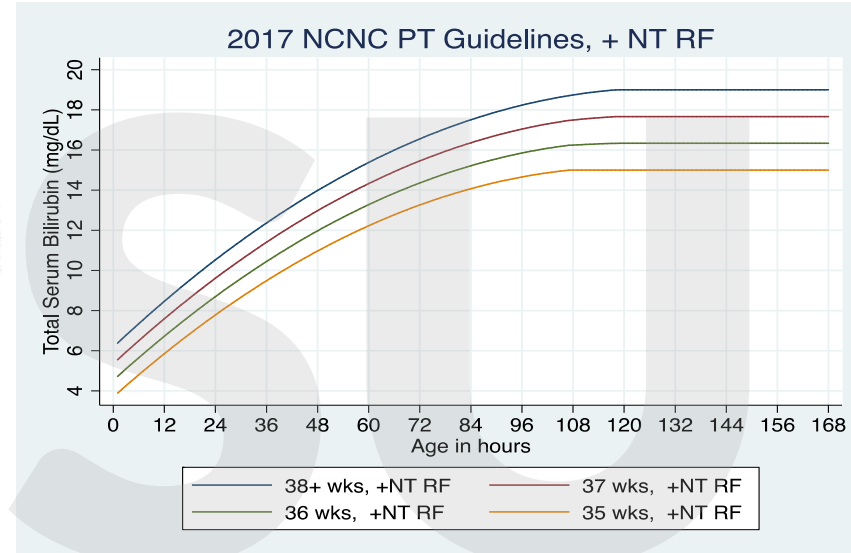
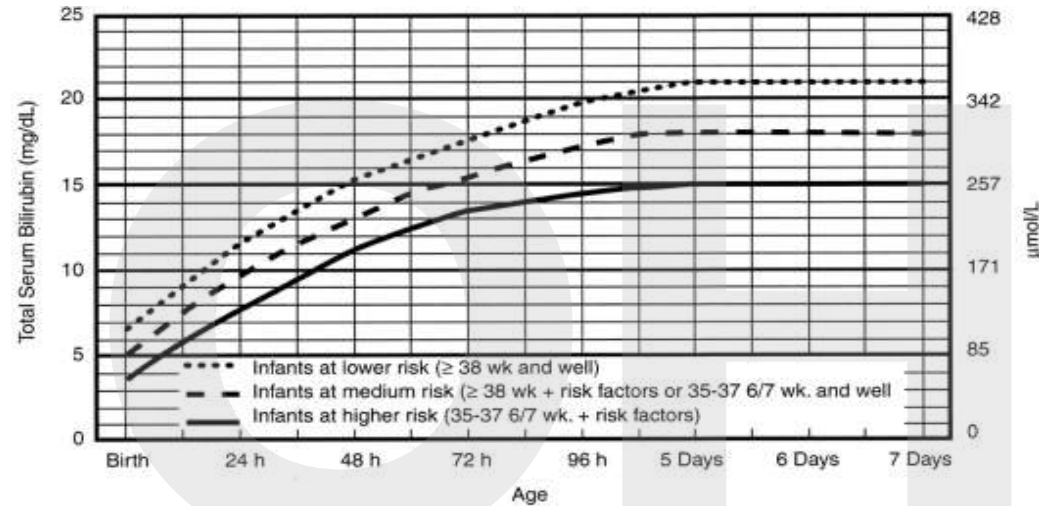
Neurotoxicity risk factors*	Start phototherapy?	NCNC Phototherapy Threshold	NCNC Exchange Transfusion Threshold	Within 2 mg/dL of Exchange Transfusion Threshold?
ABSENT	No	23.0	30.0	No
PRESENT	Yes	19.0	25.5	No

NCNC Definition of Neurotoxicity Risk Factors

Neurotoxicity risk factors include:

- Isoimmune hemolytic disease, G6PD deficiency, or other hemolytic disease
- Sepsis or suspected sepsis (sufficient to be currently on antibiotics)
- Acidosis ($\text{BE} \leq -8$ meq/L or $\text{pCO}_2 > 50$ mmHg within the last 24 hr)
- Albumin < 3.0 mg/dL
- Any clinical instability

AAP vs. NCNC (with risk factors)



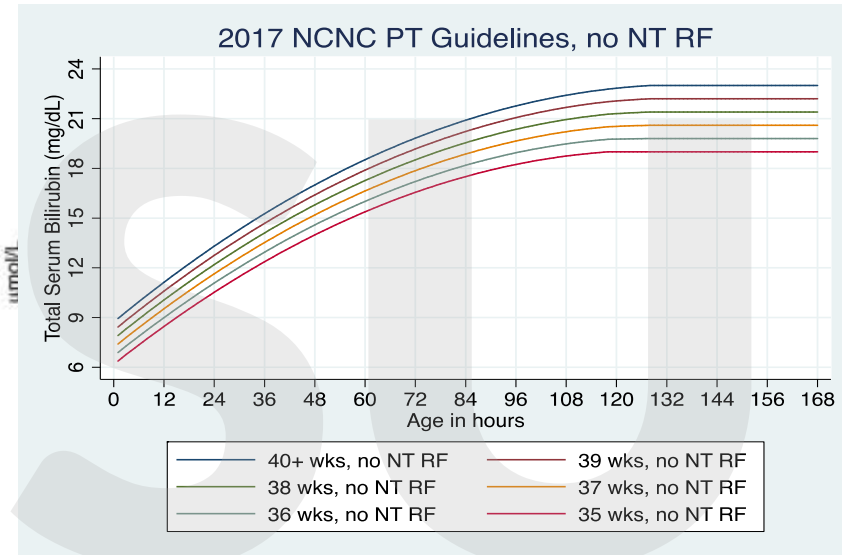
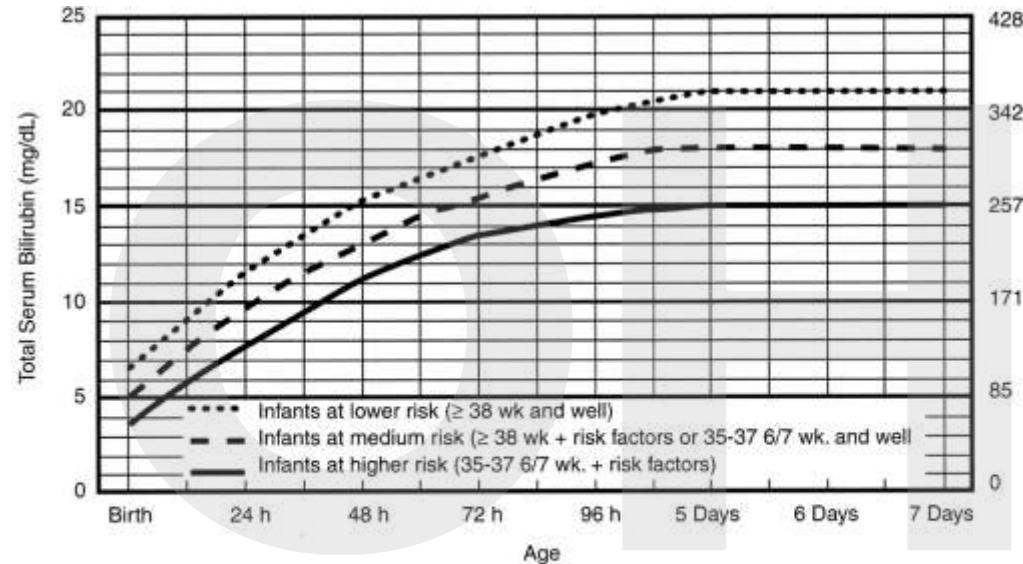
Examples for **with neurotoxicity risks**, 168 HOL infant

40 1/7 NCNC threshold = 19 (vs. 18) Exchange = 25.5 (vs. 22.5)

38 1/7 NCNC threshold = 19 (vs. 18) Exchange = 23.1 (vs. 22.5)

35 1/7 NCNC threshold = 15.2 (vs. 15) Exchange = 19.2 (vs. 19)

AAP vs. NCNC (no risk factors)



Examples for **no** neurotoxicity risks, 168 HOL infant

40 1/7 NCNC threshold = 23 (vs. 21) Exchange = 30.0 (vs. 25)

38 1/7 NCNC threshold = 21.5 (vs. 21) Exchange = 28.3 (vs. 25)

35 1/7 NCNC threshold = 19.1 (vs. 18) Exchange = 25.6 (vs. 22.5)

Case Comparisons

A baby boy in clinic is noted to have jaundice at 48 hours of life. Mother is AB+/Ab-, she is expressing colostrum and exclusively breastfeeding. The baby is feeding well with appropriate output. This is mom's third baby. Infant's weight is down 7% from birth weight. There is slight facial bruising, but no cephalohematoma. TSB is obtained and is 15.5 mcg/dL.

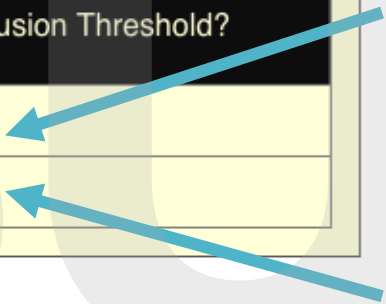
- Let's look at AAP vs. NCNC recommendations for a 41w1d, 37w 6d and 36w2d week gestational age infant

41w1d:

AAP vs. NCNC Recommendations


Calculated results for the data you entered:

Neurotoxicity risk factors *	Start phototherapy?	NCNC Phototherapy Threshold	NCNC Exchange Transfusion Threshold	Within 2 mg/dL of Exchange Transfusion Threshold?
ABSENT	No	17.0	24.5	No
PRESENT	Yes	14.0	20.6	No



For comparison purposes, here are approximate American Academy of Pediatrics' 2004 guideline phototherapy thresholds:

Neurotoxicity risk factors *	Start phototherapy?	AAP Phototherapy Threshold
ABSENT	Yes	15.0
PRESENT	Yes	13.0



37w6d:

AAP vs. NCNC Recommendations

Calculated results for the data you entered:

Neurotoxicity risk factors*	Start phototherapy?	NCNC Phototherapy Threshold	NCNC Exchange Transfusion Threshold	Within 2 mg/dL of Exchange Transfusion Threshold?
ABSENT	No	15.7	22.9	No
PRESENT	Yes	13.8	19.1	No

For comparison purposes, here are approximate American Academy of Pediatrics' 2004 guideline phototherapy thresholds:

Neurotoxicity risk factors*	Start phototherapy?	AAP Phototherapy Threshold
ABSENT	Yes	13.0
PRESENT	Yes	11.0

36w6d:

AAP vs. NCNC Recommendations

Calculated results for the data you entered:

Neurotoxicity risk factors*	Start phototherapy?	NCNC Phototherapy Threshold	NCNC Exchange Transfusion Threshold	Within 2 mg/dL of Exchange Transfusion Threshold?
ABSENT	Yes	14.8	21.6	No
PRESENT	Yes	12.3	18.0	Yes - see flow sheet

For comparison purposes, here are approximate American Academy of Pediatrics' 2004 guideline phototherapy thresholds:

Neurotoxicity risk factors*	Start phototherapy?	AAP Phototherapy Threshold
ABSENT	Yes	13.0
PRESENT	Yes	11.0

Next Steps??

Steps that reduce phototherapy, but are still in line with the AAP Guidelines:

- No phototherapy under the AAP thresholds
- Adjust around the medium risk threshold by gestational age

From the 2004 Nomograms Text:

- 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.

Adopt the NCNC Guidelines

- Evidence base is strong
- Insider intelligence is that forthcoming AAP guidelines will not be lower than the NCNC guidelines (2020? 2021?)
- OHSU's ED, Ward, MBU, and clinics adopted the NCNC guidelines **September 9, 2019**

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