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Management of Neonatal Hyperbilirubinemia

David Schutzman

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Hyperbilirubinemia of the Newborn

David Schutzman, MD
7/16/2020

Kernicterus

- Classic Kernicterus
  - Phase 1 – lethargy, hypotonia, poor feeds
  - Phase 2 – hypertonia, high pitched cry
  - Phase 3 – hypotonia
  - Long term – chorioathetoid CP, hearing loss, normal intelligence
  - Histology – neuronal necrosis
- NICU kernicterus
  - No symptomatology
  - “Normal” bilirubin levels
  - Histology – spongy changes and gliosis

How do we get kernicterus?

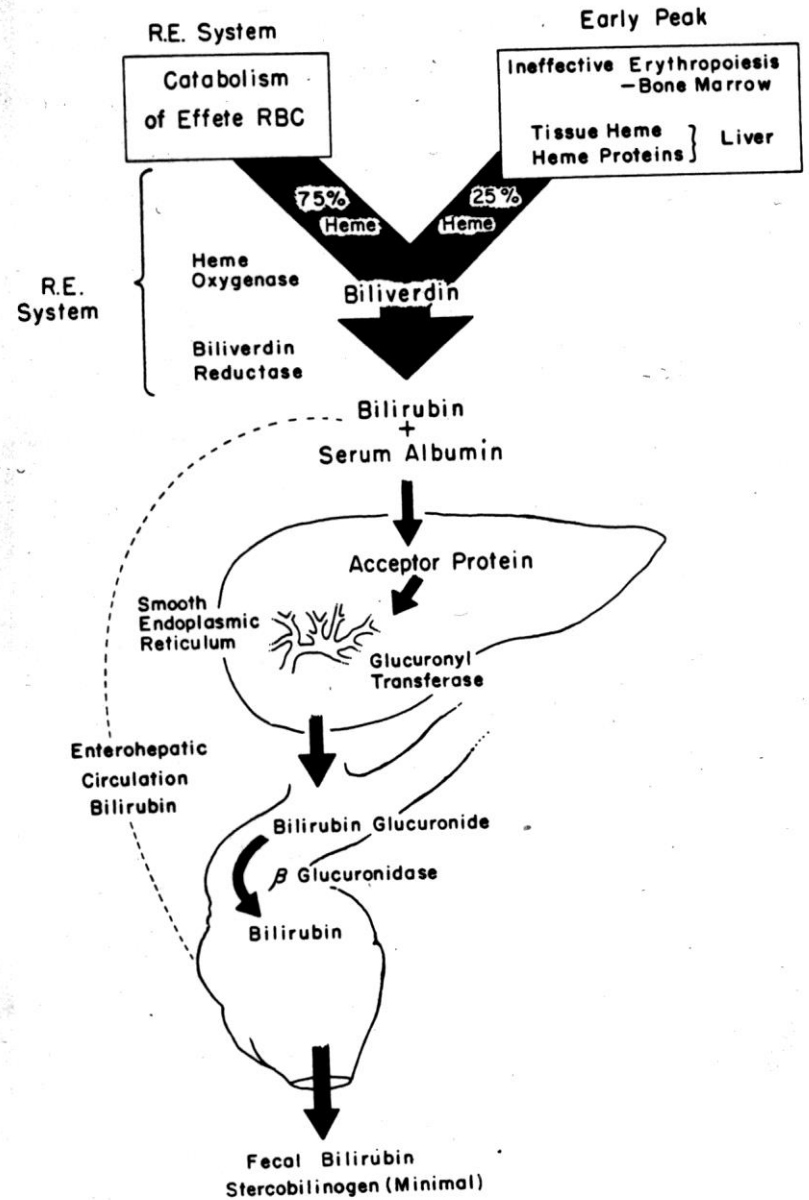


Fig. 27-9. Neonatal bile pigment metabolism.

How does bilirubin enter the brain?

Blood Brain Barrier

- Keeps things out of the brain
- Endothelial lining of the blood vessels
- Excludes most water soluble substances
  - Proteins
  - Large molecules
    - Albumin
    - Albumin with bilirubin attached
- Allows in lipid soluble substances
  - Free bilirubin
- Large complexes enter if the barrier is opened

Free bilirubin hypothesis

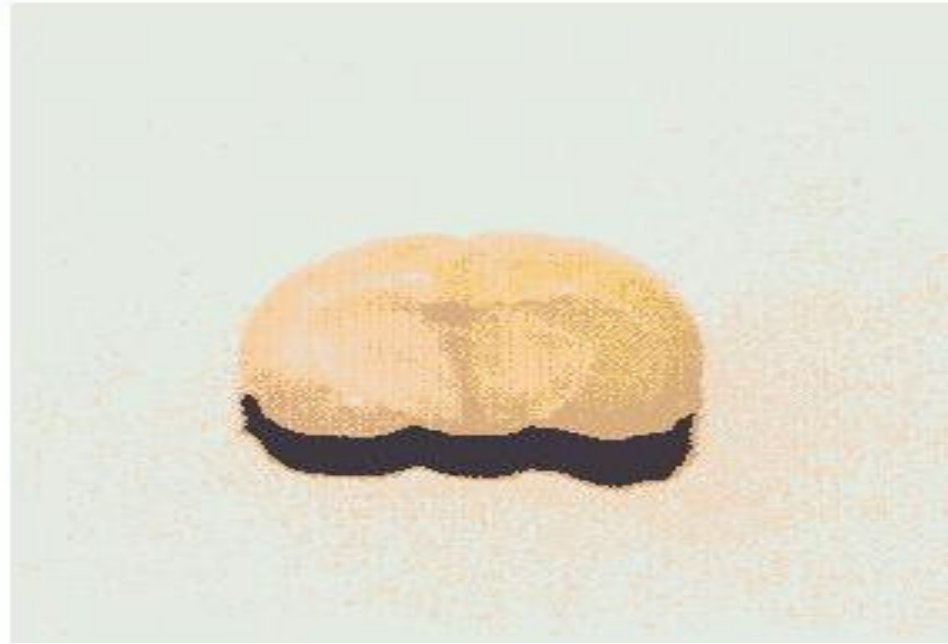
- Bilirubin insoluble at pH 7.4
- Normally bound to albumin in the blood
- Albumin – one high affinity site
  - ≥ one weak affinity sites
- Bilirubin:albumin molar ratio 1:1
  - 1 g albumin binds 8.8 mg bilirubin (if high affinity site completely saturated)
- Term – 3.5 g albumin with 1:1 binding affinity
  - Bili level 31.1 before free bilirubin available
- Preterm – 2 g albumin with only 0.5 binding affinity
  - Bili level 8.9 before free bilirubin available

Displacers of bilirubin

- Free fatty acids – Intralipid
- Drugs
  - Sulfisoxasole
  - Benzyl alcohol
- pH

Factors that open the BBB

- Hypertonic solutions
  - Levine’s rat studies
- Severe asphyxia
- Acidosis
- Meningitis



How does bilirubin cause damage?

- WE DON’T KNOW
- Depress cellular respiration
  - Uncouple oxidative phosphorylation
- Bind specific proteins
- Damage DNA

How do we prevent kernicterus?

Exchange transfusion

- Last resort
- Very invasive
- Double volume exchange
  - Insert central lines
  - Remove and replace aliquots of 1/15 baby's blood volume with O- PRBC reconstituted with AB FFP
  - Repeat (again and again) until replace what's calculated to be twice baby's blood volume
    - y=1-e^{-x}
      - y-fraction of blood removed x-number of exchanges
    - Single volume exchange replaces 63% of blood volume
    - Double volume exchange replaces 87% of blood volume
  - Removes actual circulating bilirubin
  - Removes potential bilirubin

Hsia, DY, Allen FH, Gellis SS, et.al. Erythroblastosis fetalis VIII. Studies of serum bilirubin in relation to kernicterus NEJM 1952;247:668

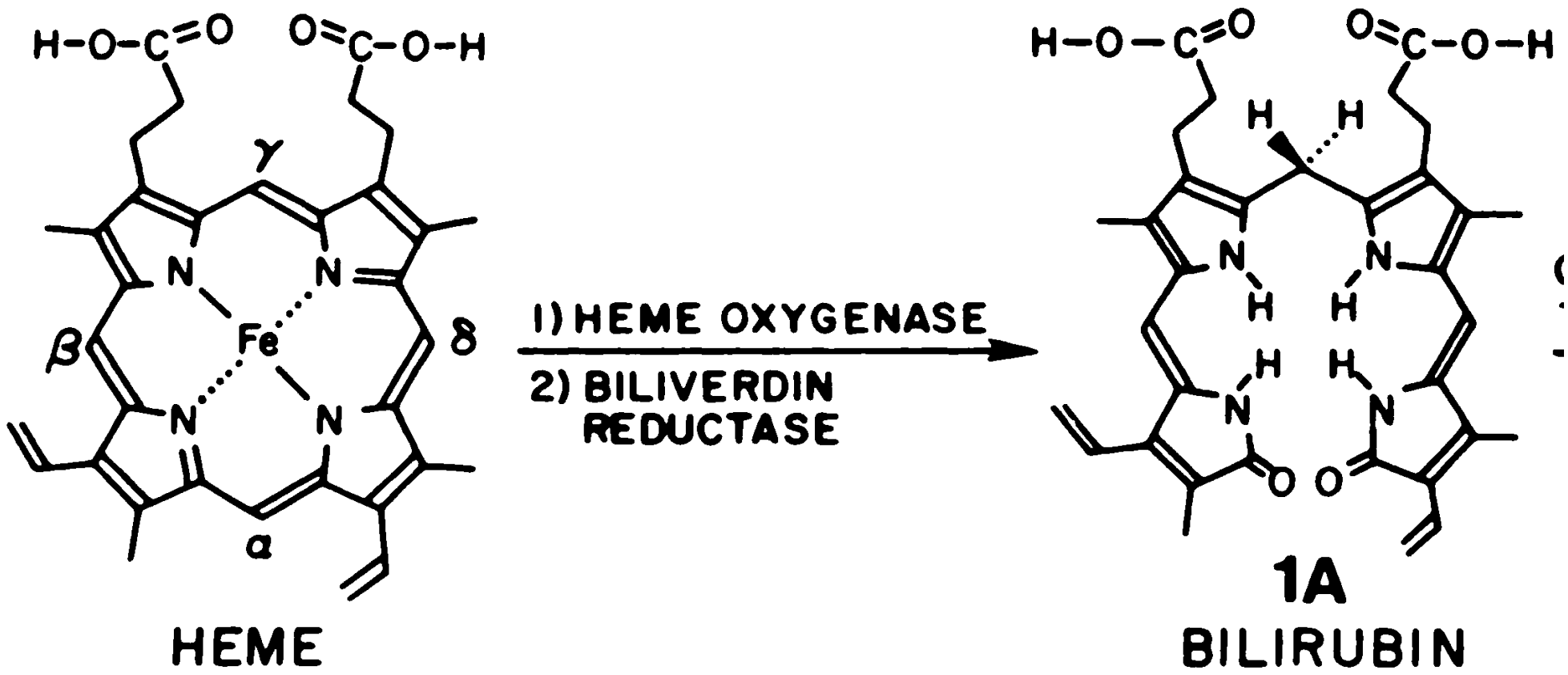
- Retrospective study
- Bilirubin 16-30 18% kernicterus
- Bilirubin >30 50% kernicterus
- Recommended keeping bilirubin <20
  - No kernicterus in their subsequent 200 consecutive cases of erythroblastosis
  - Accumulated these patients in <1 year!

Phototherapy

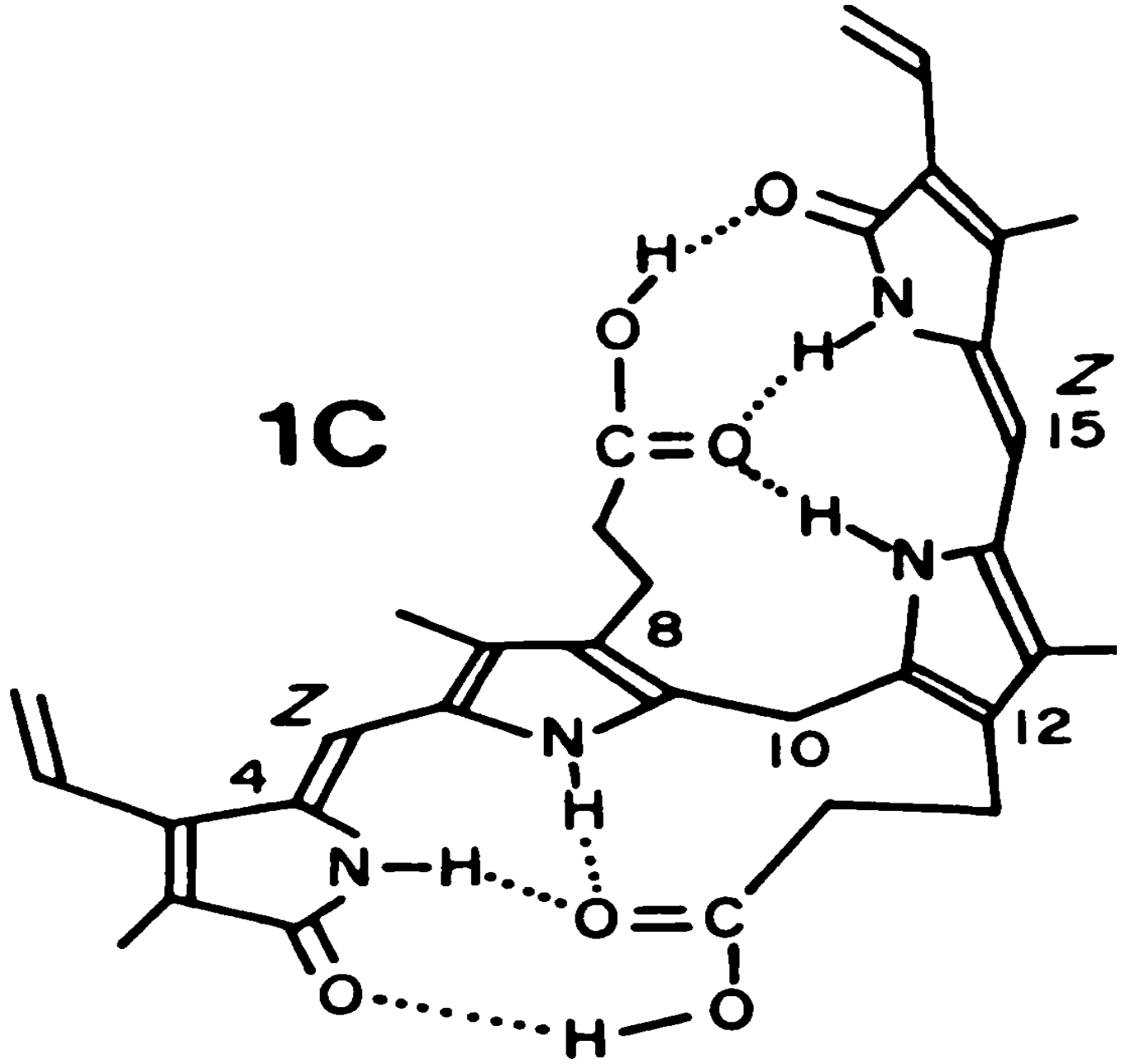
FIG.—*Miss J. Ward. S.R.N., in 1956, with one of the earliest of the infants given phototherapy at Rochford General Hospital.*

33

How does phototherapy work?



1C



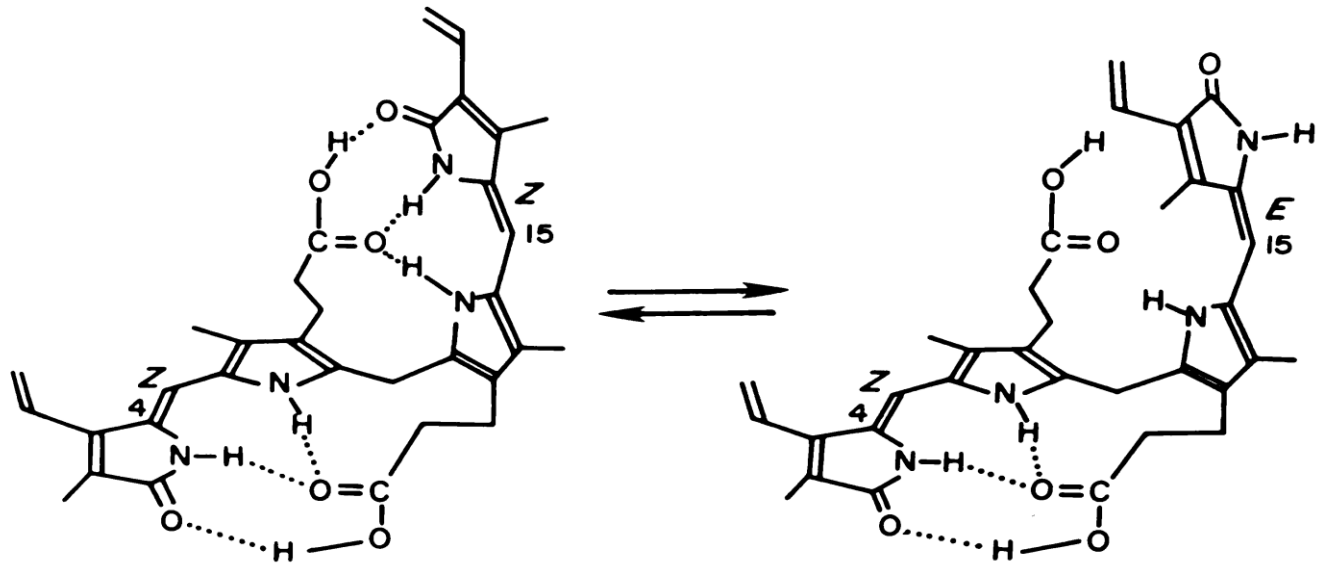


Fig 8. $Z \rightarrow E$ carbon-carbon double bond configurational isomerization of bilirubin in humans.

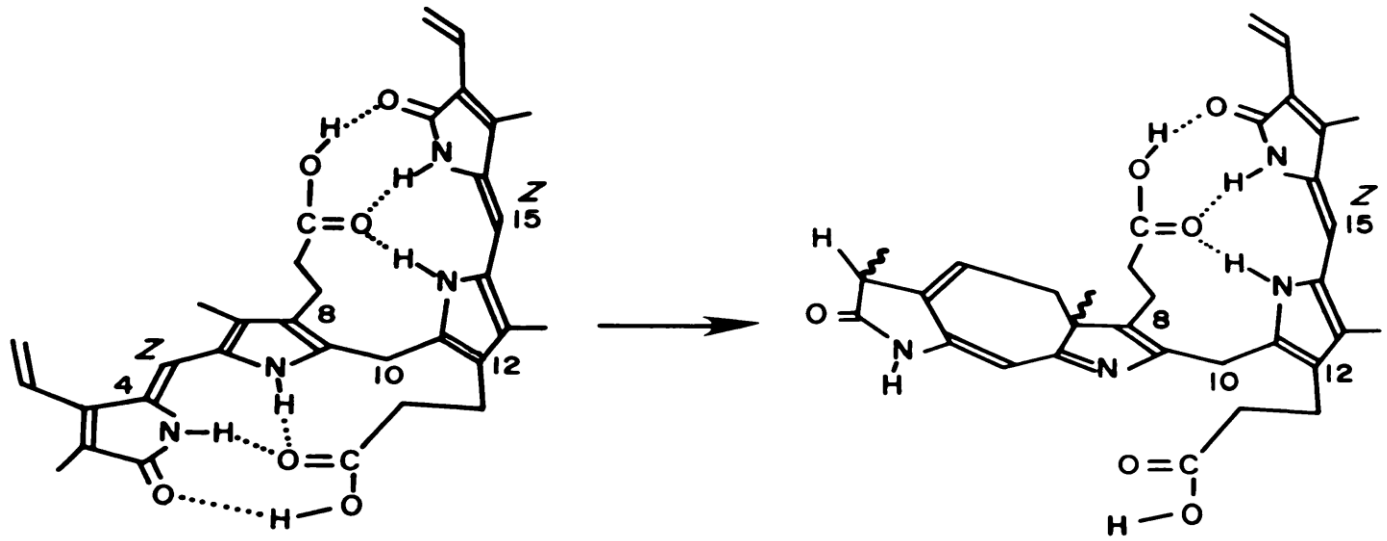


Fig 7. Intramolecular cyclization of bilirubin in presence of light to form lumirubin.

“What did he know and when did he know it?”

What do we do and when do we do it?

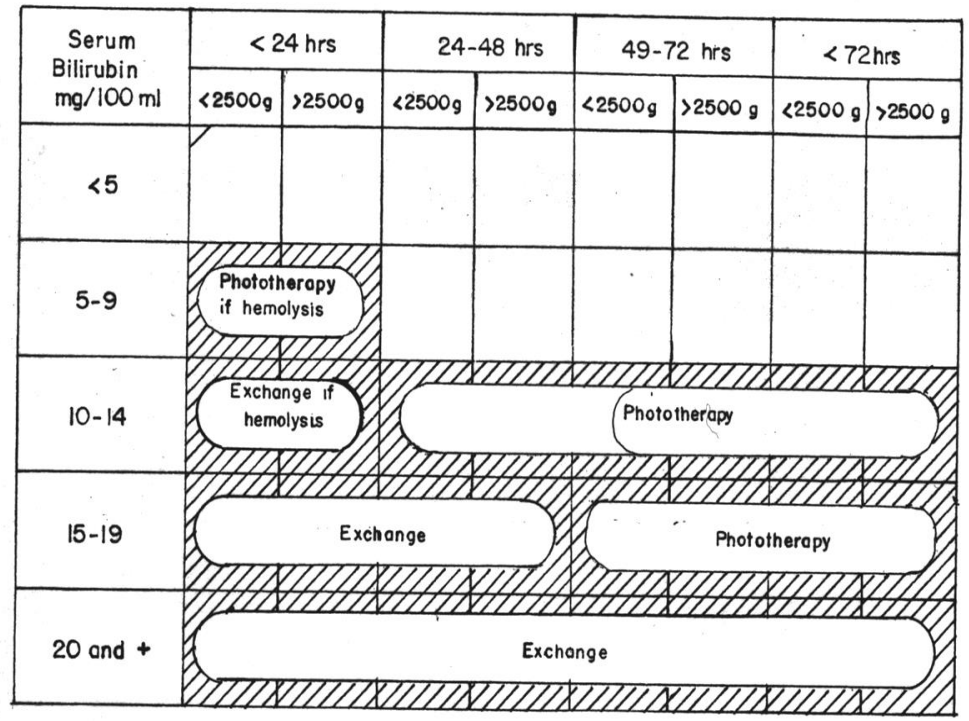
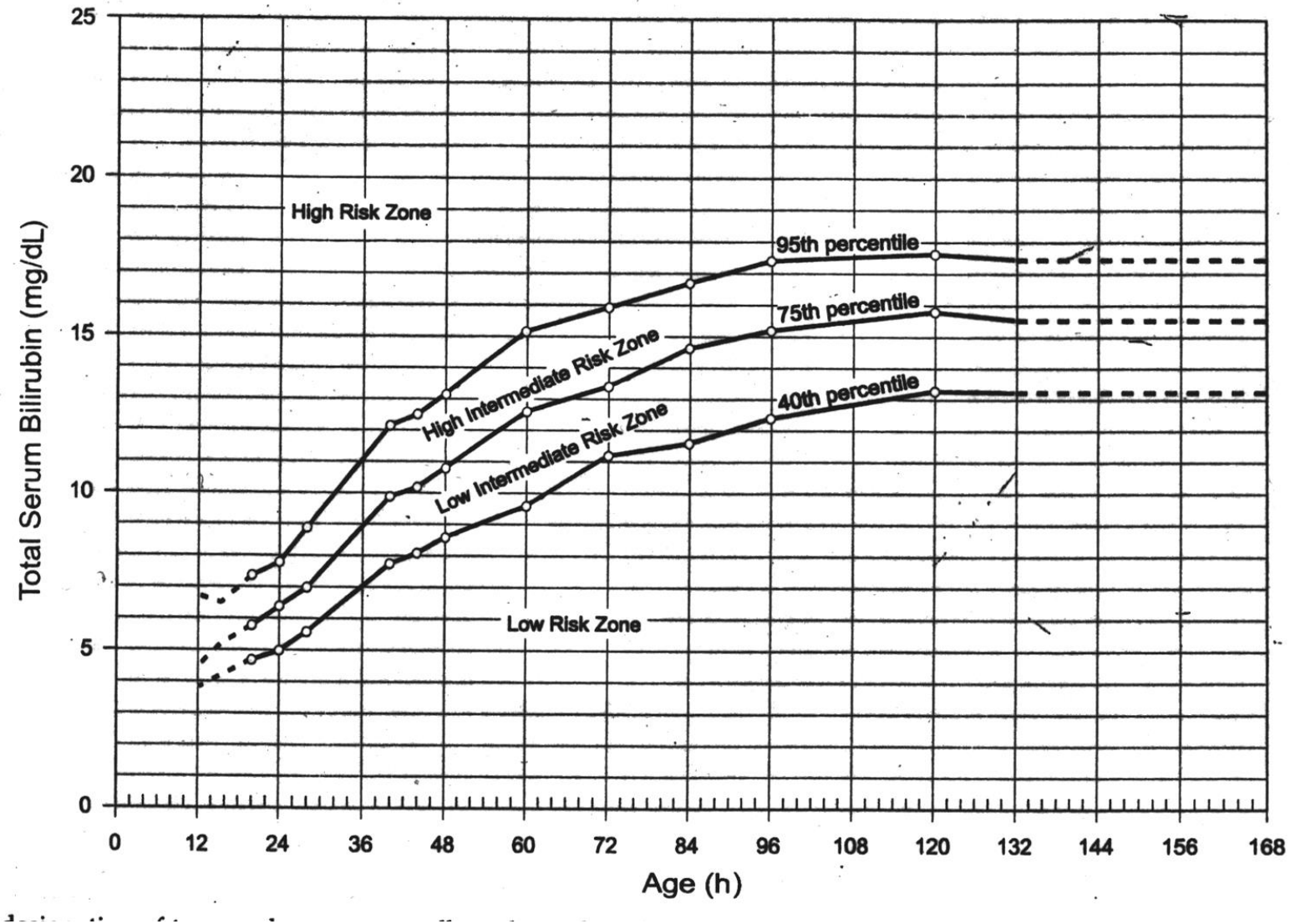


Figure 11–2 Guidelines for the management of hyperbilirubinemia taking age, birth weight, and bilirubin into consideration. (Usage of phototherapy lights in clinical icterus as employed at University Hospitals, Cleveland, Ohio. Courtesy of Dr. M. J. Maisels.)



Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999;103:6-14.

Bhutani Nomogram

- 13,003 healthy term and near term
- Screening TSB at time of newborn screen with age in hours determined
- Racially diverse
- 60% breast fed
- Exclusions
  - Phototherapy before 60 hours of life
  - Hemolysis indicated by DAT+
- 2840 in hospital supervised F/U program

TABLE 3. Predictive Ability of Predischarge TSB in the Percentile-Based Risk Zones for Subsequent Significant Hyperbilirubinemia*

Location of Predictive Predischarge TSB Vector			Outcome: Subsequent Significant Hyperbilirubinemia		Predictive Ability		
Predischarge Hour-specific TSB Risk Zone	Percentiles	Total	Present (P)*	Absent (A)	P:A Ratio†	Probability of Disease	Likelihood Ratio of Disease
High-risk zone	>95th	172	68	104	2:3	2/5	14.08
Upper-intermediate	76th–95th	356	46	310	1:7	1/8	3.20
Lower-intermediate	40th–75th	556	12	544	1:45	1/46	0.48
Low-risk zone	<40th	1756	0	1756	0	0	0
	Total	2840	126	2714	1:22	1/23‡	

Results of Bhutani nomogram for daily practice

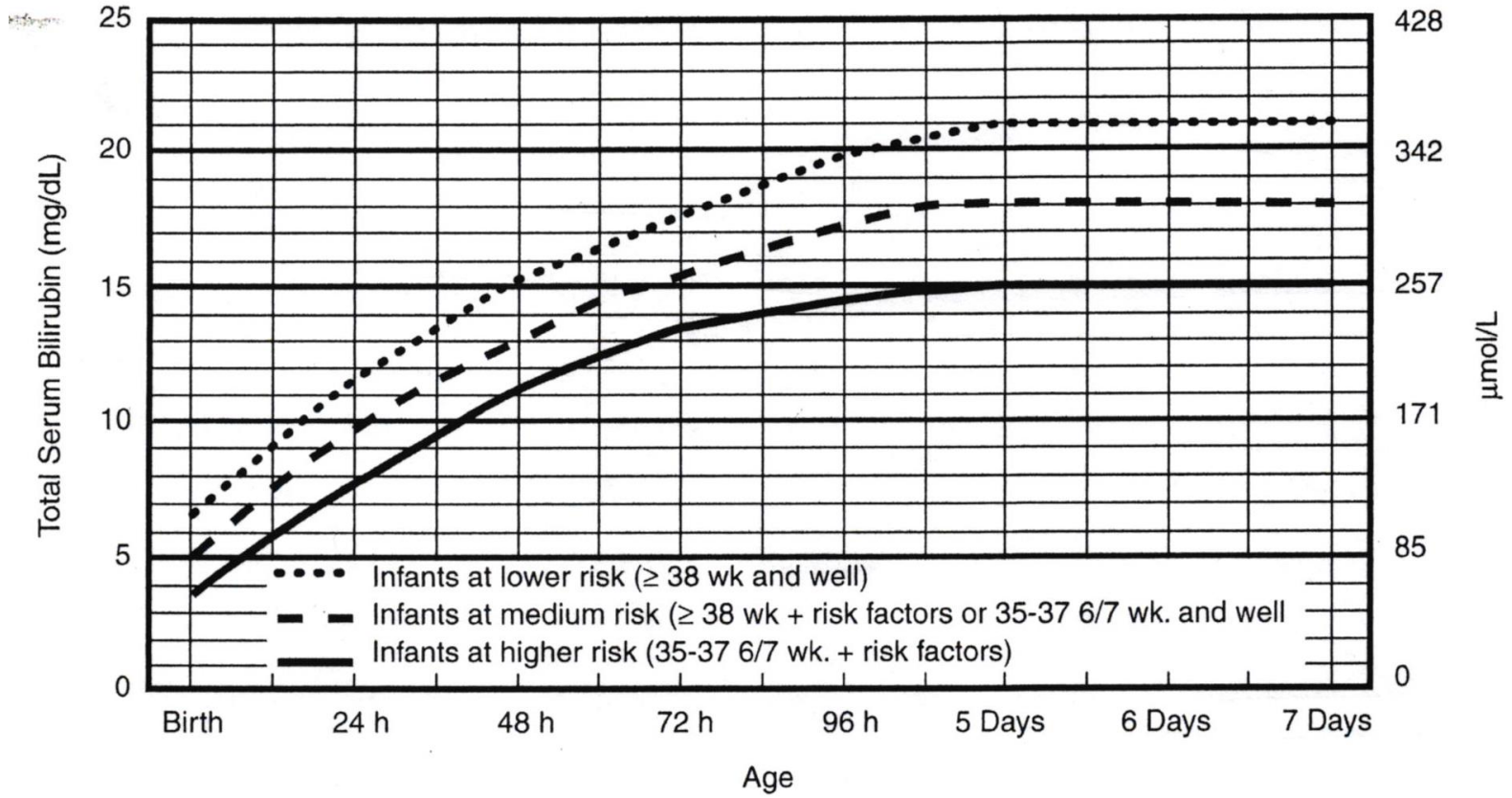
- Zone 1 – no F/U needed
- Zone 2 – F/U bilirubin in 48 hours
- Zone 3 – F/U bilirubin in 24 hours
- Zone 4 – consider phototherapy

Hour-Specific Bilirubin Nomogram in Infants with ABO Incompatibility and Direct Coombs-Positive Results.

Schutzman DL, Sekhon R, Hundalani S. Arch Pediatr Adolesc Med 2010;164:1158-1164

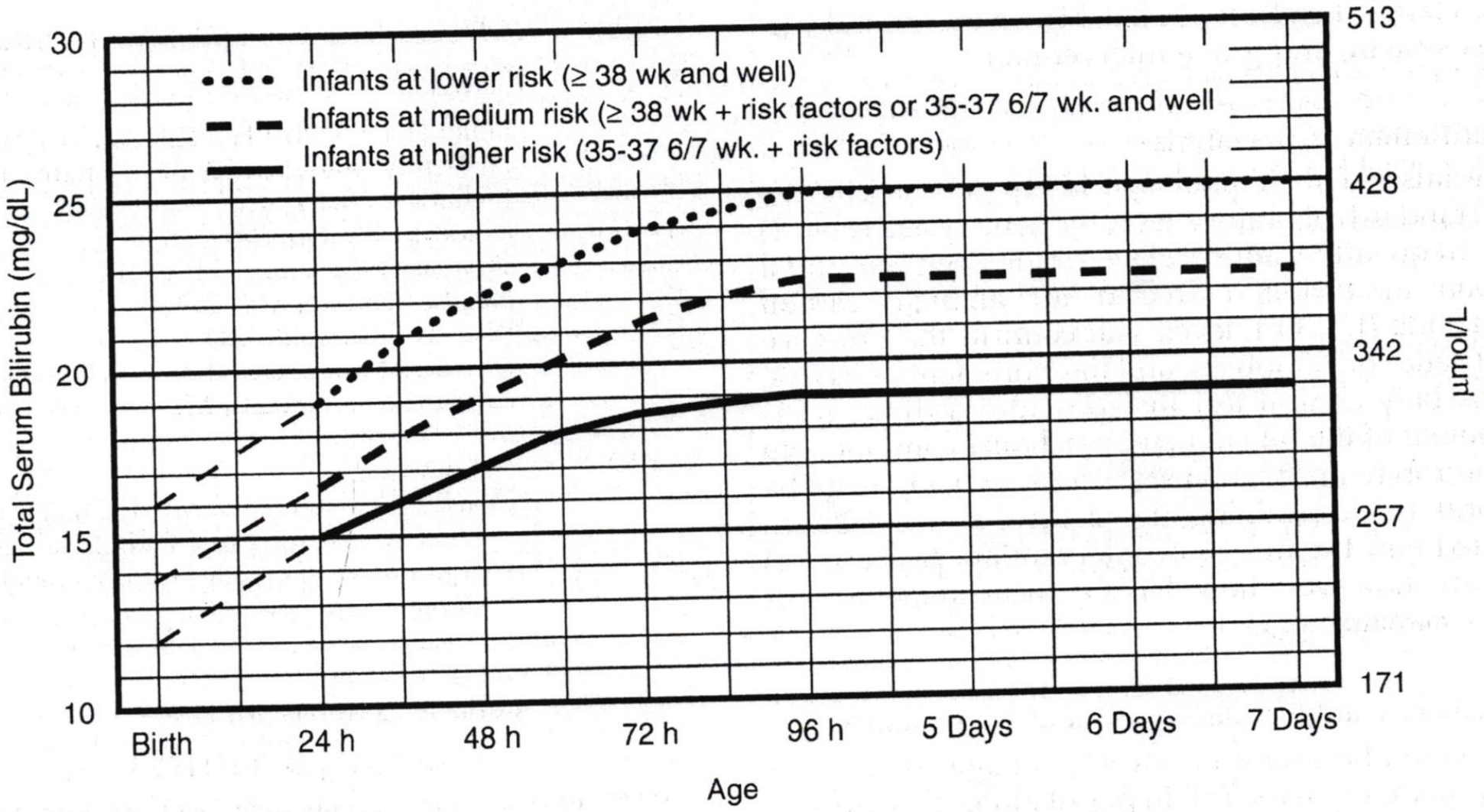
- 700 babies ≥ 35 weeks gestation
  - 460 DAT neg
  - 240 DAT+
- Age specific screening bilirubins plotted on Bhutani nomogram
- Sensitivity and specificity for infants in zone 4 or zone 3 &4 combined similar to Bhutani
- LR zone 4 twice Bhutani's
- All infants zone 3 and 4 followed post D/C
  - No XT or bilirubin encephalopathy
- Bhutani nomogram works equally well for F/U of DAT+ infants

Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. AAP Subcommittee on Hyperbilirubinemia. Pediatrics 2004;114:304



- 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.

Guidelines for exchange transfusion in infants 35 or more weeks gestation . AAP Subcommittee on Hyperbilirubinemia. Pediatrics 2004;114:304



Adjustments to AAP recommendations

Risk factors

- Use total bilirubin – do not subtract direct fraction
- Risk factors
  - Isoimmune hemolytic disease
  - G6PD deficiency
  - Asphyxia
  - Significant lethargy
  - Temperature instability
  - Sepsis
  - Acidosis
  - Albumin <3 g/dL (if measured)

Isoimmune Hemolytic Disease

- Variability in need for phototherapy in DAT+ infants
- Schutzman, et.al. Arch Pediatr Adolesc Med 2010;164:1158-1164
  - African American cohort
  - 12.9 % DAT+ infants required phototherapy
- Kaplan, et.al. E-PAS 2008:635841.21
  - Israeli Sephardi cohort
  - 49% DAT+ infants required phototherapy
- Sarici, et. al. Pediatrics 2002;109:e53-e58
  - Italian cohort
  - 100% DAT+ infants required phototherapy

- AAP Clinical Practice Guideline 2004
  - Blood group incompatibility with DAT+ a major risk factor for severe hyperbili
    - No reference given

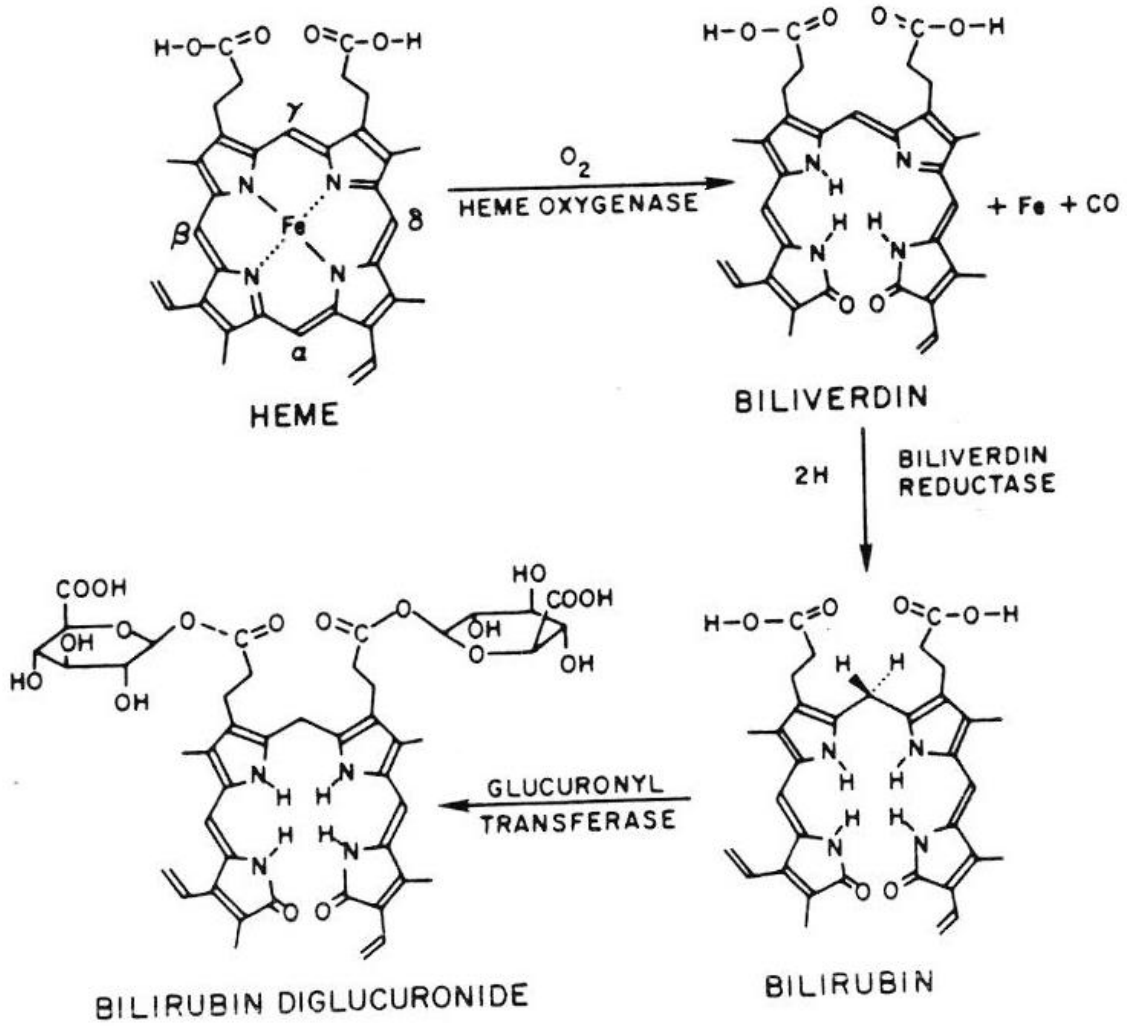
TABLE 2. Risk Factors for Development of Severe Hyperbilirubinemia in Infants of 35 or More Weeks' Gestation (in Approximate Order of Importance)

Major risk factors
Predischarge TSB or TcB level in the high-risk zone (Fig 2)[25,31]
Jaundice observed in the first 24 h[30]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (eg, G6PD deficiency), elevated $ETCO_c$
Gestational age 35–36 wk[39,40]
Previous sibling received phototherapy[40,41]
Cephalohematoma or significant bruising[39]
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive[39,40]
East Asian race[39]*
Minor risk factors
Predischarge TSB or TcB level in the high intermediate-risk zone[25,31]
Gestational age 37–38 wk[39,40]
Jaundice observed before discharge[40]
Previous sibling with jaundice[40,41]
Macrosomic infant of a diabetic mother[42,43]
Maternal age _25 y[39]
Male gender[39,40]
Decreased risk (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone (Fig 2)[25,31]
Gestational age _41 wk[39]
Exclusive bottle feeding[39,40]
Black race[38]*
Discharge from hospital after 72 h[40,44]

* Race as defined by mother's description.

CO - a better measure of hemolysis and hence risk

(Not yet endorsed by the AAP or necessarily agreed to by the Bilirubin club at PAS)



How can we measure CO in the body?

- Schutzman, et. al. J Perinatology 2016:36:386-388
- 180 AA infants
  - All mothers O+
  - 60 O+ 60 ABO/DAT neg 60 ABO/DAT+
- Mean COHbc in O+ and ABO/DAT neg 0.77±0.23%
- 2SD > mean 1.22%
- 15/60 DAT+ >1.22%
- 4/120 DAT neg >1.22%

Capnia CoSense Monitor –End Tidal CO (ETCO)

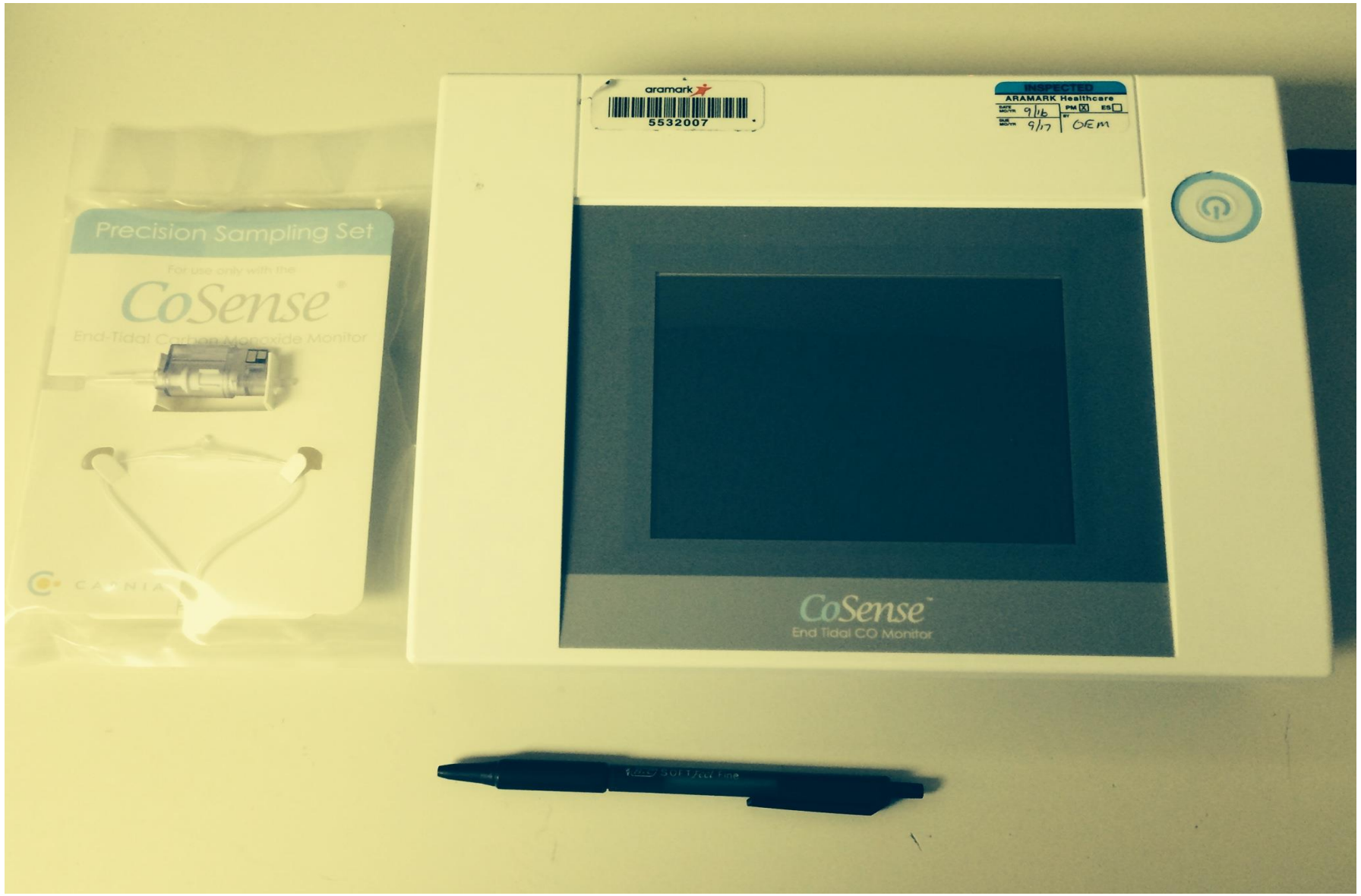


Table 2. Studies related to ETCO levels

Author[ref.]	*Clinical relevance*	n	*ETCO (p.p.m.)*	*Device(s)*
Vreman *et al.*[27]	To compare the performance of a point-of-care, non-invasive ETCO analyzer to an established marketed device	87	0.4–29.1	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer Vitalograph BreathCO Monitor
Vreman *et al.*[26]	To show that a portable breath sampler can be used to non-invasively measure ETCO in neonates and adults	34	1.5–35.9[a]	Natus Medical Inc. Baby's Breath Carbon Monoxide Analyzer
Vreman *et al.*[24]	To determine if the measurements yielded by the EC-CO instrument are comparable with those obtained by the GC assay	108	0–18.0[b]	Stanford University EC-CO Instrument
Stevenson *et al.*[25]	To determine whether measurements of CO in breath can be used as an index of bilirubin production	535	1.0–1.8[c]	Stanford University EC-CO Instrument
Stevenson *et al.*[30]	To determine whether ETCOc as a single measurement or in combination with TB levels can predict the development of hyperbilirubinemia in the first 7 days of life	1370	0.1–3.5	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
Blok *et al.*[38]	To study the predictive value of ETCOc and cytokine levels for long-term outcome	105	1.4–3.0	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
James *et al.*[37]	To examine the role of ETCOc as a screening tool for hemoglobinopathies and as an indicator for when transfusions would be required in patients receiving chronic transfusions	101	1.2–13.5	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
Sylvester *et al.*[36]	To assess whether ETCOc levels in children with SCD could be measured reproducibly, reflected hemolysis and whether ETCOc levels were elevated compared to children without SCD	113	1.3–4.9[d]	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
Herschel *et al.*[31]	To determine the sensitivity, specificity and positive predictive value of the DAT or Coombs' test compared to ETCOc and to evaluate the predictive value of these two methods to detect significant jaundice	614	0.6–11.0	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
Barak *et al.*[32]	To test the hypothesis that in normal neonates, CO production, estimated by ETCOc correlates with estimates of RBC mass such as Hct and Hgb concentration	58	1.3–3.4	Everest $COCO_2$ Puff
Javier *et al.*[29]	To evaluate the clinical usefulness of ETCOc in healthy, term, Coombs-positive neonates and correlate these measurements to the corrected RCs	100	0.6–6.1	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
Herschel *et al.*[33]	Case study: to describe the relationship between G6PD deficiency and severe hyperbilirubinemia	1	2.5–3.1	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer
Kaplan *et al.*[34]	To compare hemolysis and the risk of hyperbilirubinemia among African-American, G6PD-deficient neonates	500	1.7–2.9[d]	Natus Medical Inc. CO-Stat End Tidal Breath Analyzer

Abbreviations: DAT, direct antiglobulin test; EC-CO, electrochemical carbon monoxide; ETCO, end-tidal carbon monoxide; ETCOc, end-tidal carbon monoxide, corrected for ambient CO; GC, gas chromatography; G6PD, glucose-6-phosphate dehydrogenase; Hct, hematocrit; Hgb, hemoglobin; RBC, red blood cell; RCs, reticulocyte counts; SCD, sickle cell disease; TB, total serum/plasma bilirubin.
[a]Range reported for adults ($n = 25$). [b]Reported range of device. [c]Range of reported means. [d]Interquartile range report.

What is a normal ETCOc?

- Christensen, et. al. Neonatology 2016;109:1-5
  - 100 infants Intermountain Health Group
  - Caucasian 76% Non-Caucasian 24%
  - ETCO 95% >2.0ppm
- Bhutani, Maisels, Schutzman, et. al. Acta Paediatr. 2018 Aug;107(8):1350-1356
- 247 infants
  - Caucasian 46% African American 23% Asian 10% Hispanic 18%
  - ETCO 90% >2.0ppm
  - ETCO 95% >2.5ppm

Why Use ETCO rather than DAT

- ElSaie, Taleb, Nicosia, Zangaladze, Pease, Newton, Schutzman in submission
- 191 babies with DAT+ or ETCO for HIR or HR zones
- Theoretical decision to use photo or not based on AAP recommendations and using DAT OR ETCO to delineate hemolysis
- 27% of DAT+ actually hemolyzing per ETCO
- 29% of DAT neg actually hemolyzing per ETCO
- Management of 9.4% differed if used ETCO instead of DAT
- 8 fewer babies would have received photo using ETCO

TN Bilirubin Guideline
Page 1

Revised 10/17/2019

All infants Gestational Age ≥ 35 weeks

Transcutaneous Bilirubin (TcBili) on discharge day (@ midnight to 0400 AM)

Refer to **Table 1** to assess need for Total Serum Bili (TSB)

TSB Not indicated

- Low Risk zone → Follow-up PCP
- Low Intermediate Zone → TSB check in 48 hrs with PCP f/up in 3 days

TSB indicated

- TSB Low Risk Zone or Low intermediate zone → Follow pathway on the left
- TSB High intermediate zone → Follow AAP phototherapy* parameter
- TSB High risk zone → Follow AAP phototherapy* parameter

***TSB follow-up when phototherapy started**

ETCO

- <1.6 ppm → Discharge with TSB in 24 hrs
- 1. 6 - 2.4 ppm → Assess Risk Factors **(Table 2)**
- ≥ 2.5 ppm (moves infant to next higher risk category in AAP parameter) → Repeat TSB 6-8 hrs

Assess Risk Factors **(Table 2)** → No / Yes

- No → Discharge with TSB in 24 hrs
- Yes → Follow AAP phototherapy* parameter or Hour-specific Bilirubin Normogram

Table 1. INDICATIONS FOR SERUM BILIRUBIN

Age in Hours	TcBili
< 20	≥ 5
21-24	≥ 6
25-27	≥ 6.5
28-31	≥ 7
32-36	≥ 8
37-40	≥ 9
41-45	≥ 10
46-49	≥ 10.5
50-55	≥ 11
>55	≥ 12

Table 2. RISK FACTORS FOR HYPERBILIRUBINEMIA IN NEWBORN NURSERY

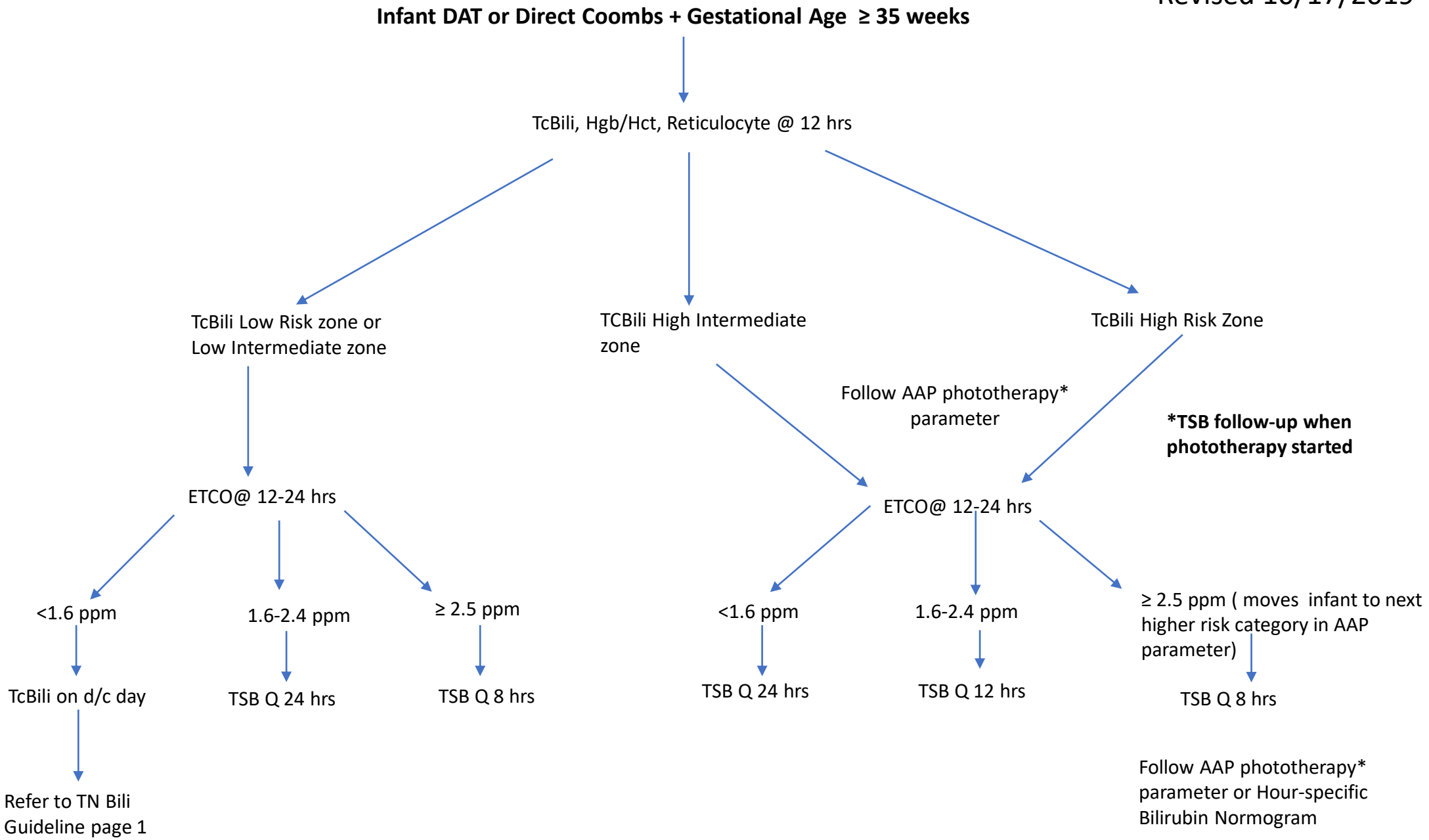
Jaundice before 24 hours
Direct Coombs +
Late preterm
Previous sibling received phototherapy
Cephalhematoma or significant bruising
Excessive weight loss
East Asian race

***If started on Phototherapy:**

1. Obtain Hgb/Hct, Reticulocyte.
2. If suspect dehydration and/or exclusive breast feeding, obtain BMP.
3. If ABO set-up, may repeat Type and Coombs if initially negative.

TN Bilirubin Guideline
Page 2

Revised 10/17/2019



BILITOOL.ORG

option one

Date and time of **birth** to closest hour:

2020 July 14 |

Date and time of **blood sampling** to closest hour:

2020 July 15 |

Total Bilirubin*: mg/dl (US) Submit

---

option two

Age (hours): (12-146 hours)

Total Bilirubin*: mg/dl (US) Submit

*Note: The default *unit of measure* for total bilirubin is **mg/dl**. Please select **µmol/L** if your bilirubin values are captured in the global standard SI metric units. Bilirubin conversion from US to SI units is 17.1.

Results are based on the Hour-Specific Nomogram for Risk Stratification published in "Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation" (2004) by the AAP journal.

Hour-Specific Nomogram for Risk Stratification

Infant age	36 hours
Total bilirubin	10.7 mg/dl
Risk zone	High Intermediate Risk

Risk zone is one of several risk factors for developing severe hyperbilirubinemia.

Recommended Follow-up

Hyperbili Risk Level	Interval
Lower Risk (>= 38 weeks and well)	Follow-up within 48 hours and consider TcB/TSB at follow-up
Medium Risk (>=38 weeks + hyperbili risk factors **OR** 35 to 37 6/7 weeks and well)	Evaluate for phototherapy and check TcB/TSB within 24 hours
Higher Risk (35 to 37 6/7 weeks and hyperbili risk factors)	Evaluate for phototherapy and check TcB/TSB in 4-24 hours

AAP Phototherapy Guidelines (2004)

Neurotoxicity Risk Level	Start phototherapy?	Approximate threshold at 36 hours of age
Lower Risk (>= 38 weeks and well)	No	13.6 mg/dl
Medium Risk (>=38 weeks + neurotoxicity risk factors **OR** 35 to 37 6/7 weeks and well)	No	11.7 mg/dl
Higher Risk (35 to 37 6/7 weeks and neurotoxicity risk factors)	**Yes**	9.6 mg/dl

It is an option to provide conventional phototherapy in the hospital or at home at TSB levels 2-3 mg/dl (35-50 µmol/L) below those shown. Home phototherapy should not be used in infants with risk factors.

If phototherapy threshold is exceeded, please also review AAP Guidelines for Exchange Transfusion.

The Curious Case of the Missing Bilirubin


Inspector Gregory: Is there any point to which you wish to draw my attention?
Holmes: To the curious incident of the dog in the night-time.
Gregory: The dog did nothing in the night-time.
Holmes: That was the curious incident.

- Full term female born by SVD
- Mother O+
- Infant O+ DAT+
- Mother anti c +
  - Titer <1:1 2 months PTD
  - Titer 1:32 2 weeks PTD
- Infant labs
  - H/H 11.3/34.1
  - Reticulocytes 17.7%
  - ETCO 6.8 PPM (>>>95%)
  - Tcbili @33 hr 3.9
  - TSB @48 hr 4.1
  - TSB@61 hr 6.0

- HO-1 promoter variant (GT)n repeats
  - 23 and 30 repeats for the two alleles
  - Long repeats (>33) would have decreased function
- SLCO1B1 transporter
  - Heterozygous *5 (c.521C>T)
  - No effect
- UGT1A1
  - Homozygous *60 (c.3275T>G) may be associated with decreased function
  - Heterozygous *89 (c.3436C>A) no effect
  - Heterozygous *66/*88 (c.997-82C>T) possible decreased activity due to compound heterozygote
  - NO TA5 repeat in promoter region which ENHANCES activity


"WHERE'S THE BEEF?"