ABCs of Neonatal Jaundice: AAP guidelines, Bilirubin Basics, and Cholestasis

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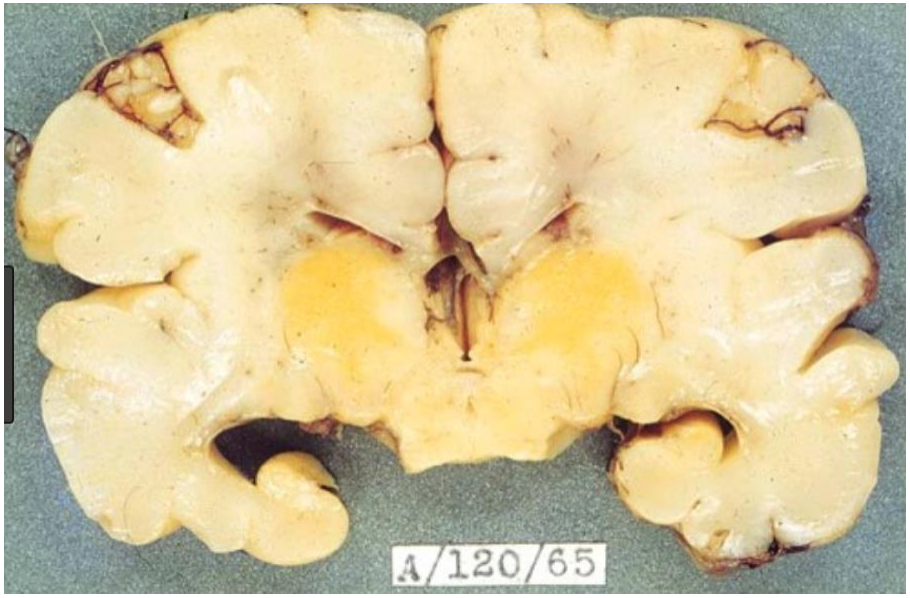
Outline

- History of neonatal jaundice
- Review of bilirubin physiology and causes of hyperbilirubinemia in the newborn period
- Balance between harms and benefits of treating neonatal jaundice
- AAP guidelines

History: Early Findings

- Christian Georg Schmorl coined term “kernicterus”
- In 1904 published findings of 280 neonatal autopsies 120 of whom were jaundiced at death and 114/120 had kernicterus



History: Continued

- 1950-1970s aggressive treatment with exchange transfusion and then phototherapy
  - Marked decline in kernicterus
- 1980-1990s thought that therapy may be too aggressive
  - Infants started being discharged prior to peak TSB concentration
  - Resurgence of kernicterus
- 1994- AAP establishes treatment guidelines
- 2002- NQF – Kernicterus ”never event”
- 2004 Most recent treatment guidelines
  - Update clarification in 2009

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Key Terms

Bilirubin	Hyperbilirubinemia	Jaundice	Kernicterus
Breakdown product of red blood cells	High level of bilirubin in the blood	Exam finding of yellow eyes and skin secondary to hyperbilirubinemia	Bilirubin exceeds the albumin-binding capacity, crosses BBB, and deposits on the basal ganglia and brainstem nuclei

Key Terms

Acute Bilirubin Encephalopathy

Acute manifestations of toxicity seen in the first weeks after birth

Kernicterus

Chronic and permanent clinical sequelae of bilirubin toxicity

Clinical Features of Kernicterus

TABLE 2. CLINICAL FEATURES OF KERNICTERUS.

Acute form

Phase 1 (first 1–2 days): poor sucking, stupor, hypotonia, seizures
Phase 2 (middle of first week): hypertonia of extensor muscles, opisthotonus, retrocollis, fever
Phase 3 (after the first week): hypertonia

Chronic form

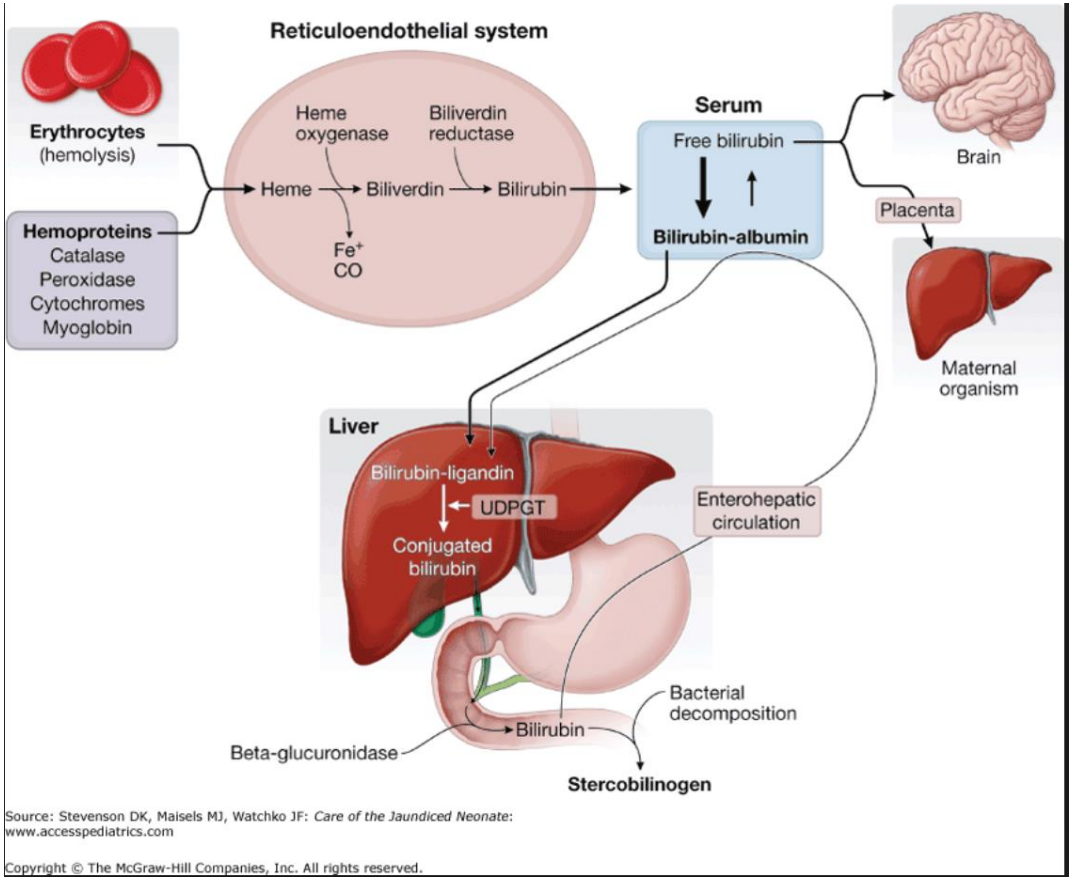
First year: hypotonia, active deep-tendon reflexes, obligatory tonic neck reflexes, delayed motor skills
After first year: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

Acute Bilirubin Encephalopathy

Kernicterus

Dennery, PA. NEJM 2001: Vol 344, No 8

Bilirubin Metabolism



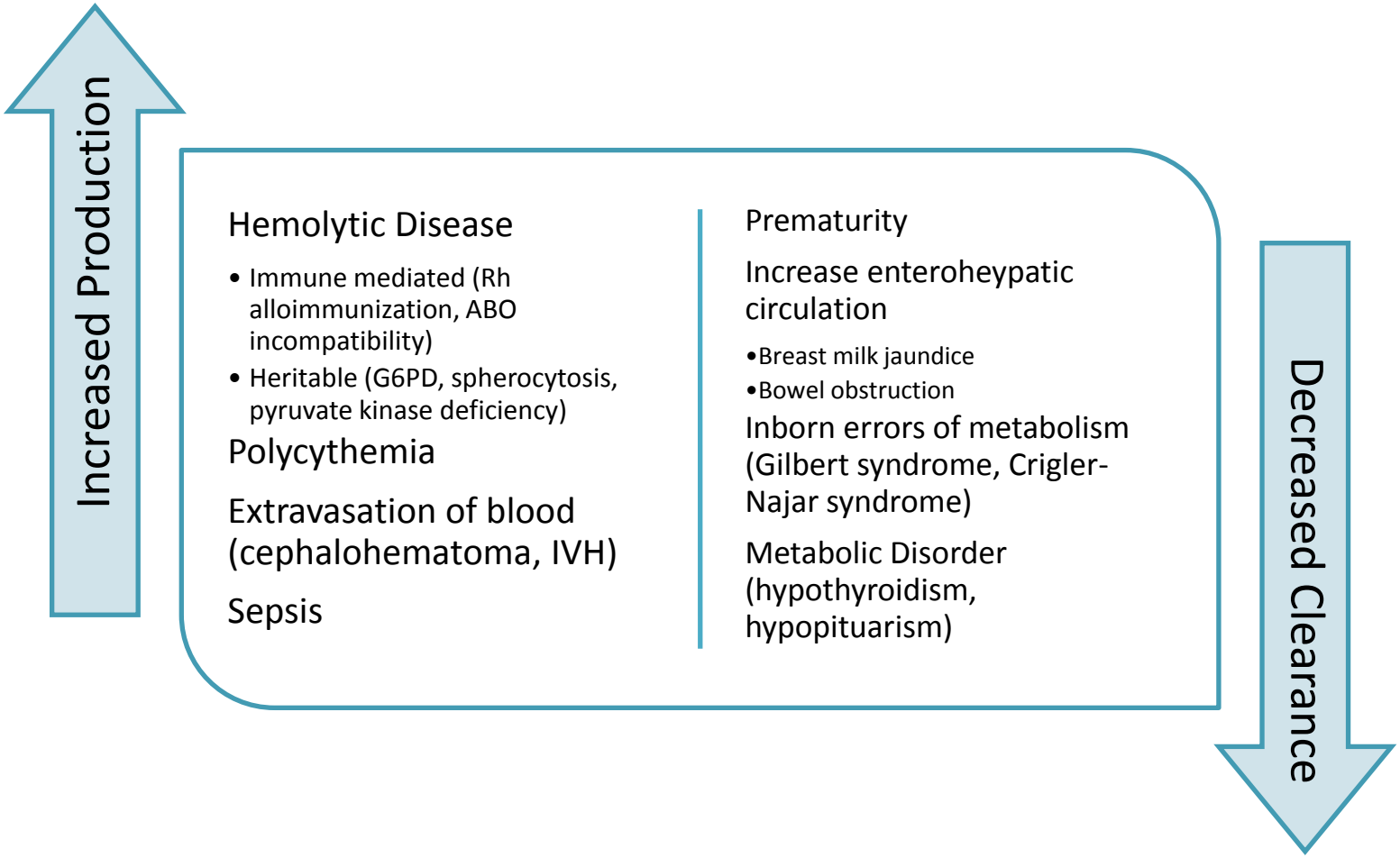
Source: Stevenson DK, Maisels MJ, Watchko JF: *Care of the Jaundiced Neonate*: www.accesspediatrics.com

Why are newborns at increased risk?

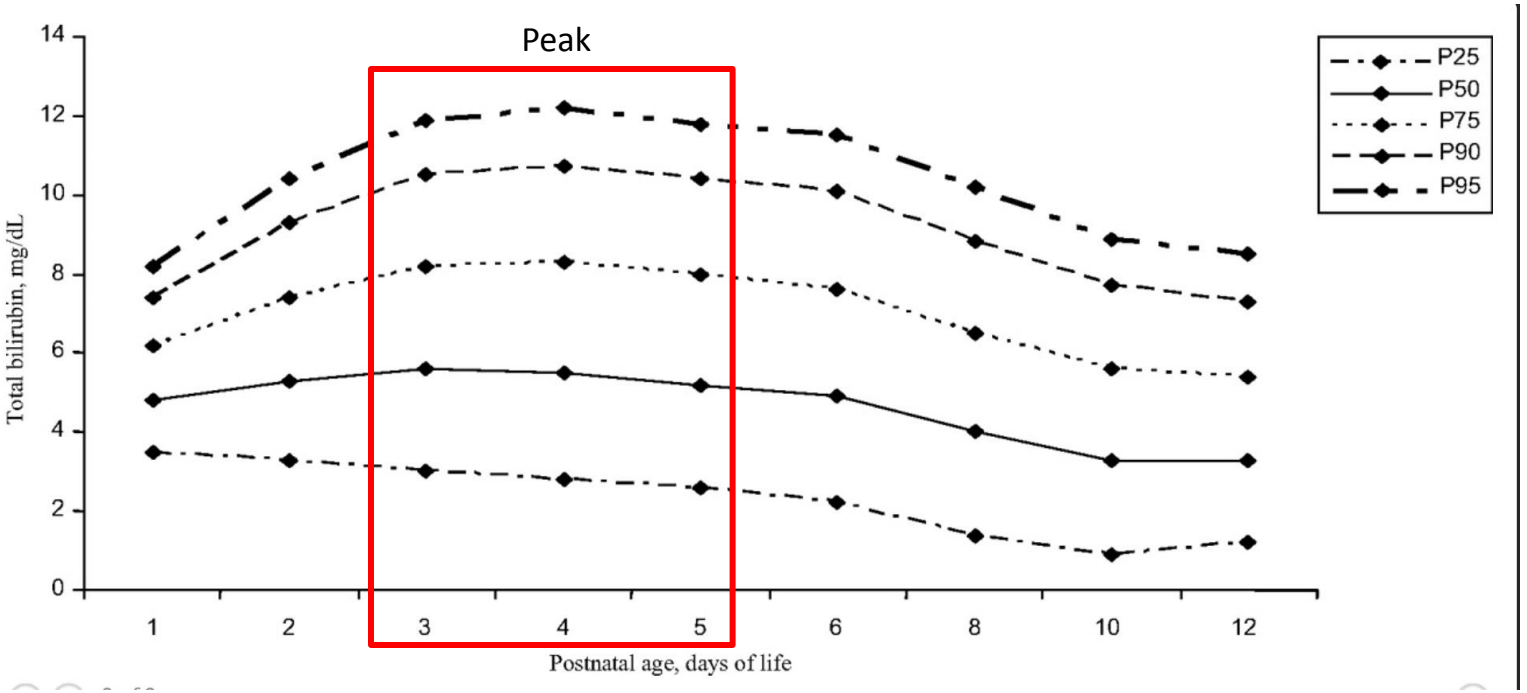
- 80% of all term and late preterm infants will have some degree of jaundice (physiologic jaundice)

- Increased turnover of erythrocytes, produce more than twice the amount of bilirubin produced daily by an adult, increased enterohepatic circulation, and have a transient deficiency in their ability to conjugate and clear bilirubin.

Causes of neonatal hyperbilirubinemia

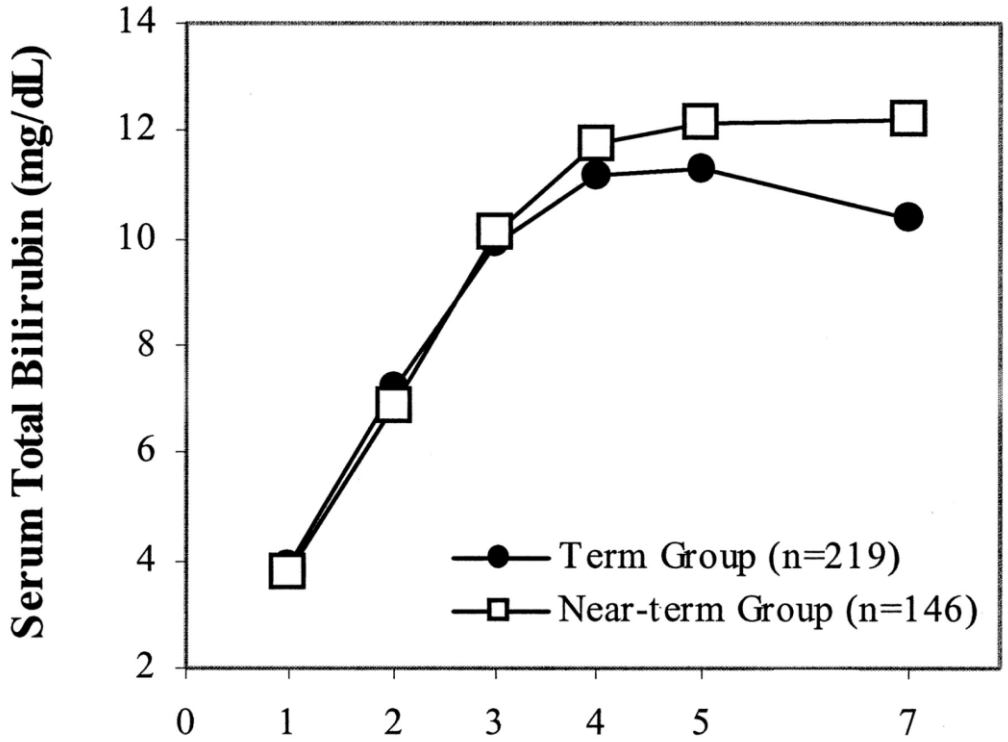


Normal Newborn Bilirubin Levels



Draque et al. *Pediatrics* 2011: 128(3)

Impact of Gestational Age



Sarici et al. *Pediatrics* 2004: 113(4)

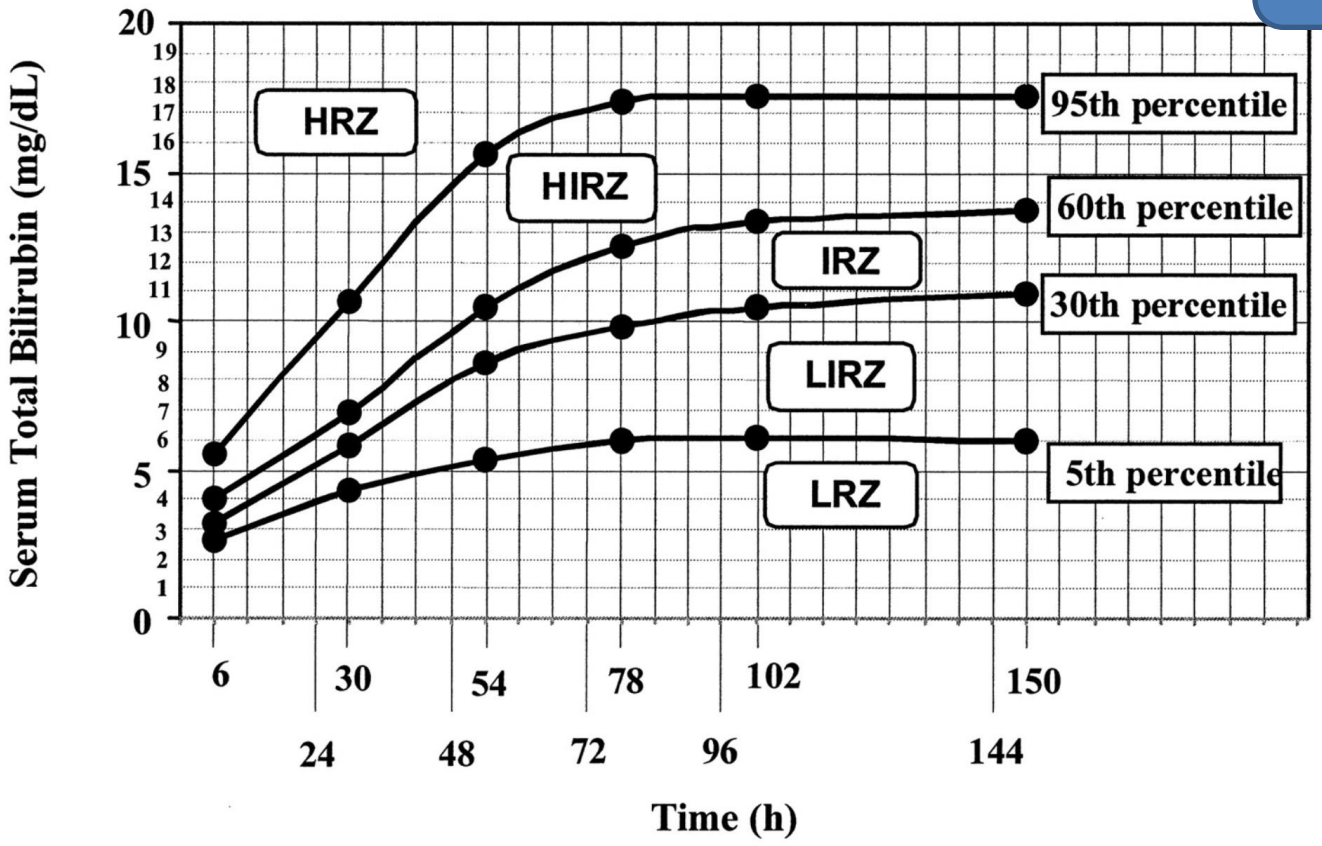
Normograms

What is “significant hyperbilirubinemia”?

	Birth Weight 2000-2500g	Birth Weight 2500g
0-24hrs	>=5mg/dL and an increase of 0.5mg/dL/h on 2 consecutive measurements	
25-48 hrs	>=8mg/dL	>=12mg/dL
49-72 hrs	>=12mg/dL	>=15mg/dL
73-96 hrs	>=14mg/dL	>=17mg/dL
97-120 hrs	>=14mg/dL	>=17mg/dL

Sarici et al. *Pediatrics* 2004: 113(4)

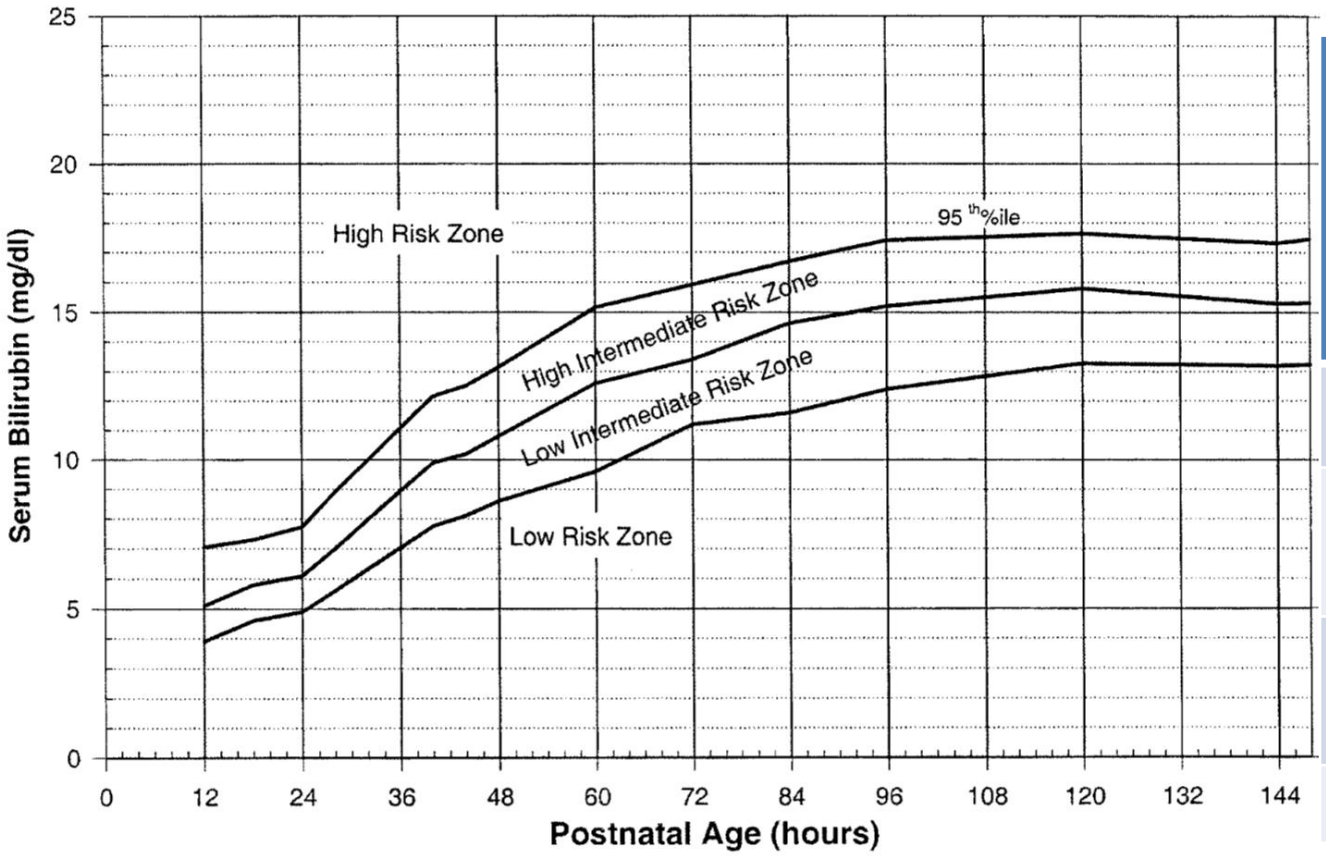
Normograms



Sensitivity at 30th hour bilirubin level to predict subsequent significant hyperbilirubinemia

- 35.1%
- 75.7%
- 91.9%
- 100%

Sarici et al. *Pediatrics* 2004: 113(4)



TSB Before Discharge	% of newborns who subsequently developed a TSB level > 95%tile
High-risk zone (>95th%tile)	39.5%
High intermediate-risk zone	12.9%
Low intermediate-risk zone	2.3#
Low risk zone	0%

AAP 2004 Guidelines
Bhutani et al. *Pediatrics* 1999: 103

Degree of Hemolysis and Risk of Hyperbilirubinemia

- ABO heterospecific newborns with DAT positive
- Demonstrated that DAT strength (nor merely presence or absence) predicted significant hyperbili (>95%tile on normogram)
- For example, significant hyperbili occurred in:
  - 42.5% with DAT +/-
  - 57.1% with DAT +
  - 80% with DAT ++

Kaplan *Pediatrics* 2014: 134 (5)

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“Describe neonatal jaundice, and distinguish those circumstances in which treatment is needed and those in which we must only await the natural course”

How Bilirubin Crosses the BBB

- Bilirubin can enter brain if not bound to albumin or is unconjugated. Direct hyperbilirubinemia doesn’t cause kernicterus!
- On average albumin can bind about 8mg bilirubin per gram.
- Conditions that alter the blood brain barrier such as infection, acidosis, hyperoxia, sepsis, prematurity, and hyperosmolarity may affect entry of bilirubin into the brain

Why treat jaundice?

- Auditory Toxicity- (~13%)
- Kernicterus among infants with Rh hemolytic disease:
  - Bilirubin level→ kernicterus
  - 19-24 mg/dL → 8%
  - 25-29 mg/dL → 33%
  - 30-40 mg/dL → 73%
- Rates of bilirubin encephalopathy much lower in infants without hemolytic disease

Amin *Pediatrics* 2017: 140 (4)
Gamaleldin *Pediatrics* 2011: 128(4)

Risks of Bilirubin Encephalopathy

- Retrospective study of 525,409 infants born >=35 weeks' gestation at 15 Kaiser Permanent Northern California hospitals, 1995-2011
- Evaluated outcomes in 47 infants with TSB >=30mg/dL
- In 94% of cases this level occurred after birth hospitalization

Kuzniewicz *Pediatrics* 2014: 134 (3)

Risks of Bilirubin Encephalopathy

- G6PD was the highest identified cause (10 of 44)
- 4 developed acute bilirubin encephalopathy
  - 2 developed CP and SNHL
  - 2 developed SNHL

Risks of Bilirubin Encephalopathy

- They observed no cases of acute bilirubin encephalopathy in infants with a peak TSB 30 to 34.9 mg/dL, but 19% in infants with a TSB ≥35 mg/dL
- Chronic, bilirubin-induced neurotoxicity was uncommon and occurred only in the setting of additional risk factors and TSB values well over (>15 mg/dL) the AAP exchange transfusion thresholds

Risk of Autism Spectrum Disorder?

- Retrospective study of 525,409 infants born >=35 weeks' gestation at 15 Kaiser Permanent Northern California hospitals, 1995-2011
- Among this birth cohort, 2% had at least 1 TSB >=20mg/dL and 8% received phototherapy

Wu et al. *Pediatrics* 2016: 138(4)

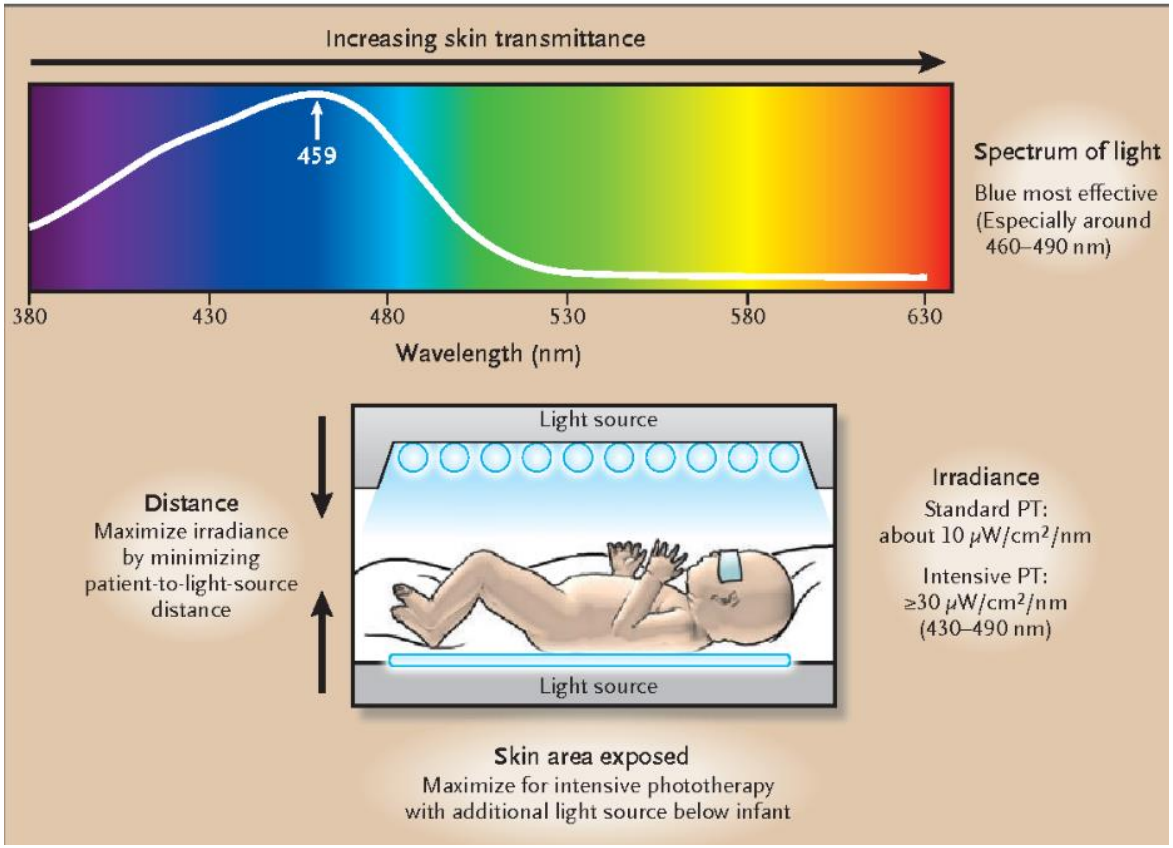
Risk of Autism Spectrum Disorder?

- In bivariate analyses both TSB and phototherapy were associated with ASD
- When controlled for confounders this relationship was not longer significant.
- **Authors concluded: "factors that increase the risk of both hyperbilirubinemia and ASD, such as male sex and lower gestational age, are likely responsible for the previously described link between hyperbili and ASD"**

Wu et al. *Pediatrics* 2016: 138(4)

Treatments:

Phototherapy!



Side Effects of Phototherapy

- OVERALL SAFE!

- Diarrhea
- Dehydration
- Riboflavin Destruction
- Hypocalcemia
- Bronze-Baby Syndrome
- Blistering/photosensitivity in infants with porphyria

Exchange Transfusion

- Complications:
  - Thrombocytopenia
  - Portal vein thrombosis
  - NEC
  - Electrolyte imbalance
  - GVHD
  - Infection

What are the harms?

- In vivo and in vitro studies suggest that phototherapy can lead to DNA damage, altered cytokine levels, and increased oxidative stress
  - Bilirubin anti-oxidant in neonates
- Phototherapy may be associated with some long-term side effects such as melanocytic nevi and skin cancer, allergic diseases, patent ductus arteriosus and retinal damage
- Vulnerable child syndrome
- Medical Costs

The Balance

Rates of kernicterus 1998-2004 in the United States:

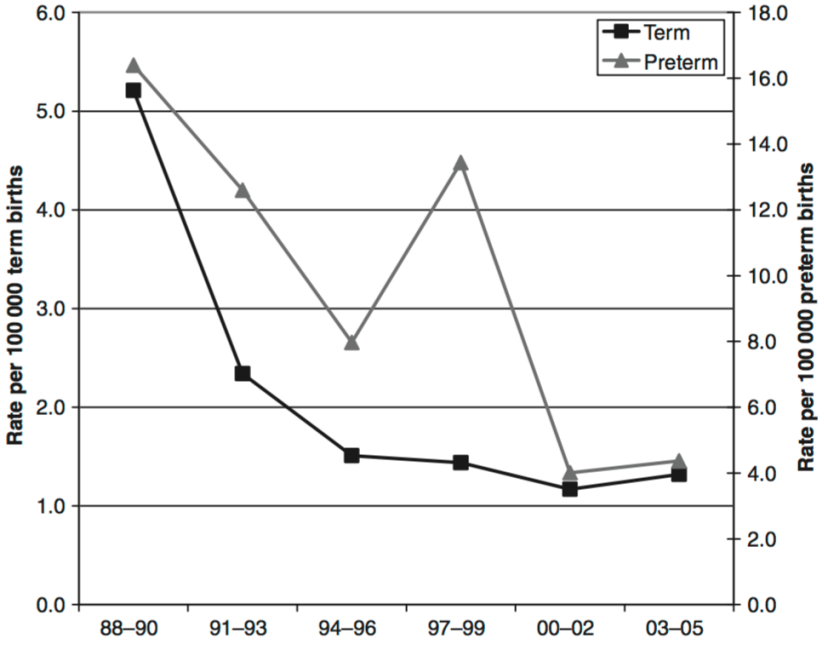


FIGURE 2
Rates of infants diagnosed with kernicterus during the neonatal period, stratified according to term and preterm gestation, 1988–2004.

Burke et al. *Pediatrics* 2009

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Putting it all Together: The AAP Guidelines

10 recommendations to help standardize care

1- Promote and support successful breastfeeding

- Clinicians should advise mothers to nurse their infants at least 8-12 times per day for the first several days
  - Increasing breastfeeding frequency reduces risk of hyperbilirubinemia
- The AAP recommends against supplementation with water or dextrose
- IV Fluids only if ”oral intake is in question”

2- Establish nursery protocols for the identification and evaluation of hyperbilirubinemia

- All newborns should be assessed for hyperbilirubinemia prior to discharge by:
  1. Total Serum Bilirubin or Transcutaneous Bilirubin Level
  2. Assessment of clinical risk factors
- Results should be plotted on a normogram
- Can obtain at time of newborn screen to minimize excess blood draws

- 2009 update: recommend all infants get a bilirubin level prior to discharge

Cost of Universal Bilirubin Screening

- Assuming an incidence of kernicterus of 1 in 100,00 live births and relative risk reduction of 70%
- The cost to prevent 1 case of kernicterus is $5.7 million
- “taking into account the lifetime cost of an infant with kernicterus, it is possible that there could be savings”

2- Establish nursery protocols for the identification and evaluation of hyperbilirubinemia

3- Measure the total serum bilirubin or transcutaneous bilirubin level on infants jaundiced in the first 24 hours

- Laboratory Evaluation for Newborn Jaundice:

Clinical Scenario:	Lab Evaluation:
Visibly jaundiced in first 24 hours or more jaundice than expected for infant's age	Measure serum and/or transcutaneous bilirubin

3- Measure the total serum bilirubin or transcutaneous bilirubin level on infants jaundiced in the first 24 hours

- Laboratory Evaluation for Newborn Jaundice:

Clinical Scenario:

TSB rising rapidly and unexplained by history and exam

Lab Evaluation:

Blood type and Coombs' test
CBC + smear
Direct bilirubin level
Consider retic count and G6PD

3- Measure the total serum bilirubin or transcutaneous bilirubin level on infants jaundiced in the first 24 hours

- Laboratory Evaluation for Newborn Jaundice:

Clinical Scenario:	Lab Evaluation:
TSB approaching exchange transfusion levels or not responding to phototherapy	Obtain retic count, G6PD, and albumin levels

3- Measure the total serum bilirubin or transcutaneous bilirubin level on infants jaundiced in the first 24 hours

- Laboratory Evaluation for Newborn Jaundice:

Clinical Scenario:	Lab Evaluation:
Elevated direct bilirubin level	UA and Ucx Consider sepsis evaluation

3- Measure the total serum bilirubin or transcutaneous bilirubin level on infants jaundiced in the first 24 hours

- Laboratory Evaluation for Newborn Jaundice:

Clinical Scenario:

Jaundice present at or beyond age 3 weeks of age

Lab Evaluation:

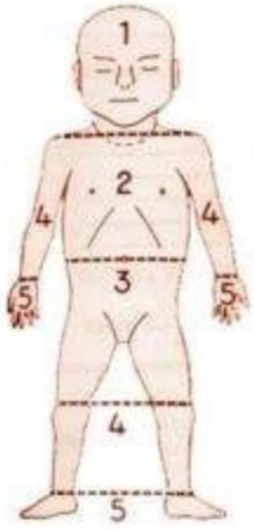
Total and direct bilirubin levels
If direct bilirubin elevated, evaluate for causes of cholestasis
Check results of newborn thyroid and galactosemia screen

Direct Hyperbilirubinemia

- Definition if TSB < 5mg/dL
  - A Direct level of 1.0mg/dL is considered abnormal
- Definition if TSB > 5mg/dL
  - A direct level of >20% TSB is considered abnormal

estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants

Schema for grading extent of jaundice

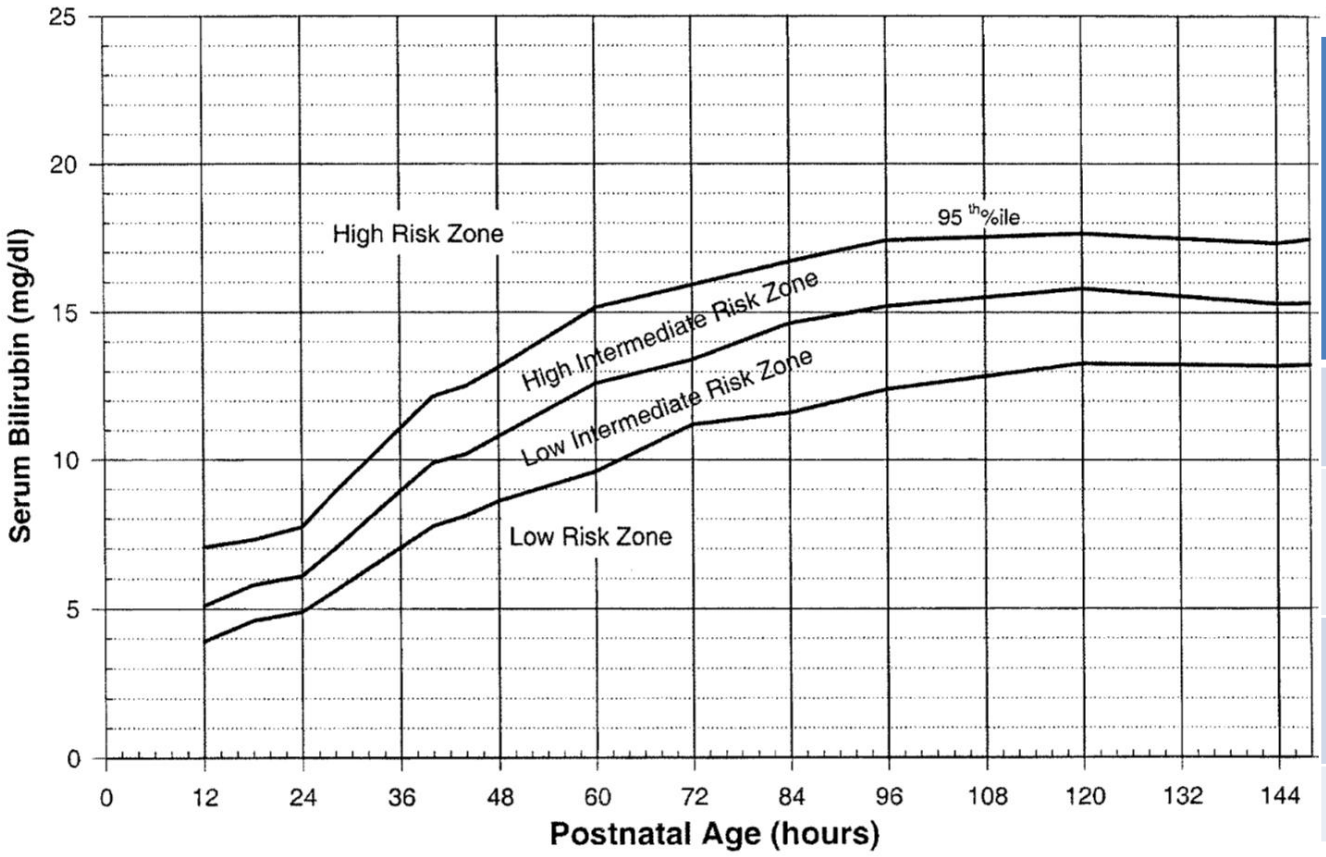


Grade	Extent of Jaundice
0	None
1	Face and neck only (4 - 6 mg/dl)
2	Chest and back (6 - 8 mg/dl)
3	Abdomen below umbilicus to knees 8 - 12 mg/dl)
4	Arms and legs below knees (12 - 14 mg/dl)
5	Hands and Feet (>15 mg/dl)

Transcutaneous Bilirubin Measurement

- Provides estimate within 2 to 3mg/dL of serum level
- Better for levels < 15mg/dL
- Not reliable in infants receiving phototherapy
- Older devices impacted by skin pigmentation

5- Interpret all bilirubin levels according to the infant’s age in hours



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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

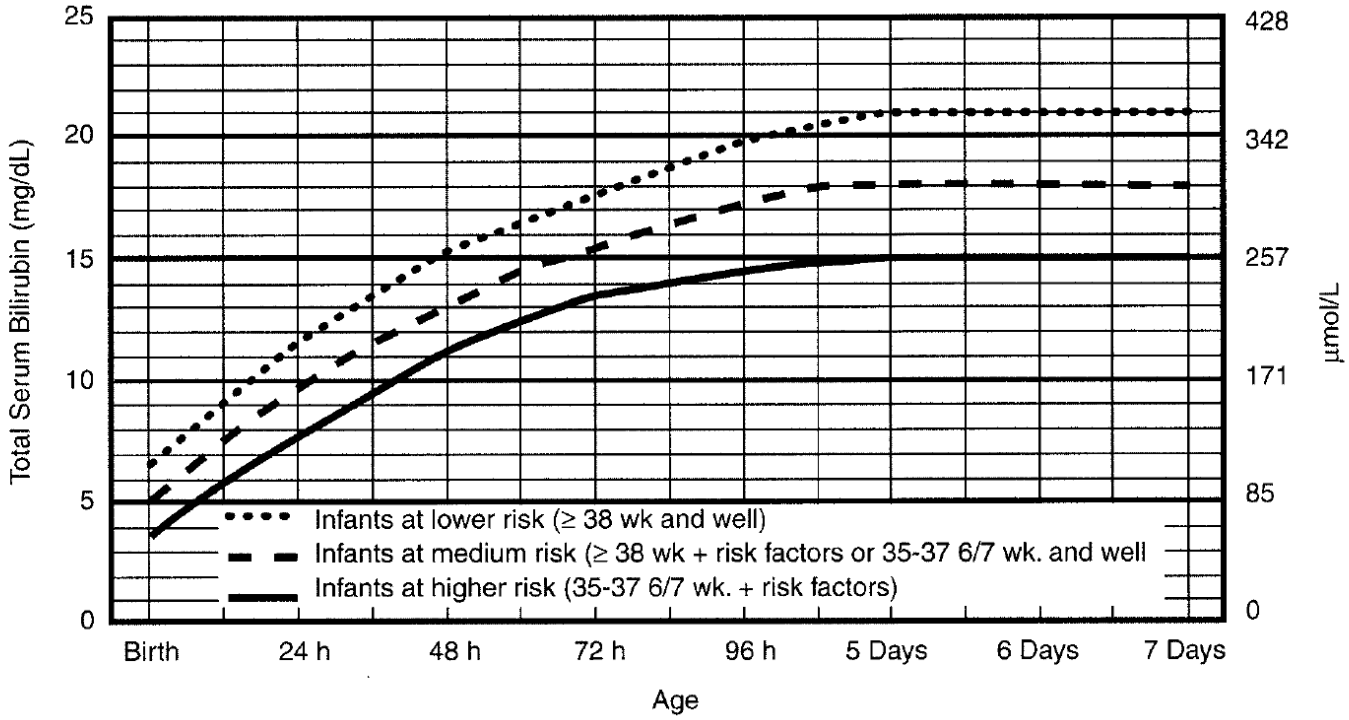
7- Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia

- Most significant risk factors for severe hyperbilirubinemia include:
  - Breastfeeding (particularly if not going well with excessive weight loss)
  - Cephalohematoma or significant bruising
  - Hemolytic disease (DAT positive, G6PD, or other)
  - <38 week gestational age
  - Phototherapy in a sibling
  - jaundice noted before discharge or bilirubin level in the high-risk zone

8- Provide parents with written and verbal information about newborn jaundice

9- Provide appropriate follow up based on the time of discharge and risk assessment

10- Treat newborns, when indicated, with phototherapy or exchange transfusion



Risk factors- isoimmune hemolytic disease, G6PD deficiency, asphyxia, lethargy, temp instability, sepsis, acidosis, or albumin < 3.0g/dL

Phototherapy: The Numbers

- 8 to 9 of every 10 infants with a level of 15-20mg/dL will not reach 20mg/dL even without treatment

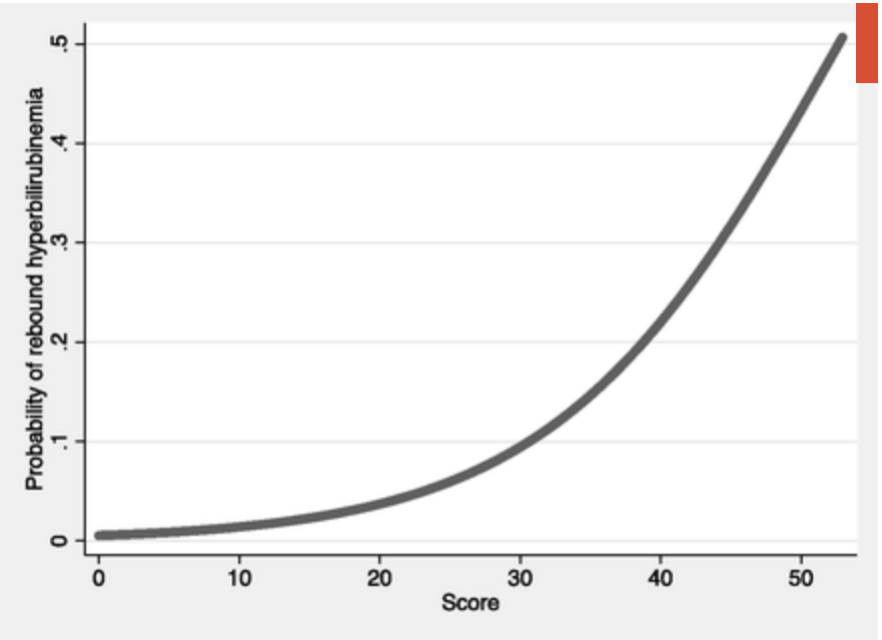
- Said another way: need to give phototherapy to 10 infants to prevent 1 infant from reaching 20mg/dL

What is expected rate of decline?

- Usually between 0.5 to 1mg/dL per hour can be expected in the first 4 to 8 hours
- Most significant decrease usually happens in first 4-6 hours
- Do not need to obtain rebound level

Stopping Phototherapy

- AAP guidelines have little guidance on when to stop phototherapy. Appendix says < 14mg/dL
- Kaiser group created formula to predict rebound hyperbilirubinemia
- *Score = 15 (if gestational age < 38 weeks) − 7 × (age in days at phototherapy initiation) − 4 × (AAP phototherapy threshold − TSB at phototherapy termination) + 50*



Chang *Pediatrics* 2017: 139(3)

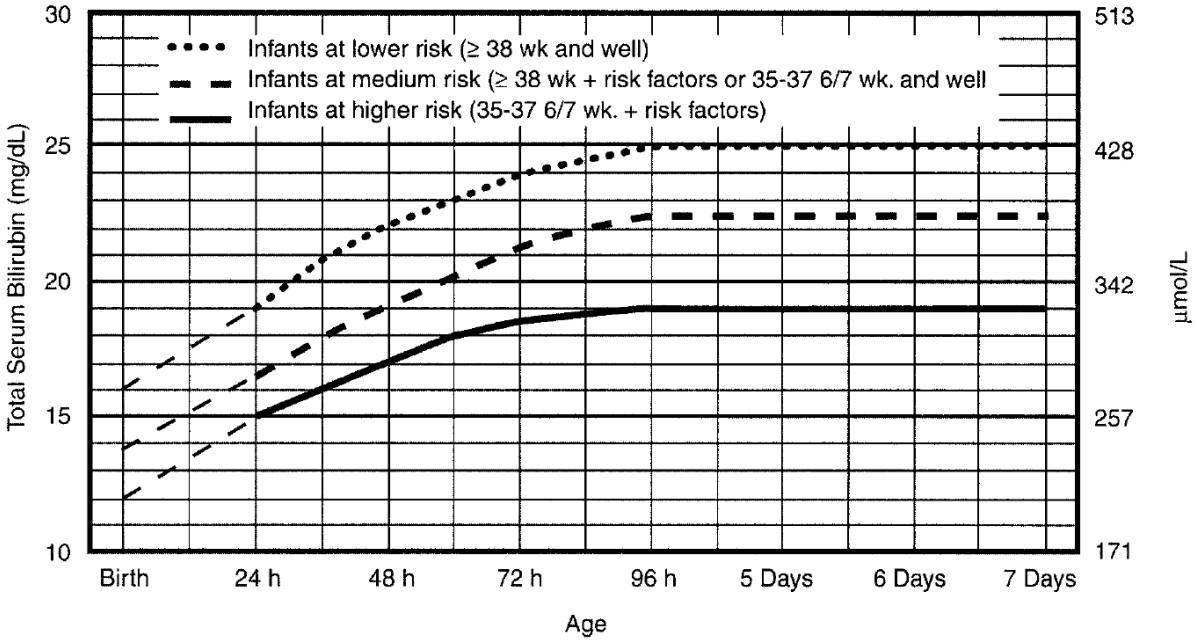
Stopping Phototherapy

- The probability of rebound hyperbilirubinemia was <10% with a prediction score of <30 and <4% with a prediction score of <20

- "results suggest that a clinician aiming to reduce the risk of rebound hyperbilirubinemia further could consider supplementing with formula, discharging an infant with home phototherapy (if available), or lowering the relative TSB by an additional 1 mg/dL at phototherapy termination with similar efficacy"

Chang *Pediatrics* 2017: 139(3)

Exchange Transfusion



Exchange Transfusion

- Recommended if:
  - infant showing signs of acute bilirubin encephalopathy (hypertonia, arching, retrocolis, opisthotonos, fever, high pitched cry)
  - TSB >5 above these lines
- Measure Albumin and calculate B/A ratio
- Use total bilirubin level

Questions?