Neonatal Hyperbilirubinemia

Kyle Millar, MD, FRCPC

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Presenter Disclosure

- Presenter: Kyle Millar
- Relationships with commercial interests:
  - None

Objectives

- Recommendations are for term and late preterm infants (34^0-36^6)
- Recognize the risk factors for different degrees of hyperbilirubinemia
- Identify the methods for measuring bilirubin
- Understand the indications for additional testing in hyperbilirubinemia
- Be familiar with the guidelines around screening neonates for hyperbilirubinemia
- Understand the treatment indications and regimens for neonatal hyperbilirubinemia

Data Source

- Review of pertinent guidelines
  - CPS[41]
  - AAP[28]
  - AAFP[42]
- Review of primary literature cited

Definitions

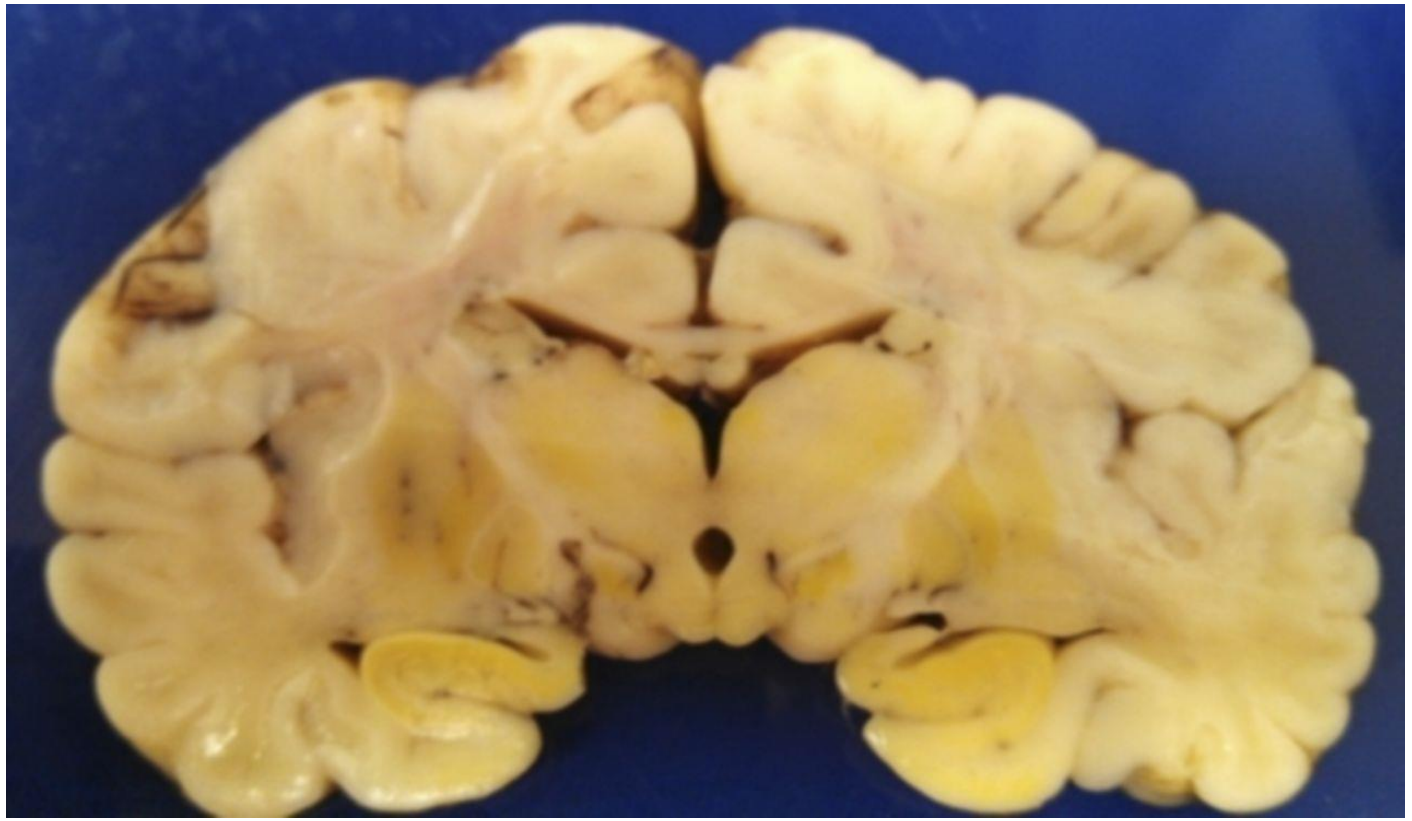
- Acute bilirubin encephalopathy (ABE) – Lethargy, hypotonia progressing to hypertonia, high-pitched cry, fever and eventual seizures and coma in the presence of severe hyperbilirubinemia
- Chronic bilirubin encephalopathy (CBE) – Athetoid cerebral palsy ± seizures, developmental delay, hearing deficit, oculomotor disturbances, dental dysplasia and mental deficiency

Acute bilirubin encephalopathy

Chronic bilirubin encephalopathy

Definitions

- Kernicterus - Yellow staining of neurons and neuronal necrosis of the basal ganglia and brainstem nuclei



Definitions

- Severe hyperbilirubinemia – Total serum bilirubin (TSB) >340 µmol/L during the first 28 days of life
- Critical hyperbilirubinemia – TSB > 425 µmol/L during the first 28 days of life.

Etiologies

Hyperbilirubinemia type	*Hemolysis present*	*Hemolysis absent*
Unconjugated	**Common**	**Common**
	Blood group incompatibility: ABO, Rh factor, minor antigens	Breast milk jaundice
	Infection	Infant of mother with diabetes
	Rare	Internal hemorrhage
	Hemoglobinopathies: thalassemia	Physiologic jaundice
	Red blood cell enzyme defects: G6PD, pyruvate kinase	Polycythemia
	Red blood cell membrane disorders: spherocytosis, ovalocytosis	**Rare**
		Hypothyroidism
		Immune thrombocytopenia
		Mutations of glucuronyl transferase (i.e., Crigler-Najjar syndrome, Gilbert syndrome)
		Pyloric stenosis
Conjugated	**Common**	
	Cytomegalovirus infection, hyperalimentation cholestasis, neonatal hepatitis, sepsis, TORCH infection, urinary tract infection	
	Rare	
	Biliary atresia, cystic fibrosis, hepatic infarction, inborn errors of metabolism (e.g., galactosemia, tyrosinosis)	

Epidemiology

- 60-84% of term newborns develop jaundice[1,2]
- 2% reach a TSB > 340 µmol/L (severe)[1]
- Most common cause of neonatal hospital readmission[3]
- ABE
  - ABE is rare unless TSB > 425 µmol/L (critical)[4,5]
  - Incidence estimated to be 1-4 / 10,000 live births[6]
  - 5% have evidence of CBE at time of discharge[7]

Epidemiology

- CBE
  - >3/4 of infants in the US kernicterus registry had a TSB > 515 µmol/L
  - 2/3 had a TSB > 600 µmol/L[8]
  - Incidence estimated to be 1/50, 000[9] to 1/100,000[6]
- Prevention of ABE remains the justification for the prevention, detection and treatment of severe hyperbilirubinemia[10,11]

Risk Factors - Hyperbilirubinemia

- Breastfeeding
- Younger age

Risk Factors – Severe hyperbilirubinemia

- Visible jaundice at younger than 24 h
- Shorter gestation (less than 38 weeks)
- Previous sibling with severe hyperbilirubinemia
- Cephalohematoma or visible bruising
- Male sex
- Maternal age older than 25 years of age
- Asian or European background
- Isoimmune or other hemolytic anemia
- Dehydration
- Exclusive and partial breastfeeding
  - Especially if difficulty establishing BF or 8-10% weight loss

Risk Factors – Acute bilirubin encephalopathy

- Earlier gestational age
- Low birth weight
- Hemolysis
- Sepsis
- Acidosis
- Dehydration
- Respiratory distress
- Hypoxia

Measuring bilirubin – Total serum bilirubin

- In a North American, multiethnic population (AGA, term, negative Coombs test):[5]
  - If TSB <40th percentile → no cases of subsequent TSB >95th
  - If TSB = 40th-75th percentiles → 2.2% of infants developed a TSB >95th
  - If TSB >75th percentile →
    - 12.9% of infants developed a TSB >95th if the infant was 36 weeks' gestation
    - 3% risk in the infant of 40 weeks' gestation[12]

Measuring bilirubin – Total serum bili

- Best method for predicting severe hyperbilirubinemia → timed TSB measurement interpreted in the context of the infant's GA
- There is no difference between the results of capillary or venous samples

Measuring bilirubin – Transcutaneous bili

- Benefits:
  - Non-invasive
  - Fast results
  - Accurate at lower levels of bilirubin
  - Use of TcB as a screening device is reasonable[13]
- Limitations:
  - Unreliable after phototherapy[14]
  - Unreliable with changes in skin colour and thickness[15]
  - Devices differ in accuracy → know the confidence intervals

Further work-up

- Those with severe hyperbilirubinemia or need for phototherapy:
  - Hemoglobin and hematocrit levels
  - Complete blood cell count (including blood smear and red cell morphology)
  - Neonatal blood type (AAP)
  - Investigations for sepsis should be performed if warranted

Further work-up

- Coombs (DAT) test:
  - Babies with O+ mothers have an increased risk for severe hyperbilirubinemia[16]
  - Need for phototherapy is increased in ABO incompatible infants who are Coombs positive[17]

  - Universal testing for ABO incompatibility/isoimmunization does not improve outcomes[18]
  - Testing all babies whose mothers are group O does not improve outcomes[19]

  - Reasonable to perform a DAT in:
    - Clinically jaundiced infants of mothers who are group O
    - infants with an elevated risk of needing therapy (high-intermediate zone)
    - Infant with severe hyperbilirubinemia or is initiated on phototherapy

Further work-up

- Conjugated bilirubin
  - Usually neonatal hyperbilirubinemia is unconjugated
  - Rhesus erythroblastosis, liver disease and cholestasis[20]
  - The conjugated bilirubin fraction should be measured in:
    - An infant with persistent jaundice (longer than two weeks)
    - Hepatosplenomegaly[21]
    - Infant with severe hyperbilirubinemia or is initiated on phototherapy
  - A total conjugated bilirubin >18 µmol/L or greater than 20% of the TSB concentration warrants further investigation[22]

Further work-up

- Glucose-6-phosphate dehydrogenase deficiency
  - Newborns with G6PD deficiency have:
    - Increased incidence of severe hyperbilirubinemia
    - Increased likelihood of requiring an exchange transfusion
  - Test in babies with Mediterranean, Middle Eastern, African or Southeast Asian ancestry with hyperbilirubinemia
  - Test in babies with severe hyperbilirubinemia or started on phototherapy
  - G6PD-deficient newborns may require intervention at a lower TSB[23]

Further work-up – Do not

- Clinical assessment of jaundice is inadequate for diagnosing hyperbilirubinemia
  - Difference of up to 100 µmol/L between visual and laboratory estimates[24]
- Umbilical cord blood TSB:
  - PPV = 4.8% - 10.9%
  - Poor sensitivity/specificity
- Universal hemoglobin assessment → does not aid in the prediction of severe hyperbilirubinemia[25]

Primary Prevention – Breastfeeding

- Breastfed infants are at a higher risk for developing severe hyperbilirubinemia but the risks of ABE are very small compared to the benefits of breastfeeding[26]
- Infants who lose more than 10% of their birth weight should be evaluated by an individual with skills in lactation consulting[27]

Screening

- A recent study[3] demonstrated that 185/289 infants with critical hyperbilirubinemia presented after hospital discharge.
- Peak TSB concentration occurs between three and five days of life
- Recommendations:
  - CPS → Perform universal screening with TSB or TcB before the period of highest risk (24h –72h) and use this to determine risk and follow-up
  - AAP → Universal screening with TSB or transcutaneous bilirubin (TcB) levels or targeted screening based on risk factors[28]

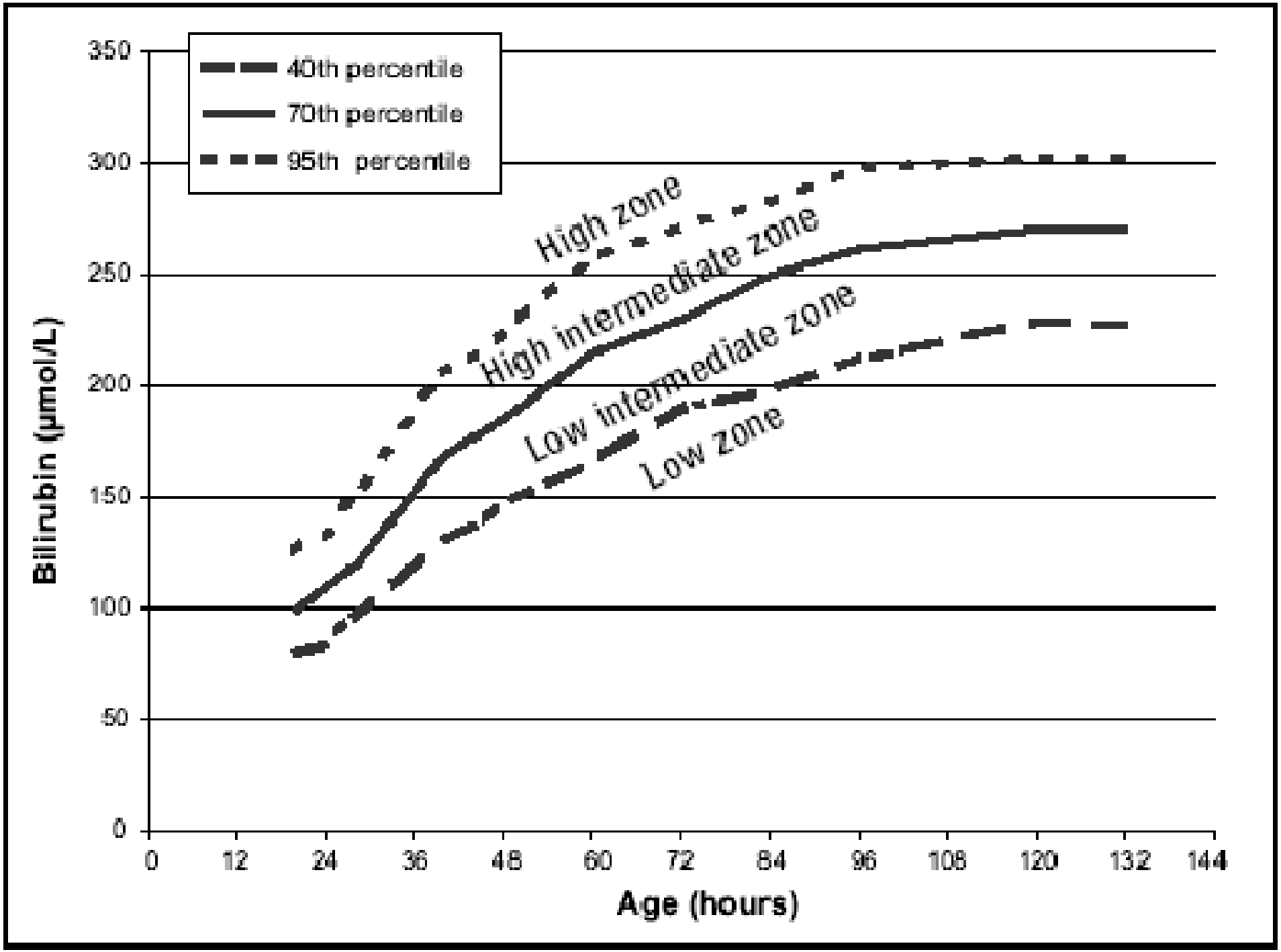
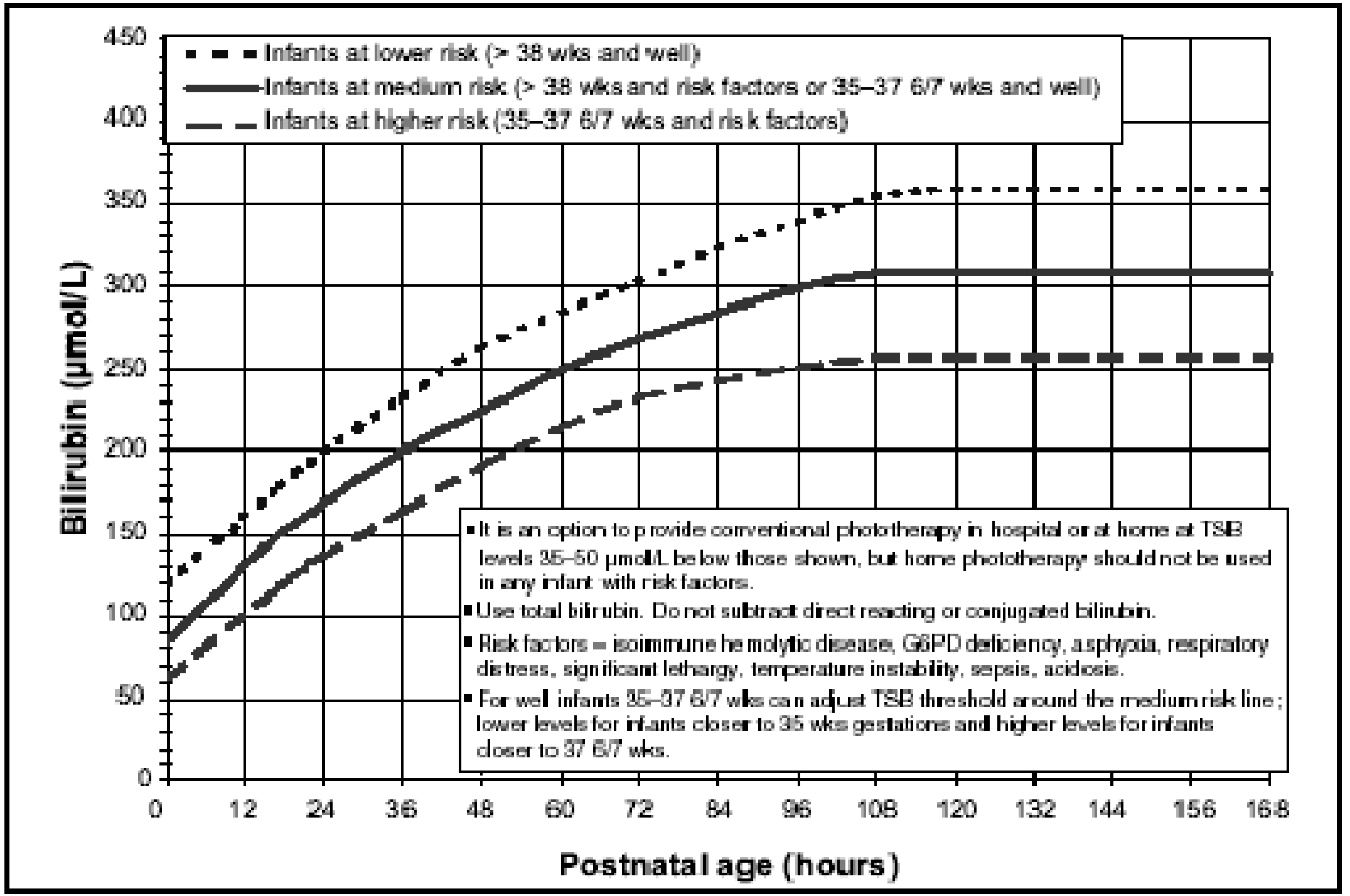

40th percentile
70th percentile
95th percentile
High zone
High intermediate zone
Low intermediate zone
Low zone
Bilirubin (µmol/L)
350
300
250
200
150
100
50
0
0
12
24
36
48
60
72
84
96
108
120
132
144
Age (hours)

TABLE 4
Response to results of bilirubin screening

Zone	Greater than 37 weeks' gestation and DAT-negative	35 to 37 6/7 weeks' gestation or DAT-positive	35 to 37 6/7 weeks' gestation and DAT-positive
High	Further testing or treatment required*	Further testing or treatment required*	Phototherapy required
High-intermediate	Routine care	Follow-up within 24 h to 48	Further testing or treatment required*
Low-intermediate	Routine care	Routine care	Further testing or treatment required*
Low	Routine care	Routine care	Routine care

*Arrangements must be made for a timely (eg, within 24 h) re-evaluation of bilirubin by serum testing. Depending on the level indicated in Figure 2, treatment with phototherapy may also be indicated. DAT Direct antiglobulin test


Infants at lower risk (> 38 wks and well)
Infants at medium risk (> 38 wks and risk factors or 35–37 6/7 wks and well)
Infants at higher risk (35–37 6/7 wks and risk factors)
Bilirubin (µmol/L)
450
400
350
300
250
200
150
100
50
0
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Postnatal age (hours)
It is an option to provide conventional phototherapy in hospital or at home at TSB levels 35–50 µmol/L below those shown, but home phototherapy should not be used in any infant with risk factors.
Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, respiratory distress, significant lethargy, temperature instability, sepsis, acidosis.
For well infants 35–37 6/7 wks can adjust TSB threshold around the medium risk line; lower levels for infants closer to 35 wks gestations and higher levels for infants closer to 37 6/7 wks.

Treatment - Phototherapy

- Light energy (460 to 490 nm) induces a conformational change in the bilirubin molecule, making it water soluble
- Effectiveness is related to the area of skin exposed and the intensity of the light at the skin[30-32]

Treatment - Phototherapy

- Prevents progression to severe hyperbilirubinemia in infants with a moderately elevated TSB concentration[29]
  - ARR of 10-17%; NNT = 5-10
  - 84% effective in preventing exchange transfusion[33]
- Acts as an initial therapy in those with severe hyperbilirubinemia

Treatment - Phototherapy

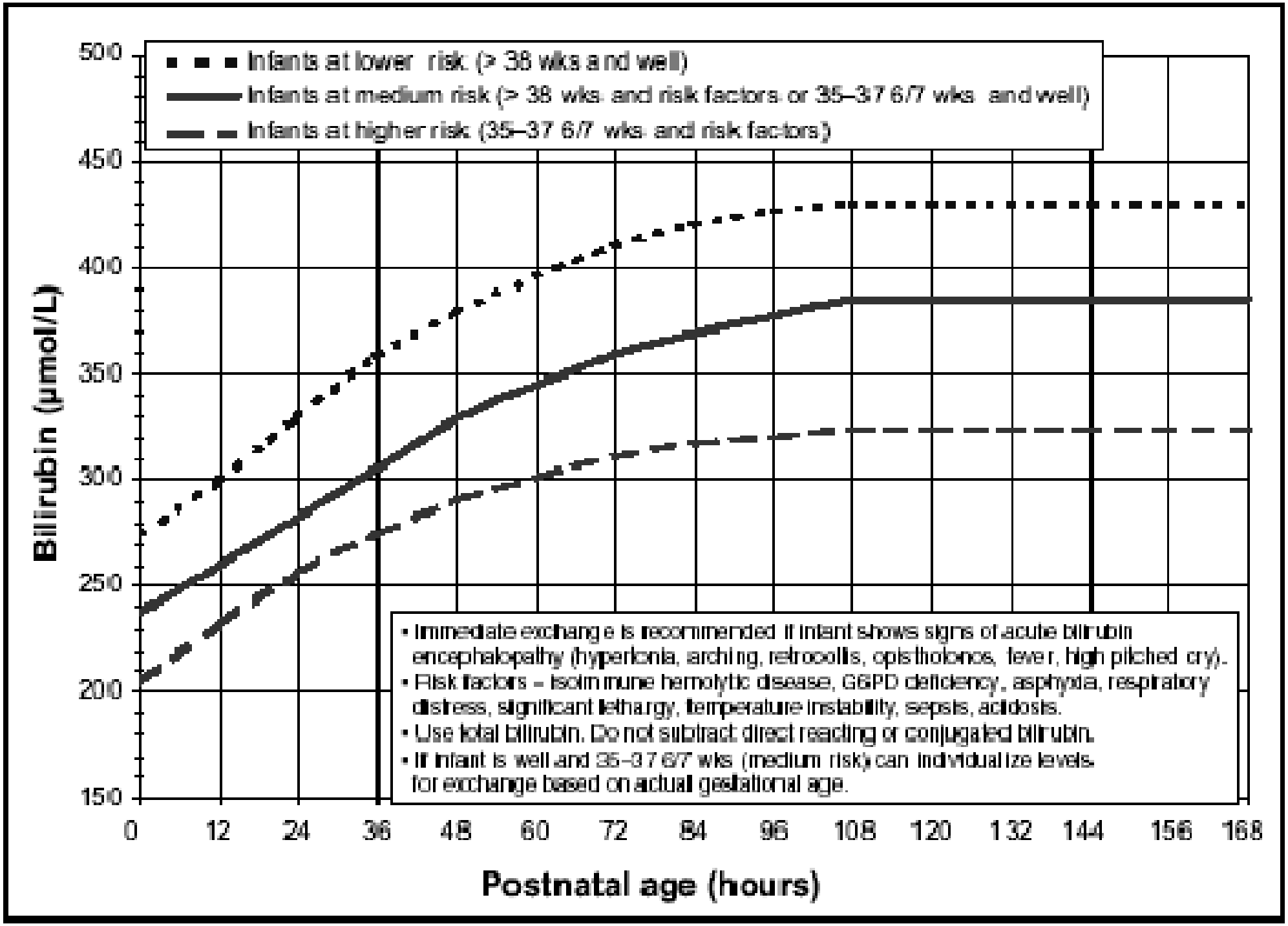
- Intensive phototherapy
  - 2 phototherapy units or special high-intensity fluorescent tubes
  - Check bilirubin within 2 h to 6 h of initiation of treatment to confirm response
  - Supplemental fluids are indicated
    - Prevents progression to exchange transfusion[34]
    - Oral/NG as good as IV[35]
- If TSB concentration is approaching the exchange transfusion threshold:
  - Addition of a fibre optic blanket under the infant
  - The diaper should be removed

Treatment- Breastfeeding

- Interrupting breastfeeding as part of therapy for hyperbilirubinemia is associated with a major increase in the frequency of stopping breastfeeding by one month
  - RR=1.79 (CI 1.04-3.06); NNH = 4)[37]
- Continued breastfeeding in infants receiving phototherapy is:
  - Not associated with adverse clinical outcomes
  - No apparent impact on the frequency of TSB reduction to normal at 48h[38]
    - RR=1.07 (CI 0.6 to 1.92)

Treatment – Exchange Transfusion

- Exchange transfusion
  - If phototherapy fails to control the rising bilirubin concentrations
  - If presents above the threshold for exchange transfusion
  - With clinical signs of ABE
  - Refer


Infants at lower risk (> 38 wks and well)
Infants at medium risk (> 38 wks and risk factors or 35–37 6/7 wks and well)
Infants at higher risk (35–37 6/7 wks and risk factors)
Bilirubin (µmol/L)
500
450
400
350
300
250
200
150
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
Postnatal age (hours)
• Immediate exchange is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry).
• Risk factors – isoimmune hemolytic disease, G6PD deficiency, asphyxia, respiratory distress, significant lethargy, temperature instability, sepsis, acidosis.
• Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
• If infant is well and 35–37 6/7 wks (medium risk) can individualize levels for exchange based on actual gestational age.

Follow up

- Infants do not need to be kept in the hospital for rebound hyperbilirubinemia [39,40]
- All jaundiced infants, especially those exclusively breastfed, should be closely monitored (24-48 hours) until:
  - Feeding established
  - Weight gain
  - TSB concentration starts to fall
- Note: Infants with isoimmunization are at risk for severe anemia after several weeks:
  - Repeat hemoglobin at two weeks if it was low at discharge
  - Four weeks if it was normal

Thank you

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Heme metabolism

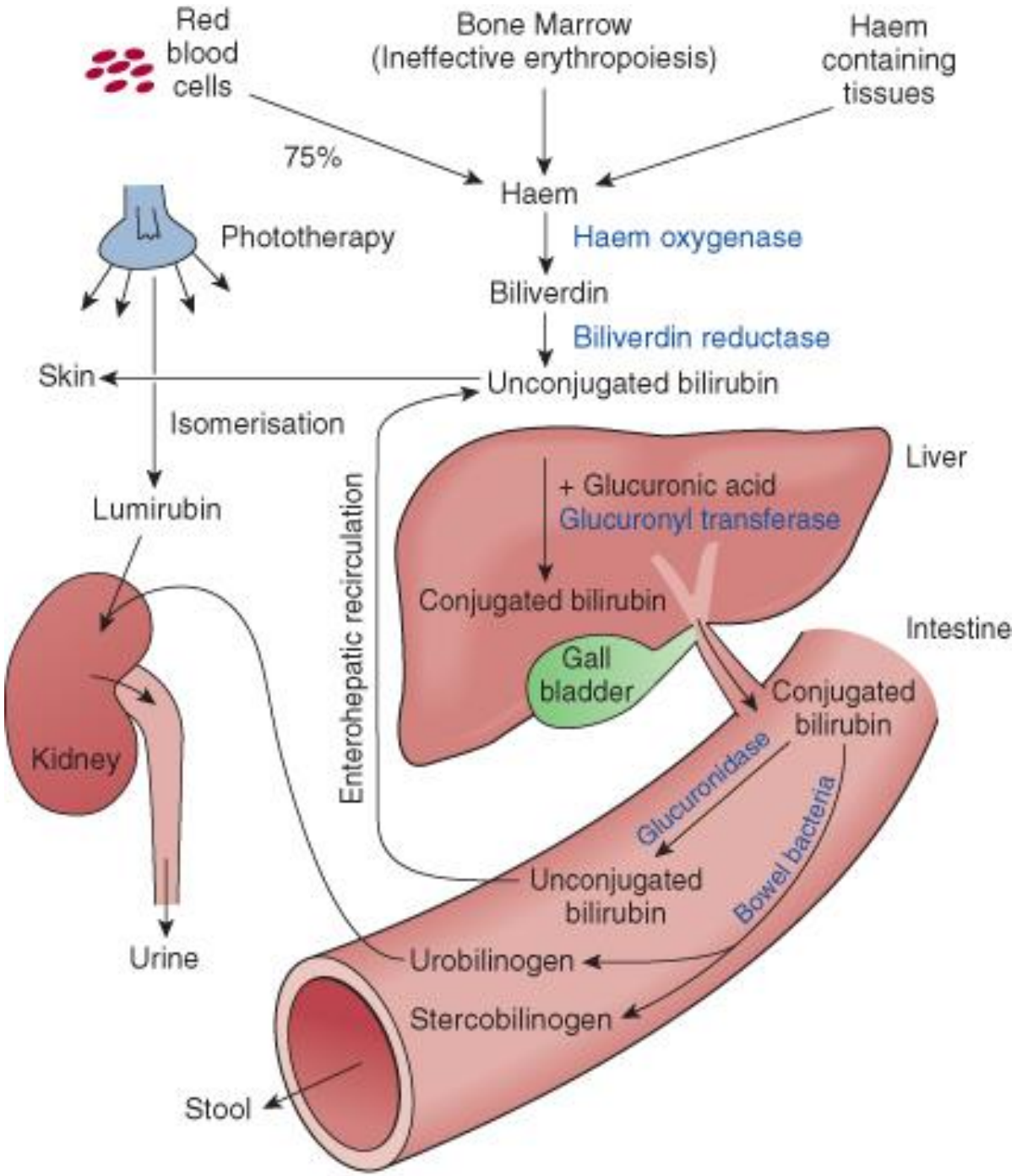
Red blood cells
Bone Marrow (Ineffective erythropoiesis)
Haem containing tissues
75%
Haem
Phototherapy
Haem oxygenase
Biliverdin
Biliverdin reductase
Skin
Unconjugated bilirubin
Isomerisation
Lumirubin
Enterohepatic recirculation
Liver
+ Glucuronic acid
Glucuronyl transferase
Conjugated bilirubin
Gall bladder
Intestine
Conjugated bilirubin
Kidney
Glucuronidase
Bowel bacteria
Unconjugated bilirubin
Urine
Urobilinogen
Stercobilinogen
Stool

Table 1. Risk Score for Neonatal Hyperbilirubinemia

Variable	*Score*
Birth weight:	
2,000 to 2,500 g (4 lb, 7 oz to 5 lb, 8 oz)	0
2,501 to 3,000 g (5 lb, 8 oz to 6 lb, 10 oz)	3
3,001 to 3,500 g (6 lb, 10 oz to 7 lb, 11 oz)	6
3,501 to 4,000 g (7 lb, 11 oz to 8 lb, 13 oz)	9
4,001 to 4,500 g (8 lb, 13 oz to 9 lb, 15 oz)	12
4,501 to 5,000 g (9 lb, 15 oz to 11 lb, 1 oz)	15
Oxytocin (Pitocin) used during delivery	4
Vacuum-assisted delivery	4
Breast and bottle feeding	4
Exclusive breastfeeding	5
Gestational age < 38 weeks	5

NOTE: *A total score of 8 or more suggests an increased risk of hyperbilirubinemia; total serum bilirubin or transcutaneous bilirubin level should be obtained.*

Adapted with permission from Keren R, Bhutani VK, Luan X, Nihtianova S, Cnaan A, Schwartz JS. Identifying newborns at risk of significant hyperbilirubinaemia: a comparison of two recommended approaches. Arch Dis Child. *2005;90(4):417.*

Screening

- Recommendations:
  - AAFP → Infants who appear jaundiced should be evaluated by a risk score or by measurement of TSB or TcB
    - Insufficient evidence that screening for hyperbilirubinemia is associated with improved clinical outcomes[8,28]
    - Little evidence that phototherapy or exchange transfusion decreases the risk of ABE[29]

Treatment - Rehydration

- Enteral feeding should be continued because:
  - It will replace fluid lost through the skin and by diarrhea during phototherapy
  - Supply energy
  - Reduce enterohepatic reuptake of the bilirubin[36]